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Note

Theoretical investigations on 2-acetamido-2-deoxy aldohexopyranoses: conformation and the anomeric effect*

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INTRODUCTION

Amino sugars occur widely in the animal kingdom; for instance the glycosaminoglycans contain 2-acetamido-2-deoxy-D-aldohexopyranose as one of their major constituents. In certain fungi and algae, cellulose is replaced by chitin, a homopolymer of 2-acetamido-2-deoxy-β-D-glucose. In almost all of the bacteria, 2-acetamido-2-deoxy-β-D-glucose and muramic acid form the glycan backbone of the macromolecule "peptidoglycan". Recent n.m.r. studies[1,2] have indicated that the pyranose rings in 2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-galactose, and 2-acetamido-2-deoxy-D-mannose exist in the $^4C_1$(D) conformation. These studies have also indicated that, in D_2O at equilibrium, the α-anomer in the former two examples preponderates, in contrast to the corresponding aldoses. Thus far, no attempt has been made to explain these results theoretically. In this note we report the potential and free energies of these molecules, computed by using semiempirical potential functions, and comparison of these with experimental data. Such a study should enable us not only to predict the favoured conformations, but also to provide more information about the stereochemistry of the six-membered rings.

METHOD OF CALCULATION

To calculate the electrostatic contribution to the total energy, the fractional charges on various atoms were obtained by the molecular-orbital method[3–7]. The calculated fractional charges on the various atoms of a 2-acetamido-2-deoxy-D-aldohexopyranose are shown in Fig. 1. The expressions used, and the procedure followed to obtain the minimum potential energy of these sugars, are the same as those reported earlier[7–10]. In computing the nonbonded energy involving a nitrogen

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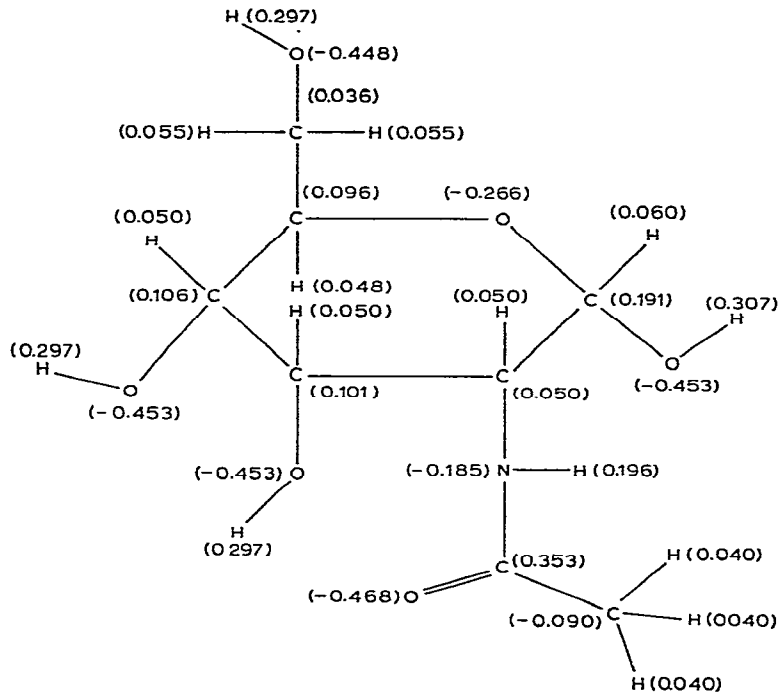

Fig. 1. Charge distribution in 2-acetamido-2-deoxyaldohexopyranoses.

atom, r_0 was taken as 3.22, 3.56, and 3.00 Å for the atom pairs N···O, N···C, and N···H, respectively. As in the other examples, the values of r_0 involving N, C, and H are chosen to be about 10% higher than the sum of the van der Waals radii of the interacting atoms.

In computing the entropy, the possible orientations for the acetamido group are assumed to be the same as those for an acetoxyl group[7]. The possible orientations of the OH and CH_2OH groups are the same as reported earlier[9], except that the anomeric OH group was assumed to adopt only one of the three staggered orientations if it is axially disposed and only two if it is equatorially disposed; Jeffrey *et al.*[11] have suggested, using methanediol as a model compound, that the O–H bond at the anomeric carbon atom favours an *anti* and *gauche* conformation for the β-anomer, and only *gauche* for the α-anomer in the $^4C_1$ (D) ring form. When this criterion is applied to the earlier data on free sugars, the value assigned for the anomeric effect of the –OH group increases from 0.4 to 0.55 kcal. mol^{-1}.

The ring atoms were fixed by using the standard pyranose-ring coordinates reported by Arnott[12]. The acetamido group was fixed by using the bond lengths and bond angles of a *trans*-planar, peptide unit[13–15]. The remaining atoms were fixed with the appropriate bond-lengths and bond-angles[7,8]. The hydroxyl groups, the hydroxymethyl group, and the acetamido group were fixed at minimum-energy positions by the iterative method explained earlier[7–10]. The overall minimum-energy

conformations of the amino sugars were studied by tilting the axially oriented groups according to the procedure described in earlier paper[8].

RESULTS AND DISCUSSION

The results of the energy calculations on 2-acetamido-2-deoxy-D-aldohexopyranoses are shown in Table I. The potential energies of the minimum-energy conformations are given in columns 2 and 3. As the anomeric effect was not taken into account in the present calculations, the free energies, corrected for the anomeric effect (0.55 kcal.mol^{-1}) of the OH group, are shown in columns 4 and 5 of Table I. The estimated percentages of α and β anomers, (determined by using the free energies shown in Table I) present in the equilibrium mixture, following the procedure described earlier[9], are shown in Table II. The agreement (Table II) observed between the percentage of α and β anomers present in an equilibrium mixture in solution for D-glucose, D-galactose, D-mannose, 2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-galactose, and 2-acetamido-2-deoxy-D-mannose (as calculated from the conformational free-energy values corrected for the anomeric effect) with those percentages determined from experimental studies, suggest that the anomeric effect is small (about 0.55 kcal.mol^{-1}) in all of these instances, and does not depend significantly on the nature and configuration of the group at the C-2 atom. This conclusion is contrary to the current views[16–18] that such a dependence does exist.

TABLE I

CALCULATED CONFORMATIONAL-ENERGY VALUES[a] FOR 2-ACETAMIDO-2-DEOXYALDOHEXOPYRANOSES (IN KCAL.MOL^{-1})

2-Acetamido-2-deoxy-D-hexopyranose	*Potential energy*		*Free energy (corrected for the anomeric effect)*		*Favoured conformation assigned from n.m.r.*
	$^4C_1$	$^1C_4$	$^4C_1$	$^1C_4$	
α-allo	0.29	1.16	0.63	1.88	
β-allo	−0.44	1.49	0.04	2.08	
α-altro	0.33	2.36	0.67	2.84	
β-altro	−0.57	2.69	−0.09	3.28	
α-galacto	−0.02	1.73	0.32	2.45	$^4C_1$
β-galacto	0.35	3.76	0.59	4.35	$^4C_1$
α-gluco	−0.57	1.26	−0.47	2.22	$^4C_1$
β-gluco	0.0	2.93	0.0	3.75	$^4C_1$
α-gulo	0.2	0.7	0.79	1.18	
β-gulo	−0.48	1.86	0.24	2.2	
α-ido	−0.41	1.71	0.18	1.95	
β-ido	−1.11	2.05	−0.39	2.39	
α-manno	−0.86	2.02	−0.76	2.98	$^4C_1$
β-manno	−0.9	3.22	−0.66	4.05	$^4C_1$
α-talo	−1.1	1.59	−0.76	2.31	
β-talo	−0.74	2.92	−0.26	3.51	

[a]The excess energy of a particular conformation in each set, over that of 2-acetamido-2-deoxy-β-D-glucose in the $^4C_1$(D) conformation in that set, is given.

TABLE II

CONFORMATIONAL EQUILIBRIA OF SOME ALDOHEXOSES AND THEIR 2-ACETAMIDO-2-DEOXY DERIVATIVES

Molecule	*Calculated*		*Experimental*[b] *(n.m.r.)*	
	$\alpha(^4C_1)$	$\beta(^4C_1)$	$\alpha(^4C_1)$	$\beta(^4C_1)$
D-Glucose	37	63	36(36)[a]	64(64)
D-Galactose	43	57	27(30)	73(70)
D-Mannose	61	39	67(69)	33(31)
2-Acetamido-2-deoxy-D-glucose	69	31	68(73)	32(27)
2-Acetamido-2-deoxy-D-galactose	61	39	65(64)	35(36)
2-Acetamido-2-deoxy-D-mannose	54	46	57(55)	43(45)

[a]Values in parentheses are obtained from optical rotation data. [b]Experimental values taken from Ref. 1.

Table I shows that, in those 2-acetamido-2-deoxy-D-aldohexopyranoses for which a single conformation is assigned from experimental studies, the calculated energy-differences between the $^4C_1$(D) and $^1C_4$(D) conformations are in agreement, being 2–4.7 kcal.mol^{-1}. It is also interesting that the presence of an acetamido group at C-2 affects the energy difference between the $^4C_1$(D) and $^1C_4$(D) conformations, as compared to the free sugars. Columns 4 and 5 of Table I show that the energy difference between the $^4C_1$(D) and $^1C_4$(D) conformations of 2-amino-2-deoxy-α-D-altro-, and -α and -β-D-ido-pyranoses increases significantly as compared to the free sugars, suggesting that the presence of the 2-acetamido group stabilizes the $^4C_1$(D) conformation. In contrast, the 2-acetamido group decreases the energy difference between the $^4C_1$(D) and $^1C_4$(D) conformations of 2-amino-2-deoxy-α-D-allo- and α-D-gulo-pyranoses, indicating that the pyranose ring is slightly more flexible as compared with the corresponding free sugars.

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