Conformations of α- and β-D-Glucopyranose from an Empirical Force Field

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Conformations of the pyranose ring are studied, using convergent energy minimisation in a simple force field. Parameters for the force field are adapted from similar studies on different classes of substances.

The global minima of the α- and β-anomers of D-glucopyranose are found; the energy difference is 0.26 kcal mol^{-1} and the anomer equilibrium at 300 K is $\alpha:\beta = 0.39:0.61$, in agreement with experimental results.**

The calculated ring geometry is in good agreement with results from crystal structure determinations, but side chain orientations are not well reproduced due to neglect of the crystal forces. The short anomeric bond is not represented by the present force field.

The present work is part of an endeavour to investigate the possibility of using energy minimisation in an empirical force field, with parameters adapted from several sources, to determine equilibrium conformations of molecules too large to handle by *ab initio* or even semi-empirical methods. Similar work using the same methods and programmes has recently been reported for tris(diamine) chelates of transition metal ions.[1] This research programme is a prerequisite to the development of a consistent force field (CFF)[2] for wide classes of compounds.

Two simple sugars were chosen for four main reasons. Firstly, reliable experimental data are available for comparison with calculated structures and, in subsequent work, vibrational frequencies. Secondly, the number of different atoms, and therefore of the necessary energy parameters, is limited. Thirdly, the adaptation

of a satisfactory provisional force field for monosaccharides would open possibilities of calculating conformations and other properties of substituted saccharides and oligosaccharides, which are not readily accessible with experimental methods. Fourthly, no theoretical conformational analysis of sugars is yet available, in which all degrees of freedom are allowed to relax.

The favoured conformations of D-glucopyranoses in aqueous solution and in crystal phases have been determined from NMR studies [3,4] and from diffraction analysis.[5—9] Angyal [10,11] has derived interaction energies for the chair conformations of aldopyranoses from experimental data obtained from the equilibria of cyclitols and sugars. Rao *et al.*[12] have calculated the potential energies of only non-bonded interactions for the two chair and six boat conformers of α-D-glucopyranose. For the 4C1 and 1C4 conformers those calculations were further developed to include non-bonded, electrostatic and angle bending terms.[13]
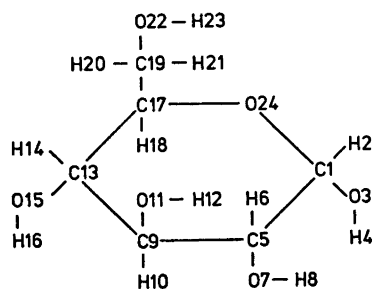

Fig. 1. Constitution and atom numbering of α-D-glucopyranose.

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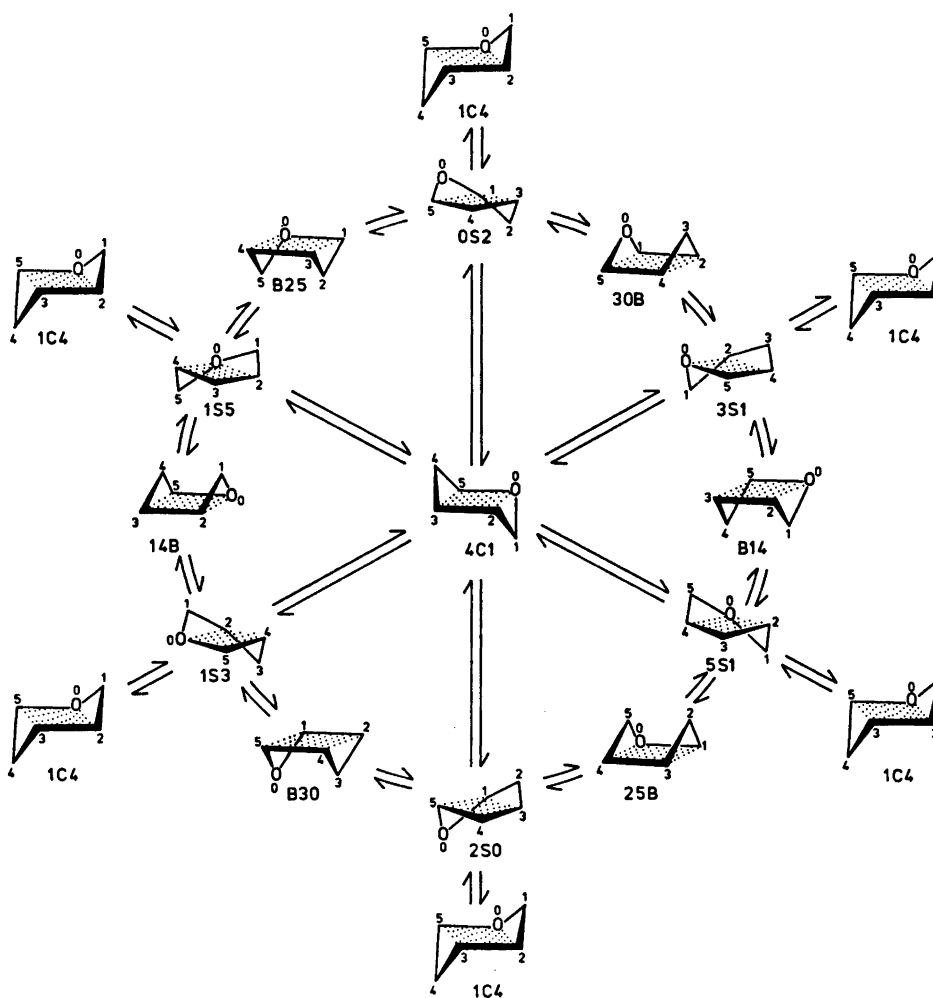** 1 kcal = 4.184 kJ.

Fig. 2. Conformers of the pyranose ring.[15]

The computational methods and programmes used here were developed from the CFF system of Lifson and Warshel [2] and will be documented elsewhere.[14]

CALCULATIONS

Nomenclature of ring conformers. Our calculations deal with the six-membered ring system of α- and β-D-glucose. The constitution, with atom numbering for later reference, is shown in Fig. 1. The various stable and metastable basic geometries of the pyranose ring will be termed C for chair, B for boat, and S for skew-

boat. Our nomenclature of *ring* conformations follows Stoddart,[15] whose proposal we consider more logical than the traditional one of Reeves.[16] The ring atoms are numbered $0 - 5$, starting on the oxygen and proceeding clockwise to end on the carbon carrying the primary alcohol group. A reference plane is defined by four ring atoms. If alternative choices of such four atoms are possible, as in certain C and S conformers, the carbon of lowest number is left out of the plane. Ring atoms lying above and below the plane are indicated before and behind the basic geometry symbol. These rules provide an easily memorised shorthand for the two C, six B,

and six S ring conformers. For the overall absolute configuration D, the unfolded sphere representation in Fig. 2 shows how the pyranose ring may attain all fourteen ring conformations through pseudorotation.

Initial conformations. In cyclohexane, C and S conformers would be equilibrium conformations, *i.e.* minima on the potential energy surface, and B conformers would be saddle points. (It is meaningless to talk about maxima on a potential energy surface covering *all* degrees of freedom.)

In our calculations on α- and β-D-glucopyranose, we did not *a priori* exclude the possibility that a local minimum conformation might be found close to a B conformer. Therefore we performed energy minimisation of all fourteen ring conformers. The various choices of side group orientations are described later.

Cartesian atomic coordinates were measured on scale models and used directly for input.

Potential energy functions. A reasonable force field should reproduce a maximum of observables with a minimum of parameters. We selected ours through an initial series of calculations on α-D-glucopyranose, composing the trial force fields from the following energy terms.[a]

Bond deformation:

$$E_b = \sum_{\text{bonds}} \tfrac{1}{2}K_b(b - b_0)^2 \qquad \text{I}$$

Valence angle deformation:

$$E_\theta = \sum_{\text{angles}} \tfrac{1}{2}K_\theta(\theta - \theta_0)^2 \qquad \text{II}$$

$$E_{UB} = \sum_{\text{angles}} \{\tfrac{1}{2}F(d - d_0)^2 + F'(d - d_0)\} \qquad \text{III}$$

Torsional deformation:

$$E_\phi = \sum_{\text{torsions}} \tfrac{1}{2}K_\phi(1 + \cos 3\phi) \qquad \text{IV}$$

Non-bonded interactions:

$$E_{nb} = \sum_{i<j} \{A_{ij}\exp(-B_{ij}r_{ij}) - C_{ij}/r_{ij}^6\} \qquad \text{V}$$

$$E_{nb} = \sum_{i<j} \varepsilon_{ij}^* \left[\left(\frac{r_{ij}^*}{r_{ij}}\right)^{12} - 2\left(\frac{r_{ij}^*}{r_{ij}}\right)^6 \right] \qquad \text{VI}$$

$$E_{el} = \sum_{i<j} q_i q_j/r_{ij} \qquad \text{VII}$$

In our first trial force field, FF1, we used terms I, II, IV, and V, with 46 parameters; in FF2 I, II, III, IV, VI, and VII, with 61 param-

eters; and in our final choice, FF3, I, II, IV, and V, with 46 parameters.

Parameters. We required parameters for interactions between atoms C, O, and H. A ready-made set for this purpose is not found in the literature, so in addition to the assumptions implicit in the choice of energy functions, we had to make assumptions as to numerical values of parameters.

For FF1 we selected parameters from optimised (CFF) [17,19,22] and non-optimised [18,20,21,23] force fields. As the results were not satisfactory we changed three key parameters, b_0 for $C-C$, $C-O$, and $O-H$. The results (see below) were still not sufficiently good and we then used the more complicated FF2, with parameters optimised on lactams. [17,19,24] For our alcohol- and ether-type O we used parameters optimised for N where possible, and otherwise parameters optimised for C. The results were rather disappointing, wherefore we resorted to the simpler FF3, using parameters developed without optimisation for coordination compounds of amines and amino acids. [25] Parameters for O were selected as above. Also here we changed the three bond energy parameters mentioned above. Parameter values for the three force fields are shown in Table 1.

Selection of force field. Tests of force fields were carried out through comparison of calculated conformations of α-D-glucopyranose with crystal structure data obtained by Brown and Levy.[6] Neutron diffraction data are well suited for this purpose, because they allow for determination of H atoms. Our test calculations were made on the same ring conformer as that found in the crystal, the $4C1$.

Our calculations are, with our present programmes, limited to molecules in a hypothetical gaseous state, and thus do not allow for crystal forces. This shortcoming is serious only for exocyclic torsional angles, as will be shown below.

In Table 2 we show deviations for the anomeric bond, mean deviations and mean square root deviations for bonds and valence angles, and all absolute deviations and mean square root deviations in endocyclic, hybrid, and exocyclic torsional angles. It is clearly seen from Table 2 that there is no reason to prefer the 61-parameter FF2 to the 46-parameter FF1 and FF3. It is also seen that, apart from the

Table 1. Energy function parameters. Units are chosen to give energy in kcal mol⁻¹, with distances in Å. All θ_0 were set to 1.911 rad. Values marked with an asterisk are those changed from original ones to give better fits; the final values are shown. F' values marked □ were set to $F'' = -0.1\,F d_0$. For torsional terms, X and Y can be C, O, and H.

Bond stretching (K_b)

Type	FF1 K_b	FF1 b_0	FF1 Ref.	FF2 K_b	FF2 b_0	FF2 Ref.	FF3 K_b	FF3 b_0	FF3 Ref.
C–C	224	1.52*	17	224	1.46	17	720	1.52*	25
C–O	324	1.42*	18	522	1.46	18	863	1.42*	25
C–H	574	1.10	17	574	1.10	17	720	1.09	25
O–H	810	0.97*	19	810	0.98	19	806	0.97*	25

Angle bending (K_θ)

Type	FF1 K_θ	FF1 Ref.	FF2 K_θ	FF2 F	FF2 F'	FF2 d_0	FF2 Ref.	FF3 K_θ	FF3 Ref.
C–C–C	43.2	17	43.2	75.0	−1.608	2.50	24	143.9	25
C–C–O	58.0	20	42.0	101.0	−24.75 □	2.45	24	143.9	25
C–C–H	54.0	17	54.0	86.4	−0.699	2.20	24	93.5	25
C–O–C	80.0	21	43.2	75.0	−1.608 □	2.50	24	143.9	25
C–O–H	58.0	22	62.8	52.0	−9.36 □	1.80	24	80.6	25
O–C–O	50.0	20	43.2	75.0	−1.608	2.50	24	143.9	25
O–C–H	40.0	20	60.2	82.0	−15.58 □	1.90	24	93.5	25
H–C–H	76.4	17	76.4	5.58	−0.099	1.80	24	74.8	25

Torsion (K_ϕ)

Type	FF1 K_ϕ	FF1 Ref.	FF2 K_ϕ	FF2 Ref.	FF3 K_ϕ	FF3 Ref.
X–C–C–Y	1.25*	22	2.82	22	2.4	25
X–O–C–Y	2.33	22	3.0	22	1.54	25

Non-bonded ($A \times 10^{-4}$, B, C)

Type	FF1 $A\times10^{-4}$	FF1 B	FF1 C	FF1 Ref.	FF3 $A\times10^{-4}$	FF3 B	FF3 C	FF3 Ref.
C---C	92.4	4.6	599.9	23	23.70	4.32	297.8	25
C---O	43.3	4.6	461.6	23	21.21	4.44	244.0	25
C---H	7.79	4.6	165.8	23	3.14	4.20	121.1	25
O---O	21.7	4.6	368.9	23	18.64	4.55	200.0	25
O---H	3.83	4.6	124.1	23	2.81	4.32	99.2	25
H---H	0.829	4.6	46.8	23	0.66	4.08	49.2	25

Non-bonded / charge (FF2: $\varepsilon^*\times10^3$, r^*, q)

Type	$\varepsilon^*\times10^3$	r^*	q	Ref.
C--	19.6	4.22	−0.28	24
O--	193.6	3.60	−0.30	24
H--	4.489	2.94	0.14	24

Table 2. Selection of energy function parameters through deviations of calculated from measured [6] internal coordinates. For bonds are shown: Deviations for the anomeric bond, mean deviations $\sum(b_{calc}-b_{meas})/24$ and mean square root deviations $(\sum(b_{calc}-b_{meas})^2/24)^{\frac{1}{2}}$; for bond angles: mean deviations $\sum(\theta_{calc}-\theta_{meas})/42$ and mean square root deviations $(\sum(\theta_{calc}-\theta_{meas})^2/42)^{\frac{1}{2}}$; for torsions: absolute deviations $|\phi_{calc}-\phi_{meas}|$ and mean square root deviations.

	FF1	FF2	FF3
Bond lengths, Å			
C1−O3	0.036	0.097	0.037
Mean dev.	0.0062	0.0359	0.0026
Mean sq. rt. dev.	0.0108	0.0476	0.0107
Valence angles, °			
Mean dev.	0.1	−0.6	0.1
Mean sq. rt. dev.	1.4	4.4	1.5
Endocyclic torsions, °			
O24−C1−C5−C9	3.1	4.4	3.5
C1−C5−C9−C13	4.9	11.7	4.9
C5−C9−C13−C17	1.8	9.0	0.0
C9−C13−C17−O24	1.5	0.1	0.9
C13−C17−O24−C1	2.0	8.6	1.8
C17−O24−C1−C5	0.5	7.5	0.4
Mean sq. rt. dev.	2.7	7.8	2.6
Hybrid torsions, °			
O24−C1−C5−O7	0.3	9.6	0.4
C1−C5−C9−O11	4.7	20.8	4.4
C5−C9−C13−O15	0.4	17.7	0.5
C9−C13−C17−C19	0.5	7.9	0.3
C17−O24−C1−O3	1.7	19.2	1.4
Mean sq. rt. dev.	2.3	15.9	2.1
Exocyclic torsions, °			
H4−O3−C1−C5	17.8	23.3	16.2
H8−O7−C5−C1	39.1	38.7	38.3
H12−O11−C9−C5	11.7	15.6	9.8
H16−O15−C13−C9	40.9	40.1	31.5
O22−C19−C17−C13	10.9	5.8	12.5
H23−O22−C19−C17	36.0	34.6	35.8
Mean sq. rt. dev.	29.1	29.2	26.6

anomeric centre at C1, the structure is well represented by FF1 and FF3. A choice between them can be made only from mean deviations of bonds, and we should therefore look for other types of observables. Different types of experiments [3,4,26] show that β-D-glucopyranose is more stable than the α configuration. We therefore minimised also a conformation of the 4C1 ring conformer of β-D-glucopyranose in FF1 and FF3. The result was $E_{\alpha}-E_{\beta}=-0.06$ kcal mol^{-1} in FF1 and $E_{\alpha}-E_{\beta}=0.88$ kcal mol^{-1} in FF3, both cases referring to minimisation of the conformations found in crystals, [6,9] and not

to the global minima described later. It may also be mentioned that preliminary calculations showed that vibrational frequencies are better reproduced by FF3 than by FF1.

Local and global minima of the glucopyranoses. We therefore used FF3 for a detailed analysis of the fourteen conformers of α-D-glucopyranose, and for determination of the global minima of the α and β configurations. Input conformations were measured on models as described above, and minimisation was considered finished when the norm of the energy gradient became less than 10^{-6} kcal mol^{-1} Å^{-1}.

Table 3. Endocyclic torsional angles in degrees and equilibrium energies in kcal mol⁻¹ of fourteen conformers of α-D-glucopyranose.

Initial conformer	4C1 init.	4C1 fin.	1C4 init.	1C4 fin.	0S2 init.	0S2 fin.	30B init.	0S2 fin.	3S1 init.	3S1 fin.	B14 init.	5S1 fin.	5S1 init.	5S1 fin.
O24—C—C5—C9:	−63.4	−57.8	36.1	58.0	27.6	27.2	−5.4	25.2	−31.1	−24.9	−62.0	−62.3	−55.0	−62.1
C1—C5—C9—C13:	51.0	55.7	−42.2	−53.5	−74.5	−61.7	−65.5	−63.5	−36.5	−35.1	8.0	28.1	9.3	26.4
C5—C9—C13—C17	−54.7	−55.1	48.6	50.3	39.4	32.1	66.8	36.9	75.1	58.9	48.1	27.3	66.0	28.4
C9—C13—C17—O24	62.7	56.6	−55.4	−50.2	28.7	29.6	5.2	25.1	−35.4	−20.1	−63.6	−57.0	−64.6	−55.6
C13—C17—O24—C1	−69.6	−60.1	58.2	55.8	−74.0	−68.6	−61.7	−67.6	−34.5	−43.6	14.2	24.3	32.8	21.2
C17—O24—C1—C5	74.8	60.7	−52.5	−60.2	37.5	37.2	59.8	39.4	76.5	68.7	51.8	34.1	33.7	36.4

Final conformer	4C1	1C4	0S2	0S2	3S1	5S1	5S1
E_{total}	1.982	3.846	7.582	8.018	9.271	10.247	9.927
E_b	0.345	0.427	0.471	0.497	0.563	0.543	0.516
E_θ	0.884	2.097	1.233	1.411	1.502	3.186	3.051
E_ϕ	0.168	0.709	3.866	3.908	4.839	4.767	4.568
E_{nb}	0.585	0.613	2.012	2.202	2.367	1.751	1.792

Initial conformer	25B init.	2S0 fin.	2S0 init.	2S0 fin.	B30 init.	1S3 fin.	1S3 init.	1S3 fin.	14B init.	1S3 fin.	1S5 init.	1S5 fin.	B25 init.	1S5 fin.
O24—C1—C5—C9	−66.5	−19.0	−32.1	−20.8	7.7	37.4	29.9	37.7	49.0	34.3	54.5	64.4	55.3	63.8
C1—C5—C9—C13	69.6	63.2	73.8	63.3	45.7	23.9	36.8	23.6	7.3	27.9	−23.7	−26.7	−56.7	−25.3
C5—C9—C13—C17	−22.3	−46.4	−38.5	−44.6	−57.2	−61.8	−75.1	−61.7	−74.2	−62.7	−38.3	−31.7	−3.8	−33.2
C9—C13—C17—O24	−32.1	−12.3	−37.9	−13.9	5.9	37.3	25.7	37.3	67.2	33.2	86.4	62.9	66.2	63.4
C13—C17—O24—C1	44.1	61.0	72.0	61.0	58.5	25.8	44.1	25.7	1.6	31.0	−53.1	−27.0	−70.3	−26.7
C17—O24—C1—C5	4.6	−43.4	−37.8	−41.7	−73.0	−66.0	−82.0	−66.2	−57.3	−68.1	−21.2	−35.1	6.4	−35.5

Final conformer	2S0	2S0	1S3	1S3	1S3	1S5	1S5
E_{total}	10.365	9.708	7.923	7.870	7.509	8.095	8.608
E_b	0.527	0.555	0.506	0.489	0.462	0.483	0.468
E_θ	2.139	2.310	1.920	1.749	1.339	1.467	1.615
E_ϕ	5.130	4.898	3.667	3.696	3.669	4.078	4.281
E_{nb}	2.569	1.945	1.830	1.936	2.039	2.067	2.244

Table 4. Determination of the exocyclic torsions of α-D-glucopyranose, tO22, tH16, tH12 and tH8, tH4, tH23, in degrees.

tH4	tH8	tH12	tH16	tO22	tH23	E_{total}
179.3	−62.5	175.7	60.4	179.1	179.9	1.637
179.3	−62.5	175.6	60.6	67.3	−179.6	1.983
179.2	−62.5	175.8	60.4	−60.8	179.8	1.739
179.3	−62.6	64.4	−64.5	179.0	179.9	1.663
179.2	−62.7	64.5	−64.9	67.1	−179.6	2.042
179.2	−62.7	64.4	−64.5	−60.9	179.8	1.762
179.3	−62.6	64.3	−166.1	−177.1	179.7	2.223
179.3	−62.6	64.2	60.4	179.1	179.9	1.649
179.3	−62.6	64.4	−64.5	179.0	179.9	1.663
179.3	−62.4	−60.2	60.3	179.1	179.9	1.694
179.3	−62.5	−60.2	−64.6	178.9	179.9	1.690
179.3	−62.5	175.7	60.4	179.1	179.9	1.637
179.3	−175.9	175.5	60.4	179.1	179.9	1.696
179.2	−169.5	70.8	60.4	179.1	179.9	2.117
179.3	−175.9	−60.1	60.3	179.1	179.9	1.737
179.3	62.2	175.8	60.4	179.0	179.9	1.766
179.2	62.2	64.3	60.4	179.0	179.9	1.773
179.3	62.2	−60.0	60.4	179.0	179.9	1.828
179.3	−62.5	175.7	60.4	179.1	179.9	1.637
179.3	−62.6	64.2	60.4	179.1	179.9	1.649
179.3	−62.4	−60.2	60.3	179.1	179.9	1.694
63.9	−62.8	175.8	60.4	179.0	179.9	1.811
63.9	−175.9	175.5	60.4	179.0	179.9	1.887
179.3	−62.5	175.7	60.4	179.1	179.9	1.637
179.3	−62.5	175.7	60.4	177.0	64.0	1.688
179.4	−62.5	175.8	60.4	−179.6	−62.4	1.626

RESULTS

Bond lengths and valence angles were found to be independent of ring conformation. Therefore it will be sufficient to list endocyclic torsions for description of ring conformations. Results for the fourteen *B*, *C*, and *S* conformers are shown in Table 3. For each conformer two sets of torsional angles are given. The first set designated "init.", applies to values calculated from the initial conformation specified by cartesian coordinates measured on models; the second set, "fin.", applies to the final conformation.

It is clearly seen that *C* and *S* conformers correspond to local minimum energy conformations, and that each *B* conformer during minimisation changes to one of the two *S* conformers which are its nearest neighbours on the topological map (Fig. 2). The differences between minimum conformations of the same

ring conformer, *e. g.* 1*S*3, are due to different exocyclic conformations.

Global minimum of α-D-glucopyranose. Table 3 shows that all *S* conformers have much higher energy than *C* conformers, and that 4*C*1 has the lowest energy of all. This is in accordance with crystal structure [5-7] and NMR [3,4] data. In the following search for the global minimum, therefore, the ring conformer 4*C*1 was retained while the exocyclic torsions were changed from one input to the next. We still allow all 72 degrees of freedom to relax.

A shorthand for exocyclic torsions is introduced: H4−O3−C1−C5, H8−O7−C5−C1, H12−O11−C9−C5, H16−O15−C13−C9, O22−C19−C17−C13, and H23−O22−C19−C17 will be named tH4, tH8, tH12, tH16, tO22, and tH23, respectively. A torsional angle A−B−C−D is defined through a Newman projection:

Table 5. Determination of the exocyclic torsions of β-D-glucopyranose, in degrees.

tH4	tH8	tH12	tH16	tO22	tH23	E_{total}
− 179.2	− 64.4	175.8	60.5	− 179.5	− 62.4	1.385
62.3	− 64.4	175.7	60.5	− 179.5	− 62.5	1.407
− 179.3	− 175.8	175.6	60.5	− 179.5	− 62.4	1.364
62.3	− 175.8	175.5	60.5	− 179.5	− 62.5	1.401
− 64.3	− 175.6	175.5	60.5	− 179.5	− 62.5	1.523
− 179.3	− 175.8	175.5	60.5	179.2	179.9	1.365
− 179.3	− 175.8	175.5	60.5	177.3	64.1	1.414
− 179.3	− 175.8	175.6	60.5	− 179.5	− 62.4	1.364
− 179.2	− 64.6	64.2	− 167.3	− 55.2	− 62.7	1.922
− 179.2	− 64.6	64.3	− 64.5	− 60.7	179.8	1.494

ϕ is the angle through which A − B must be rotated around B − C to cover C − D when looking from B towards C; the sign is positive if the sense of rotation is positive, *i.e.* anticlockwise.

With the assumed threefold potential around a C − O or C − C bond, any ring conformer will give rise to $3^6 = 729$ distinct conformations. It would be futile to minimise all, and the less favourable conformations must be excluded in a stepwise way.

A series of test calculations starting with exocyclic torsions close to the values found in the crystal phase [6] and changing tH4 and tH8 one after the other by ± 60 ° gave a series of local minima.

These tests suggested that it would be acceptable to consider only first-neighbour exocyclic groups when determining the most favourable value of a specific exocyclic torsion. For the following twenty-one calculations a provisional value for tH4 of 180° was used.

O22 − C19 − C17 − C13. tO22 is primarily influenced by tH16. For tH16 = − 60° a sterically unfavourable situation occurs for tH12 = 180°. This led us to choose the first set of six runs shown in Table 4. It is seen that tO22 = 180° is most favourable.

H16 − O15 − C13 − C9. tH8 was fixed at − 60° to influence tH12 as little as possible. The second set of six runs in Table 4 shows that tH16 = 60° is the best choice.

H8 − O7 − C5 − C1 and *H12 − O11 − C9 − C5.* For tH8 and tH12 all nine possibilities were investigated, as shown in the third set of Table 4. tH8 = − 60° and tH12 = 180° were selected.

H4 − O3 − C1 − C5. tH4 = − 60° is sterically unfavourable, but the possibility of tH4 = 60° can be excluded only on inspection of the two next runs. Therefore tH4 = 180° is still preferred.

H23 − O22 − C19 − C17. The three last runs lead to the conclusion that tH23 = − 60° in the global minimum of α-D-glucopyranose.
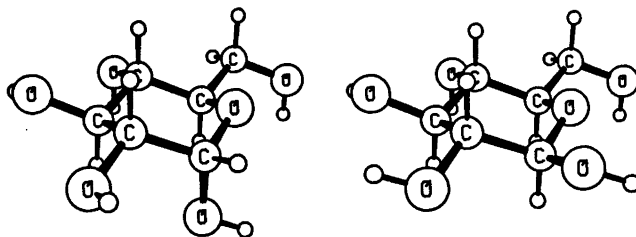

Fig. 3. Global minima of glucopyranoses drawn by ORTEP. Left: α-D-glucopyranose; right: β-D-glucopyranose.

Table 6. Crystal structure data and calculated global minima conformations. For bonds and bond angles are shown: deviations, mean deviations and mean square root deviations; for torsions: absolute deviations and mean square root deviations. Experimental standard deviations are given in parentheses.

	α-D-Glucopyranose Neutrondiff.[6] Calc.		Calc.—meas.	β-D-Glucopyranose X-ray diff.[9]	Calc.	Calc—meas.
Bond lengths, Å						
C1—O3	1.389(2)	1.425	0.036	1.384(4)	1.423	0.039
C1—H2	1.095(4)	1.091	−0.004		1.092	
C1—C5	1.532(1)	1.530	−0.002	1.526(5)	1.528	0.002
O3—H4	0.968(5)	0.971	0.003		0.971	
C5—O7	1.415(2)	1.425	0.010	1.429(4)	1.425	−0.004
C5—H6	1.091(4)	1.092	0.001		1.092	
C5—C9	1.528(2)	1.527	−0.001	1.519(4)	1.529	0.010
O7—H8	0.964(5)	0.971	0.007		0.971	
C9—O11	1.416(2)	1.425	0.009	1.433(5)	1.425	−0.008
C9—H10	1.107(4)	1.092	−0.015		1.092	
C9—C13	1.518(2)	1.531	0.013	1.512(4)	1.531	0.019
O11—H12	0.973(4)	0.971	−0.002		0.971	
C13—O15	1.425(2)	1.426	0.001	1.419(4)	1.426	0.007
C13—H14	1.102(3)	1.091	−0.011		1.091	
C13—C17	1.529(1)	1.533	0.004	1.529(5)	1.532	0.003
O15—H16	0.971(4)	0.971	0.000		0.971	
C17—C19	1.510(2)	1.529	0.019	1.513(5)	1.529	0.016
C17—H18	1.104(4)	1.092	−0.012		1.092	
C17—O24	1.427(2)	1.430	0.003	1.437(3)	1.428	−0.009
C19—O22	1.413(2)	1.424	0.011	1.419(5)	1.424	0.005
C19—H20	1.095(4)	1.091	−0.004		1.091	
C19—H21	1.096(5)	1.091	−0.005		1.091	
O22—H23	0.964(5)	0.971	0.007		0.971	
C1—O24	1.425(2)	1.429	0.004	1.433(3)	1.428	−0.005
Mean dev.			0.003			0.006
Mean sq. rt. dev.			0.011			0.014
Bond angles, °						
O3—C1—H2	112.0(0.2)	108.7	−3.3		108.8	
O3—C1—C5	109.4(0.1)	110.5	1.1	108.1(0.3)	109.3	1.2
C1—O3—H4	107.8(0.3)	110.7	2.9		110.7	
O3—C1—O24	111.6(0.1)	110.6	−1.0	107.0(0.3)	109.0	2.0
H2—C1—C5	108.9(0.2)	108.8	−0.1		109.6	
H2—C1—O24	104.2(0.2)	108.0	3.2		109.9	
C1—C5—O7	111.0(0.1)	110.2	−0.8	108.5(0.3)	109.1	0.6
C1—C5—H6	107.0(0.2)	109.2	2.2		109.2	
C1—C5—C9	111.0(0.1)	110.0	−1.0	112.1(0.3)	109.6	−2.5
C5—C1—O24	110.1(0.1)	110.2	0.1	108.5(0.2)	110.1	1.6
O7—C5—H6	107.4(0.2)	109.0	1.6		109.3	
O7—C5—C9	112.1(0.1)	109.4	−2.7	109.8(0.3)	110.1	0.3
C5—O7—H8	112.2(0.2)	111.0	−1.2		111.2	
H6—C5—C9	108.1(0.2)	109.1	1.0		109.7	
C5—C9—O11	108.1(0.1)	109.0	0.9	108.7(0.3)	109.2	0.5
C5—C9—H10	109.7(0.2)	109.4	−0.3		109.3	
C5—C9—C13	109.8(0.1)	109.1	−0.7	110.5(0.3)	109.3	−1.2
O11—C9—H10	109.8(0.2)	109.3	−0.5		109.3	
O11—C9—C13	110.6(0.1)	110.1	−0.5	109.1(0.3)	109.9	0.8
C9—O11—H12	112.1(0.2)	111.2	−0.9		111.2	
H10—C9—C13	108.8(0.2)	110.0	1.2		109.9	
C9—C13—O15	108.3(0.1)	110.2	1.9	111.1(0.3)	110.2	−0.9

Table 6. Continued.

C9—C13—H14	108.3(0.2)	109.0	0.7		108.9	
C9—C13—C17	111.2(0.1)	109.8	−1.4	109.8(0.2)	109.8	0.0
O15—C13—H14	109.8(0.2)	108.3	−1.5		108.3	
O15—C13—C17	110.9(0.1)	110.4	−0.5	108.2(0.2)	110.4	2.2
C13—O15—H16	107.0(0.3)	111.5	4.5		111.5	
H14—C13—C17	108.3(0.2)	109.2	0.9		109.2	
C13—C17—C19	111.6(0.1)	110.4	−1.2	114.9(0.2)	110.5	−4.4
C13—C17—H18	109.8(0.2)	109.4	−0.4		109.5	
C13—C17—O24	108.7(0.1)	110.2	1.5	107.6(0.2)	109.8	2.2
C19—C17—H18	109.0(0.2)	108.5	−0.5		108.7	
C19—C17—O24	108.1(0.1)	108.8	0.7	107.1(0.3)	108.9	1.8
C17—C19—O22	110.4(0.1)	110.5	0.1	111.9(0.3)	110.5	−1.4
C17—C19—H20	109.0(0.3)	109.6	0.6		109.6	
C17—C19—H21	109.0(0.3)	110.1	1.1		110.1	
H18—C17—O24	109.6(0.2)	109.5	−0.1		109.4	
C17—O24—C1	113.8(0.1)	113.4	−0.4	112.7(0.2)	112.6	−0.1
O22—C19—H20	110.1(0.2)	108.7	−1.4		108.7	
O22—C19—H21	110.5(0.3)	109.2	−1.3		109.2	
C19—O22—H23	107.7(0.3)	111.0	3.3		111.0	
H20—C19—H21	107.9(0.4)	108.7	0.8		108.7	
Mean dev.			0.2			0.2
Mean sq. rt. dev.			1.6			1.8

			$\|\phi_{calc}-\phi_{meas}\|$			$\|\phi_{calc}-\phi_{meas}\|$
Endocyclic torsions,°						
O24—C1—C5—C9	−54.1(0.2)	−57.0	2.9	−53.7(0.3)	−57.8	4.1
C1—C5—C9—C13	51.2(0.1)	55.4	4.2	50.8(0.4)	54.8	4.0
C5—C9—C13—C17	−53.2(0.1)	−55.4	2.2	−53.4(0.4)	−54.8	1.4
C9—C13—C17—O24	57.5(0.2)	57.0	0.5	59.8(0.3)	57.4	2.4
C13—C17—O24—C1	−62.2(0.2)	−60.3	1.9	−66.3(0.3)	−61.8	4.5
C17—O24—C1—C5	61.0(0.2)	60.3	0.7	62.8(0.3)	62.1	0.7
Mean sq. rt. dev.			2.4			3.2
Hybrid torsions,°						
O24—C1—C5—O7	−179.6(0.2)	−177.7	1.9	−175.0(0.2)	−178.2	3.2
C1—C5—C9—O11	172.0(0.1)	175.6	3.6	170.5(0.3)	175.0	4.5
C5—C9—C13—O15	−175.3(0.1)	−177.1	1.8	−173.1(0.3)	−176.6	3.5
C9—C13—C17—C19	176.6(0.1)	177.2	0.6	179.0(0.3)	177.5	1.5
C17—O24—C1—O3	−60.6(0.1)	−62.2	1.6	179.4(0.2)	−177.9	2.7
Mean sq. rt. dev.			2.1			3.2
Exocyclic torsions,°						
H4—O3—C1—C5	163.1(0.3)	179.4	16.3		−179.3	
H8—O7—C5—C1	100.4(0.2)	−62.5	162.9		−175.8	
H12—O11—C9—C5	165.9(0.3)	175.8	9.9		175.6	
H16—O15—C13—C9	−134.2(0.2)	60.4	165.4		60.5	
O22—C19—C17—C13	170.3(0.1)	−179.6	10.1	59.1(0.4)	−179.5	121.4
H23—O22—C19—C17	143.9(0.2)	−62.4	153.7		−62.4	
Mean sq. rt. dev.			114.0			

Global minimum of β-D-glucose. β-D-Gluco-pyranose differs from the α form only in the configuration around the anomeric centre at C1. We determined the global minimum of the 4C1 conformer of the β anomer by variation of tH4 for two values of tH8, and of tH23. This led to the first eight of ten runs shown in Table 5. The first run corresponds to the global minimum of the α-anomer, except of course for the anomeric centre. For the two last runs input coordinates were taken from crystal structure data.[8,9]

The internal coordinates of the global minima are given in Table 6. Computer-produced model drawings are shown in Fig. 3. Cartesian coordinates may be obtained from the authors.

DISCUSSION

Comparison with crystal structure analyses. Table 6 shows a comparison of our results with data from one crystal structure determination for each anomer. Only one, the neutron diffraction study of the α-anomer by Brown and Levy,[6] gives reliable values for hydrogen positions and internal coordinates dependent thereon. This study was carried through to an R value of 0.060. The X-ray diffraction structure of the 1:1 complex of α-D-glucopyranose with urea [7] was refined to $R = 0.041$. The older X-ray diffraction study of the β-anomer [8] is not extremely accurate, $R \sim 0.25$; the more recent one [9] was refined to $R = 0.043$. For both anomers, we thus have good experimental structures for comparison.

We transformed all fractional coordinates to cartesians, from which we calculated the internal coordinates including the standard deviations. These operations were done with a programme supplied by Professor John A. Schellman, University of Oregon, and modified by Dr. Svetozar R. Niketić, University of Beograd.

For bond lengths and valence angles our calculated values are in good agreement with the experimental values, with the length of the anomeric bond C1 − O3 as a notable exception.

Endocyclic and hybrid torsional angles are well reproduced, exocyclic not. This is understandable since the orientations of the sidegroups depend very much on crystal forces, which are not taken into account in our method.

The anomeric effect. An abnormally short C1 − O3 bond was observed in the earliest structure determinations of pyranose.[5] Berman et al. showed in a compilation [27] that this anomeric property is common to the whole class of substances. The term "anomeric effect" is due to Lemieux [28] who defined it as an effect favouring axial orientation for certain substituents on the anomeric carbon atom.

Ab initio calculations on model substances [29] suggest that the relatively electronegative O24 has attracted electronic charge from C1, depopulating a C1 2*p* orbital, and thus forced a measure of double bond character upon the C1 − O3 bond.

In the context of our calculations, the anomeric effect does not show up at all. This means that our force field, in order to reproduce it, would have to supply different energy function parameters for at least the C1 − O3 bond. Although this would be a minor task with our programme, we have refrained from it, because we intend to proceed to more complex molecules involving glycosidic linkages. It is known [15] that glycosidic substituents modify the anomeric effect markedly, and we prefer to handle the inconsistency in a larger context.

Distribution of potential energy. The contributions to the energy from bond and angle deformations, and torsional and non-bonded interactions, vary from one conformer to another in an unsystematic manner, even within the same basic ring conformer. This is borne out by data in Table 3. The explanation is that any strain introduced by a local change of geometry will, during relaxation, be distributed on all energy terms. This emphasizes the necessity of allowing for relaxation of all degrees of freedom. This is not always observed in similar work, where bonds and often even angles are kept fixed.

The manifold of minima. With any C and S ring conformer there is associated a multitude of local energy minimum conformations, corresponding to different values of exocyclic torsional angles. They lie close on the energy scale, characteristically less than 1 kcal mol⁻¹ apart; for 4C1, *e.g.*, the basic ring conformer studied in greatest detail, the largest energy difference between local minima encountered was 0.60 kcal mol⁻¹. At equilibrium, therefore, the local minima would be almost equally populated.

The saddle points between them would be of the order of the torsional potential height, 1.5 or 2.4 kcal mol^{-1} (Table 1) and, at ordinary temperature, the equilibrium would be quickly established. Therefore each basic ring conformer represents almost a continuum of conformations, and the same statistical weight can thus be assigned to each basic ring conformer.

Equilibrium distributions. The S conformers of α-D-glucopyranose have 6 − 9 kcal mol^{-1} higher energies than the global minimum (Tables 3 and 4), and will therefore not be populated at ordinary temperature. The energy difference between the two C conformers, $1C4$ and $4C1$, will be of the order of 2 kcal mol^{-1}. The precise value cannot be given, as the most favourable exocyclic torsions were not determined for the $1C4$ conformer. Neglecting a change in volume arising from a change of conformer from $1C4$ to $4C1$, the enthalpy difference equals the energy difference. Any entropy difference would arise from differences in the vibrations of lowest frequencies and from differences in moments of inertia. These differences are assumed to be small (in aqueous solution the rotational term is largely quenched), and the entropy difference therefore negligible. We can then equate free enthalpy difference with energy difference. As the two conformers are given the same statistical weight, the equilibrium ratio of $1C4$ to $4C1$ will be ∼ 1:25. Presumably this holds also for the β anomer, and both anomers will to a good approximation be represented by their $4C1$ conformers. Therefore the free enthalpy difference between the two anomers will be 0.262 kcal mol^{-1}, and their equilibrium ratio at 300 K will be α : β = 0.39 : 0.61. This should be compared with kinetic and NMR studies [26,3,4] which show a ratio of α : β = 0.36 : 0.64.

Comparison with earlier calculations. As mentioned before, our calculations seem to be the first to include relaxation of all degrees of freedom, which is imperative for attainment of minimum energy conformation. Also in other respects, earlier investigations employed methods basically different from ours. The most serious difference was the introduction of an extra energy term for the anomeric effect in order to improve specifically the agreement with experimentally derived free enthalpies. With this addition Angyal [10] and Vijayalakshmi and Rao [13] were able to calculate α:β equilibrium

ratios of 0.36 : 0.64 and 0.38 : 0.62, respectively. To avoid circular argument, we did not use such adjustment.

CONCLUSIONS

We have calculated equilibrium conformations of α- and β-D-glucopyranoses by truly convergent energy minimisation using a simple force field with parameters adapted from studies of different classes of compounds.

The simple force field cannot reproduce the anomeric effect, but does give the correct anomer distribution at equilibrium.

Calculated ring geometries conform to those found in crystal structure analysis, but orientations of side chains do not. This is due to a basic limitation in our approach, which at present can handle only isolated molecules. The extension of our programme to treat crystal structures is a major project, which has now been initiated.

The force field used here will be employed and augmented in studies of glycosidic linkages and other substitutions of pyranose rings.

An optimisation procedure for fitting energy function parameters simultaneously to conformations and vibrational spectra determined experimentally is being developed.

REFERENCES

1. Niketić, S. R., Rasmussen, K., Woldbye, F. and Lifson, S. *Acta Chem. Scand. A 30* (1976) 485.
2. Lifson, S. and Warshel, A. *J. Chem. Phys. 49* (1968) 5116.
3. Rudrum, M. and Shaw, D. F. *J. Chem. Soc.* (1965) 52.
4. Lemieux, R. U. and Stevens, J. D. *Can. J. Chem. 44* (1966) 249.
5. McDonald, T. R. R. and Beevers, C. A. *Acta Crystallogr. 5* (1952) 654.
6. Brown, G. M. and Levy, H. A. *Science 147* (1965) 1038.

7. Snyder, R. L. and Rosenstein, R. D. *Acta Crystallogr. B 27* (1971) 1969.
8. Ferrier, W. G. *Acta Crystallogr. 16* (1963) 1023.
9. Chu, S. S. C. and Jeffrey, G. A. *Acta Crystallogr. B 24* (1968) 830.
10. Angyal, S. J. *Aust. J. Chem. 21* (1968) 2737.
11. Angyal, S. J. *Angew. Chem. Int. Ed. Engl. 8* (1969) 157.
12. Rao, V. S. R., Sundararajan, P. R., Ramakrishnan, C. and Ramachandran, G. N. In Ramachandran, G. N., Ed., *Conformation of Biopolymers II*, Academic, New York 1967, p. 721.
13. Vijayalakshmi, K. S. and Rao, V. S. R. *Carbohydr. Res. 22* (1972) 413.
14. Niketić, S. R. and Rasmussen, K. *The Consistent Force Field: A Documentation*, Lecture Notes in Chemistry, Springer, Heidelberg. *To be published.*
15. Stoddart, J. F. *Stereochemistry of Carbohydrates*, Wiley-Interscience, New York 1971, p. 54 ff.
16. Reeves, R. E. *Adv. Carbohydr. Chem. 6* (1951) 107.
17. Karplus, S. and Lifson, S. *Biopolymers 10* (1971) 1973.
18. Vijayalakshmi, K. S. and Rao, V. S. R. *Carbohydr. Res. 29* (1973) 427.
19. Warshel, A., Levitt, M. and Lifson, S. *J. Mol. Spectrosc. 33* (1970) 84.
20. Rao, V. S. R., Vijayalakshmi, K. S. and Sundararajan, P. R. *Carbohydr. Res. 17* (1971) 341.
21. Sundararajan, P. R. and Rao, V. S. R. *Biopolymers 8* (1969) 313.
22. Rasmussen, K. *Conformations and Vibrational Spectra of Tris(diamine) Chelate Complexes*, Thesis, The Technical University of Denmark, Copenhagen 1970, p. 76 ff.
23. Ramachandran, G. N., Venkatachalam, C. M. and Krimm, S. *Biophys. J. 6* (1966) 849.
24. Schellmann, J. A. and Lifson, S. *Biopolymers 12* (1973) 315.
25. Buckingham, D. A., Maxwell, I. E., Sargeson, A. M. and Snow, M. R. *J. Am. Chem. Soc. 92* (1970) 3617.
26. Bates, F. J., Ed., *Polarimetry, Saccharimetry and the Sugars, Nat. Bur. Stand. (U.S.), Circ. C440* (1942), p. 436.
27. Berman, H. M., Chu, S. S. C. and Jeffrey, G. A. *Science 157* (1967) 1576.
28. Lemieux, R. U. In Mayo, P. de, Ed., *Molecular Rearrangements*, Interscience, New York 1963, Part 2, p. 713.
29. Jeffrey, G. A., Pople, J. A. and Radom, L. *Carbohydr. Res. 38* (1974) 81.