Favorable Conformations of 2-Amino-2-deoxy-D-hexopyranose Derivatives

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The conformational free energies of 2-amino-2-deoxy (hydrochloride) and 2-acetamido-D-deoxy derivatives of D-glucose, D-galactose, and D-mannose were calculated by using the empirical potential functions. The most stable conformations of these amino sugars were obtained for α- and β-anomers in the Cl and 1C chair forms through the procedure of searching for the energy minimum. The results of the energy calculations indicate that the increased anomeric effect in the protonated and *N*-acetylated amino derivatives in an aqueous solution is mainly due to the electrostatic interaction between the positive-charged amino group on C(2) and the hydroxyl group on the anomeric carbon atom, C(1).

This paper will present a theoretical calculation of the conformational free energies of the protonated, non-protonated, and *N*-acetylated amino derivatives of 2-amino-2-deoxy-D-glucose, -D-galactose, and -D-mannose. The anomeric equilibria of these amino sugars in an aqueous solution have been studied by many workers using the NMR[1] or optical rotatory methods.[2-9] The present work was undertaken in order to determine the most favored conformation of each of these amino sugars and to explain the increased proportion of the α-anomer in the protonated and *N*-acetylated amino derivatives of D-glucose and D-galactose, as pointed out by Neuberger and Fletcher.[8]

The theoretical prediction of the favored conformation of simple reducing sugars has been attempted by many workers by considering various factors, including the Hassel-Ottar effect,[9] the $\triangle_2$ effect[10,11] and the anomeric effect.[12-16] Angyal[14] has assigned the interaction energies for aldopyranoses by using the empirical rule. Rao *et al.*[17-19] have shown that the energy calculations taking the nonbonded and electrostatic interactions into account are consistent with the experimental data for aldopyranoses. In the present work, the potential energies for α- and β-anomers of each amino sugar in the Cl and 1C conformations have been calculated from the empirical potential functions, using a modification of the method of Rao *et al.*[18] The conformational entropies have also been estimated and added to the corresponding potential energies to obtain the total free energies.

Calculation of Free Energy

Potential Energy. The potential energy of a molecule can be expressed in terms of the nonbonded interaction, the electrostatic interaction, and the steric effect associated with the bond distortion.

The nonbonded interaction energy was evaluated by the use of the Lennard-Jones '6—12'-type potential function:

$$V_n = \frac{A}{R_{ij}^{12}} - \frac{B}{R_{ij}^{6}} \quad (1)$$

where R_{ij} is the distance between the interacting atoms, i and j. The A and B coefficients determined by Scott and Sheraga[20] were used in the present calculation.

The electrostatic interaction energy was calculated by using the following function:

$$V_e = \frac{Q_i \cdot Q_j}{\varepsilon \cdot R_{ij}} + \frac{Q_i \cdot \mu \cdot \cos\phi_i}{\varepsilon \cdot R_i^2} \quad (2)$$

where Q_i and Q_j are the charges of a pair of interacting atoms, i and j, where R_{ij} is the distance between them, ε is the effective dielectric constant of the medium, μ is the dipole moment of the lone pairs on the ring-oxygen atom, R_i is the distance between the i atom and the ring-oxygen atom, and Φ_i is the angle between the dipole vector on the ring-oxygen atom and the vector directed from the ring-oxygen atom to the i atom. The first term in Expression (2) is the Coulombic interaction between the partial charges localized at each atom. The values of Q used in the calculation are given in Table 3. They were obtained from the results of the molecular orbital calculations for aldopyranose and amino acid molecules by several workers.[19,21,23] The second term in Expression (2) is the charge-dipole interaction. The value of the dipole moment of the unshared electron pairs on the ring-oxygen atom is 0.37D, a value derived from the results of the theoretical calculation for 2-methoxytetrahydropyran by Zhadanov *et al.*[24] The effective dielectric constant, ε, is usually much smaller than the actual dielectric constant.[20] In the present calculation, the value of 4.5 was assigned, since the use of this value gave a good agreement between the calculated and observed free energies for aldopyranoses in an aqueous solution.

The energy caused by the steric effect of the covalent bonds was evaluated with the deviation of a single-bond angle, θ, from the normal tetrahedral angle, θ_t (109.5°), by using the following function:

$$V_b = \kappa \cdot (\cos\theta - \cos\theta_t)^2 \quad (3)$$

where κ is a constant dependent on the bonded atoms involved. The values of κ were assigned as 65 kcal/mol for C–C–C and C–C–O, 55 kcal/mol for O–C–O, and 45 kcal/mol for C–C–H and O–C–H.[25]

The energies associated with the internal rotation and the intramolecular hydrogen bond were neglected.

Entropy. The conformational entropy can be calculated by using the formula:

$$S = R \ln N \quad (4)$$

were R is the gas constant and where N is the total number of possible conformations of the molecule.[18]

Generally, the OH bond in the equatorial hydroxyl group has three favored orientations of the staggered form, while the OH bond in the axial hydroxyl group

has two favored orientations. Since, in an aqueous solution, the sugar molecules are extensively hydrated through hydrogen-bonding with the surrounding water molecules, the OH bond might be directed to the oxygen atom of the neighboring water molecule to form a strong hydrogen bond. Therefore, the orientations of the OH bonds are greatly restricted, not only by the intramolecular interactions, but also by the intermolecular hydrogen bonds. As a result, the possible orientations of the OH bond are dependent on the position of the hydroxyl group linked to the ring. For instance, the OH bond of the equatorial hydroxyl group linked to C(1) has only two favorable orientations. By taking account of all the possible orientations of OH bonds, together with the orientations of the CH_2OH and amino groups, the total number of possible conformations was calculated for each derivative.

Procedure of Calculation. The ring atoms and atoms linked directly to the ring were fixed in the Cl and 1C chair forms by using average values derived from 25 crystal structure analyses of pyranoses.[26-33] The CH_2OH side group was fixed in the *gauche-trans* conformation, which is one of the preferable orientations often found in the crystals.[34] The hydrogen atoms in the hydroxyl groups were fixed in one of the favorable staggered forms. The atoms in amino groups were fixed by using the bond lengths and angles given in Table 2. The NH_2 and *N*-acetyl groups were assumed to be planar. The positional parameters given for β-D-glucose are listed in Table 1. The bond lengths and angles calculated from these parameters are in good agreement with the values given by Arnott *et al.*[27]

The most stable conformation of each derivative was determined from the initial structure by the following procedure. As has been mentioned before, the OH bond in the equatorial hydroxyl group has three favored orientations, and the most favorable orientation of the three might be determined by taking the relative positions of the neighboring OH bonds into account. Thus, in the first step, the most preferable conformation was selected from the 81 possibilities which arose from the different orientations of OH bonds in the staggered form. The interaction energies were calculated for each conformation by using the (1) and (2) potential functions, and their values were compared. In the next step, the OH, CH_2OH, and amino groups were independently rotated around their free rotational bonds, and the minimum energy position of each substituent group was sought by the reiterative process. For example, the O(1)-H(O1) bond was rotated around the C(1)-O(1) bond at suitable angular intervals, and at each position the interaction energy between H(O1) and each fixed atom was calculated by using the (1) and (2) functions.

Table 1. Positional parameters (Å) of β-D-glucopyranose

Atom	*X*	*Y*	*Z*
C(1)	1.406	0.090	−0.231
C(2)	0.761	−1.212	0.209
C(3)	−0.692	−1.272	−0.231
C(4)	−1.437	−0.024	0.222
C(5)	−0.692	1.227	−0.231
C(6)	−1.314	2.504	0.281
O(1)	2.676	0.177	0.313
O(2)	1.481	−2.323	−0.296
O(3)	−1.304	−2.435	0.317
O(4)	−2.741	0.005	−0.346
O(5)	0.655	1.191	0.262
O(6)	−0.572	3.601	0.048
H(1)	1.441	0.178	−1.229
H(2)	0.800	−1.266	1.219
H(3)	−0.710	−1.314	−1.252
H(4)	−1.523	−0.021	1.224
H(5)	−0.673	1.278	−1.245
H(61)	−1.322	2.482	1.512
H(62)	−2.262	2.559	0.179
H(O1)	2.608	0.125	1.542
H(O2)	1.483	−2.304	−1.064
H(O3)	−1.266	−2.412	1.546
H(O4)	−2.678	−0.004	−1.113
H(O6)	−0.983	4.446	0.387

Table 2. Bond lengths and angles in amino groups

Nonprotonated amino group			
C(2)-N(2)	1.48 Å	C(2)-N(2)-H(N)	120°
N(2)-H(N)	1.0 Å	H(N)-N(2)-H′(N)	120°
Protonated amino group			
C(2)-N(2)	1.50 Å	C(2)-N(2)-H(N)	109.5°
N(2)-H(N)	1.0 Å	H(N)-N(2)-H′(N)	109.5°
N-Acetylated amino group			
C(2)-N(2)	1.47 Å	C(2)-N(2)-C(7)	123°
N(2)-C(7)	1.33 Å	C(2)-N(2)-H(N)	115°
C(7)-C(8)	1.47 Å	C(7)-N(2)-H(N)	122°
C(7)-O(7)	1.24 Å	N(2)-C(7)-C(8)	118°
N(2)-H(N)	1.0 Å	N(2)-C(7)-O(7)	123°
C(8)-H(8)	1.0 Å	C(8)-C(7)-O(7)	119°
		C(7)-C(8)-H(8)	109.5°
		H(8)-C(8)-H′(8)	109.5°

Table 3. Partial charges on the atoms for the amino sugars in fractions of an electronic charge

Atom name	Fractional charge
C(1)	0.19
C(2), C(5), C(6)	0.06
C(3), C(4)	0.12
O(1)	−0.445
O(3), O(4), O(6)	−0.455
O(5)	−0.25
All hydrogen atoms linked to the carbon atoms	0.05
All hydrogen atoms in the hydroxyl group	0.30
N(2) in NH_2 group	−0.53
H(N) in NH_2 group	0.22
N(2) in NH_3 group	0.13
H(N) in NH_3 group	0.25
N(2) in *N*-acetyl group	−0.305
C(7) in *N*-acetyl group	0.45
C(8) in *N*-acetyl group	−0.12
O(7) in *N*-acetyl group	−0.12
H(N) in *N*-acetyl group	0.27

The minimum energy position for H(O1) was sought. After fixing the H(O1) atom in its minimum-energy position, the H(O2) atom was fixed in the same manner and the process was continued until all atoms were located. A similar reiterative procedure was applied to determine the distortion of the bond angles about the ring carbon atoms. In this process, each of the OH, CH_2OH, and amino groups and each of the hydrogen atoms linked to the ring were sequentially tilted by varying the bond angles about the ring atoms. For each bond angle, the steric energy was calculated using the (3) function, and the interaction energy, using the (1) and (2) functions, thus, the minimum-energy position was determined for each substituent group. The rotation and tilting procedures were repeated alternatively until, after four cycles, a convergence was observed. The potential energy of the molecule was found by the summation of the nonbonded and electrostatic interactions and the steric energies calculated in the last cycle.

The entropy of each derivative was calculated by using Formula (4), and the contribution of the entropy term, $-ST$, was added to the corresponding potential energy to obtain the total free energy at 300 K. The values of the entropies assigned for the amino derivatives are given in Table 4.

Table 4. Conformational entropies of various amino hexose derivatives

Amino hexose derivative	Calculated conformational entropy(S) in cal·mol^{-1}·deg^{-1}			
	α-anomer		β-anomer	
	Cl	1C	Cl	1C
2-Amino-2-deoxy-D-glucose	8.98	6.31	11.30	8.49
2-Amino-2-deoxy-D-galactose	8.85	6.31	11.10	8.49
2-Amino-2-deoxy-D-mannose	10.18	7.69	10.18	8.38
2-Amino-2-deoxy-D-glucose HCl	8.80	7.12	10.18	9.47
2-Amino-2-deoxy-D-galactose HCl	8.32	7.12	9.70	9.47
2-Amino-2-deoxy-D-mannose HCl	10.18	7.12	8.80	6.31
2-Acetamido-2-deoxy-D-glucose	12.17	8.49	12.74	9.51
2-Acetamido-2-deoxy-D-galactose	11.53	8.49	12.10	9.51
2-Acetamido-2-deoxy-D-mannose	11.37	8.49	11.37	9.51

Table 5. Free energy (kcal/mol) for some aldopyranoses

Sugar	Calculated value		Angyal's value	
	Cl	1C	Cl	1C
α-D-glucose	0.45	4.45	0.35	4.5
β-D-glucose	0.0	6.01	0.0	5.95
α-D-galactose	0.84	2.97	0.80	4.25
β-D-galactose	0.57	5.78	0.45	5.7
α-D-mannose	0.43	3.68	0.45	3.5
β-D-mannose	1.05	5.65	0.90	5.6

Results and Discussion

The conformational free energies calculated for D-glucose, D-galactose, and D-mannose in the Cl and 1C conformations are given in Columns 2 and 3 of Table 5. These values are in good agreement with Angyal's values,[14] given in Columns 4 and 5 of the same table. The results of the energy calculations for the amino derivatives are given in Table 6. The free energies given in Columns 2—5 of Table 6 show that the Cl conformation is more stable than the 1C conformation for all the derivatives and that the α-anomers in the Cl form are more stable than the β-anomers except in the cases of 2-amino-2-deoxy-D-glucose and -galactose and 2-amino-2-deoxy-D-mannose hydrochloride. The percentages, p, of the proportions of the α- and β-anomers in the Cl and 1C conformations in an equilibrium mixture of each derivative were calculated using the following formula:

$$p_i = \frac{\exp(-F_i/RT)}{\sum_i \exp(-F_i/RT)} \qquad (5)$$

where the summation includes all four conformations and where F_i is the free energy of the i component. Calculations by means of Expression (5) incorporating the free energy values given in Table 6 show that the proportions of both anomers existing in the 1C conformation in an equilibrium mixture are negligible for all amino derivatives except for α-D-glucosamine hydrochloride. The calculated anomeric ratios (α/β) in an equilibrium mixture of each derivative are given in Column 2 of Table 7, while the corresponding NMR and optical rotatory data observed from aqueous solutions are given in Columns 3 and 4 of the same table. The α/β ratios calculated here include both Cl and 1C conformations, whereas the NMR ratios are derived from the Cl peaks only. However, it is possible that the Cl peaks may include contributions from the 1C conformation, and, as the energy calculation indicates that the Cl conformation is much more stable than the 1C, a valid comparison can be made. In the case of D-glucosamine hydrochloride, the α/β ratio calculated from the Cl conformation is 52:48; this value is slightly different from the observed value.

As is well known, the anomeric effect makes an equatorial group on the anomeric carbon of D-glucose less stable than it would be in other positions on the ring. This effect has been explained in terms of the unfavorable parallel interaction between the anomeric carbon-oxygen dipole and the dipole formed by the unshared electron pairs on the ring-oxygen atom.[12,13] In the present case, such an anomeric effect seems likely to be increased further. However, we have no evidence that such dipole-dipole interaction would be enhanced by the amino group on C(2). Table 6 shows that the electrostatic interaction terms given in Columns 6—9 tend to reduce the free energy of the α-anomer significantly in the case of the protonated and *N*-acetylated amino derivatives. It may be, therefore, that the main factor responsible for the increased anomeric effect in these amino sugars is the charge-charge interaction between the positively charged amino group and the hydroxyl group on the anomeric carbon atom. The presence of an oxygen atom in the pyranose ring produces a significant deformation as compared with the cyclohexane ring, with the result

Table 6. Free energies and electrostatic interaction energies for 2-amino-2-deoxy-hexose derivatives

Name of amino sugar	Free energy (kcal/mol)				Electrostatic interaction energy (kcal/mol)			
	α-anomer		β-anomer		α-anomer		β-anomer	
	Cl	1C	Cl	1C	Cl	1C	Cl	1C
2-Amino-2-deoxy-D-glucose	4.47	7.48	4.13	8.99	3.14	3.51	3.65	2.89
2-Amino-2-deoxy-D-galactose	4.66	6.48	4.50	8.51	3.32	2.75	3.83	2.81
2-Amino-2-deoxy-D-mannose	3.45	6.49	4.21	9.20	2.70	3.06	3.45	3.00
2-Amino-2-deoxy-D-glucose HCl	41.37	42.22	41.43	46.18	9.47	7.93	9.92	9.87
2-Amino-2-deoxy-D-galactose HCl	41.75	44.17	42.02	48.35	9.62	10.30	10.25	12.55
2-Amino-2-deoxy-D-mannose HCl	41.65	43.46	40.88	46.45	10.38	9.38	9.16	9.29
2-Acetamido-2-deoxy-D-glucose	70.80	72.82	71.05	75.54	8.89	8.60	9.62	8.92
2-Acetamido-2-deoxy-D-galactose	70.93	73.24	71.23	76.90	9.05	8.88	9.82	10.09
2-Acetamido-2-deoxy-D-mannose	70.56	73.98	70.67	76.68	9.03	9.50	9.26	9.49

Table 7. Anomer ratio (α/β) in equilibrium mixtures of amino sugar derivatives

Amino sugar derivative	Calcd	From NMR[a)]	From optical rotation	Ref.
2-Amino-2-deoxy-D-glucose	36:64	—	39:61	2
2-Amino-2-deoxy-D-galactose	39:61	—	—	—
2-Amino-2-deoxy-D-mannose	78:22	—	—	—
2-Amino-2-deoxy-D-glucose HCl	61:39	63:37	63.3:36.7	3
2-Amino-2-deoxy-D-galactose HCl	62:38	47:53	56.3:43.7	4
2-Amino-2-deoxy-D-mannose HCl	22:78	43:57	—	—
2-Acetamido-2-deoxy-D-glucose	61:39	68:32	65.8:34.2	5
2-Acetamido-2-deoxy-D-galactose	63:37	65:35	64:36	6
2-Acetamido-2-deoxy-D-mannose	55:45	57:43	55:45	7

a) The NMR data was taken from Ref. 1.

that the amino group on C(2) is closer to the hydroxyl group on C(1) in the α-anomer than that in the β-anomer. This unequal distance in the two anomers might cause the increased anomeric effect.

The most stable conformations derived from several amino sugars by means of the potential energy calculations indicate the following structural features of the amino sugars. The hydroxyl group in an axial position has a tendency to be tilted toward the equatorial orientation as a result of the repulsive interaction between the axial substituents. The C–C–O angles outside of the ring for the axial hydroxyl group are larger than those for the equatorial group by 1° on the average. The CH_2OH side group in an axial position also has a similar tendency. It is more tilted when the hydroxyl groups occupy the axial positions of the C(1) and C(3) ring atoms. For example, the C(4)–C(5)–C(6) angles are calculated as 115° for α-D-glucose in the 1C form and as 117° for β-D-glucose in the 1C form, while the mean value of the corresponding angles in the equatorial epimers is 113°. However, the amino groups do not show such a tendency. In this case, the C–C–N angle is close to the tetrahedral angle in both the axial and the equatorial groups. This may be accounted for by the electrostatic attractive force due to the positive charge on the amino group. The stable conformation of the NH_3 group with respect to the pyranose ring is the staggered form, as observed in the β-D-galactosamine hydrochloride crystal.[28)] The planar NH_2 and *N*-acetyl groups have two possible conformations when they link to the equatorial position of C(2) in a Cl-chair form. Each conformfftion is close to a *trans* form about C(2)–N, whith the N–H bond *trans*-antiparallel with respect to the hydrogen atom on C(2). The present calculations give the minimum energies at 90° and 145° for the C(1)–C(2)–N(2)–C(7) torsional angle. These calculated angles may be compared with the corresponding angles of 137°, 83°, 72°, and 113° observed in the crystal structures of the *N*-acetylated derivatives of α-D-glucose,[30)] α-D-galactose,[31)] α-D-muramic acid,[32)] and 4-*N*-(α-D-glucopyranosyl)-L-asparagine[33)] respectively.

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