Polysaccharide Conformation. Part VIII.[1] Test of Energy Functions by Monte Carlo Calculations for Monosaccharides

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Internal energies have been calculated for the aldopentopyranoses, as the thermodynamic average over all exocyclic bond conformations for each of the sixteen nonsuperimposable, Reeves *C*1 chair structures. Contributions were included from van der Waals attraction, van der Waals repulsion, polar interactions, and bond torsion. These results for isolated molecules are compared with relative free energies from experimental measurements on aqueous solutions. Within one group of sugars (α-D-xylose, α-L-lyxose, α-D-lyxose, β-L-arabinose, β-D-lyxose, β-D-ribose, and β-D-arabinose) the calculations agree closely with experiment and the neglect of conformational entropy and specific solvation effects would seem to be justified. The agreement would further suggest that the anomeric effect is included in the energy terms that we would have considered and can therefore be attributed mainly to the interactions between bond dipoles, in line with conclusions from recent quantum mechanical calculations. For the two sugars which have the most favourable stereochemistry for solvation by the structured component of liquid water (α-L-arabinose and β-D-xylose) the calculations fail to predict the full extent of conformational stability. We suggest that the discrepancy is to be attributed to a ' structured hydration ' that is highly co-operative and rather selective for all-equatorial sugar residues. The remaining sugars (α-D-ribose, α-L-ribose, α-D-arabinose, β-L-ribose, β-L-lyxose, α-L-xylose, and β-L-xylose) are those with 1,3-interactions between diaxial oxygen substituents. Agreement is poor, probably because the calculations are not adapted to treat such high degrees of steric compression and perhaps also because the experimental data are less reliable for these forms. We conclude that our approach has promise for the calculation of conformational energies of carbohydrates in aqueous solution provided that steric compression is not severe and that allowance is made for the co-operative hydration of structures in which several equatorial oxygen functions are adjacent.

CLASSICAL conformational analysis has been less useful for polymer chains than for small molecules, mainly because overall polymer shapes are so sensitive to small changes in the individual dihedral angles that it is not good enough to make the usual approximation that each angle will correspond to one of a few discrete, idealised states (the various eclipsed and staggered rotamers). It is necessary to consider each angle as continuously variable. In addition, the behaviour of the polymer may be influenced not only by the ' preferred ' (*i.e.*, minimum free energy) conformation but also by other conformations made accessible by thermal fluctuations.

An approach to the conformational analysis of polymers is needed which will show quantitatively how the energy alters during continuous change of conformation. Attempts have been made to use numerical methods for this purpose, especially for the ordered [2] and disordered [3] conformations of polypeptide chains and the disordered (random-coil) conformations of synthetic polymers.[3] This requires energy functions that can be evaluated rapidly in the computer and, at present, these must be derived empirically with many assumptions.[4] We have always taken the view that the relative influence of van der Waals attraction, hydrogen bonding, polar effects, and solvent effect cannot yet be confidently balanced against each other and that *reliable predictions* can only be made when van der Waals repulsion dominates the other terms.

Many calculations have been made of the conformational energies of carbohydrates [4] but there have been few attempts to compare the results with energies that have been measured by experiment even though this would be the best basis for evaluation of the method. The calculations yield relative internal energies of different conformational or configurational states of carbohydrates which should be directly comparable with measured differences. Unfortunately no data yet exist which are sufficiently extensive or reliable. Good experimental values are available for free energy differences, however, largely from Angyal's collection and careful evaluation of equilibrium constants.[5] These free energy differences can be related to individual contributions from particular elements of stereochemistry to form a scheme which, whilst experimentally based, can be used predictively. Free energies obtained in this way will be called ' experimental free energies ' even though their derivation may involve some interpolation using the regularities which Angyal has pointed out.

We decided to use a new approach which we believe to be the best that is currently practicable for the numerical calculation of conformational energies of carbohydrates, and to compare the results with Angyal's free energies. The two sets of values must in principle differ by $T\Delta S$ where ΔS is the entropy difference at absolute temperature T. The entropy differences between the pairs of isomers that we have chosen is not necessarily zero. However, unless there are special solvent effects of the type that we shall discuss later, these differences are expected to be negligible because entropy of mixing and symmetry number terms are absent.[6] Interactions with solvent molecules and between solvent molecules are totally ignored in our initial treatment, even though these could contribute to both the energy and the

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[1] Part VII, D. A. Rees and A. W. Wight, *J. Chem. Soc.* (*B*), 1971, 1366.

[2] H. A. Scheraga, *Chem. Rev.*, 1971, **71**, 195.

[3] P. J. Flory, ' Statistical Mechanics of Chain Molecules,' John Wiley, New York, 1969.

[4] For a review, see D. A. Rees, *MTP Internat. Rev. Sci.*, *Org. Chem.*, *Series One*, 1973, **7**, 251.

[5] S. J. Angyal, *Austral. J. Chem.*, 1968, **21**, 2737; S. J. Angyal and K. Dawes, *ibid.*, p. 2747.

[6] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, ' Conformational Analysis,' John Wiley and Sons, New York, 1965, pp. 53—58; compare also D. A. Brant, W. G. Miller, and P. J. Flory, *J. Mol. Biol.*, 1967, **23**, 47.

entropy terms.[7-10] It will be of interest to consider whether any systematic discrepancies are to be seen in the results to suggest specific hydration effects.

When this work was in progress, the results were published of a series of investigations that were similar in conception but which differed in the methods used and in the final conclusions.[11,12] Comments on this will be made in the Discussion section.

METHOD

Intramolecular conformational energies were calculated as the sum of three terms, representing respectively non-bonded van der Waals interactions, non-bonded coulombic charge interactions, and single-bond rotation torsional energies.

The van der Waals interaction energy, E_{ij}, for any non-bonded atom pair i and j, separation r_{ij}, was assumed to follow a Lennard-Jones potential of the form (1). Scott and

$$E_{ij} = -Ar_{ij}^{-6} + Br_{ij}^{-9} \qquad (1)$$

Scheraga[13] have used a similar function with an exponent of 12 for the repulsive term; the value 9, however, gives a softer repulsion resembling more closely the commonly used exponential term.[3] The values of A were taken from Scott and Scheraga[13] and those of B calculated by their method (Table 1). A non-bonded atom pair was taken as any pair of atoms not bonded to each other or to a common third atom.

TABLE 1

van der Waals potential parameters. r_0 is the minimum energy separation

Interaction	r_0 (Å)	$10^{-2} A$ (kcal Å^6 mol^{-1})	$10^{-3} B$ (kcal Å^9 mol^{-1})
C–C	3·40	3·70	9·70
C–O	3·22	3·67	8·18
C–H	2·90	1·28	2·08
O–O	3·04	3·67	6·88
O–H	2·72	1·24	1·66
H–H	2·40	0·47	0·43

The coulombic charge interaction energy was calculated using the monopole approximation of del Re,[14] whereby partial electronic charges, q_i, are assigned to each atom (Table 2) on the basis of a molecular orbital treatment based on observed dipole moments. The interaction energy was calculated for any non-bonded atom pair from equation (2).

$$E_{ij} = q_i q_j / \varepsilon r_{ij} \qquad (2)$$

The value of the effective dielectric constant, ε, has been widely debated:[15] for this work it was taken as 3·5, independent of r_{ij}, following the theoretical considerations of Ramachandran and Srinivasan.[16]

TABLE 2

Atomic partial charges for a pentopyranose sugar calculated by the method of del Re

Atom	Partial charge (electrons)	Atom	Partial charge (electrons)
C(1)	0·190	C(4)	0·105
C(2)	0·114	C(5)	0·035
C(3)	0·106		
O(1)	−0·446	O(4)	−0·458
O(2)	−0·457	O(5)	−0·260
O(3)	−0·458		
H(1)	0·061	H(4)	0·052
H(2)	0·053	H(5)	0·052 [a]
H(3)	0·052		
H(O1)	0·303	H(O3)	0·301
H(O2)	0·302	H(O4)	0·301

[a] There are two such atoms in the molecule.

The torsional term is a necessary correction of the semi-classical approximation for single-bond rotations, as explained by Pauling[17] amongst others. For the rotation of pendant hydrogen atoms on the sugar ring, it was taken as a sinusoidal function of the rotation angle with amplitude, τ_i, corresponding to the barrier determined for methanol,[18] reduced by the van der Waals contribution already calculated (Table 1). Taking a barrier height of 1·07 kcal mol^{-1}, the van der Waals contribution is calculated as 0·11 kcal mol^{-1} giving τ_i 0·96 kcal mol^{-1}. The effect of varying this parameter was explored as described below. For a conformation displaced θ from the staggered (minimum energy) position, the interaction energy was then calculated from equation (3) for a bond between tetrahedrally bonded atoms.

$$E_i = \tau_i(1 - \cos 3\theta)/2 \qquad (3)$$

Each pentopyranose sugar has four free rotation angles (I) whose values determine the positions of the hydroxy-hydrogen atoms, and thus the conformational energy. Previous workers[11,12] have taken the conformational energy obtainable by variation of these angles, thus assuming either that the molecule exists predominantly in this conformation, or that the proportional contributions from higher energy states are similar for all isomers. Although the molecule might exist in an energy minimum in the solid state, preliminary calculations show that this is likely to be a poor approximate in solution since relatively large changes in the conformation angles produce only small (*i.e.*, around thermal) increases in energy. Particularly when equatorial and axial hydroxy-groups are compared, the range of accessible conformations varies widely and hence the contributions from higher energy states will also vary between isomers. Accordingly, for the present calculation, thermodynamically averaged energies were calculated assuming that each conformation j, as defined by the four rotation angles β_1, β_2, β_3, and β_4 exists with a relative abundance proportional to its Boltzmann weight $\exp(-E_j/kT)$, where E is the calculated

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[7] M. A. Kabayama and D. Patterson, *Canad. J. Chem.*, 1958, **36**, 563.

[8] A. S. Perlin, *Canad. J. Chem.*, 1966, **44**, 539; W. Mackie and A. S. Perlin, *ibid.*, p. 2039.

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[10] T. J. Painter, *Acta Chem. Scand.*, 1973, **27**, 2463.

[11] K. S. Vijayalakshmi and V. S. R. Rao, *Carbohydrate Res.*, 1972, **22**, 413.

[12] V. S. R. Rao, K. S. Vijayalakshmi, and P. R. Sundararajan, *Carbohydrate Res.*, 1971, **17**, 341; P. R. Sundararajan, Ph.D. Thesis, University of Madras, 1969; K. S. Vijayalakshmi and V. S. R. Rao, *Carbohydrate Res.*, 1973, **29**, 427; K. S. Vijayalakshmi, N. Yathindra, and V. S. R. Rao, *Carbohydrate Res.*, 1973, **31**, 173.

[13] R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, 1966, **45**, 2091; T. Ooi, R. A. Scott, G. Vanderkooi, and H. A. Scheraga, *ibid.*, 1967, **46**, 4410.

[14] G. del Re, *J. Chem. Soc.*, 1958, 4031; *ibid.*, in ' Electronic Aspects of Biochemistry,' B. Pullman, ed., Academic, New York, 1964, p. 221.

[15] K. D. Gibson and H. A. Scheraga, *Proc. Nat. Acad. Sci., U.S.A.*, 1967, **58**, 420 and 1317.

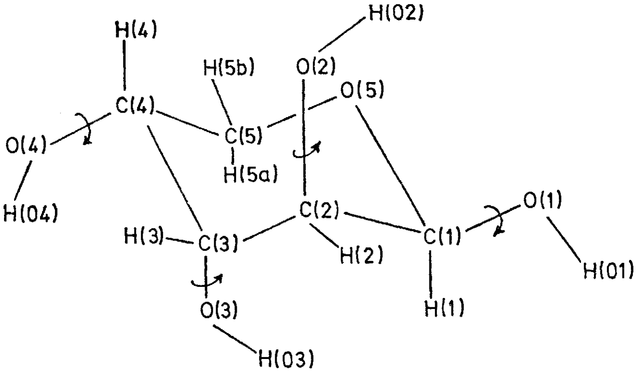
[16] G. N. Ramachandran and R. Srinivasan, *Indian J. Biochem.*, 1970, **7**, 95.

[17] L. Pauling, *Proc. Nat. Acad. Sci., U.S.A.*, 1958, **44**, 211.

[18] D. J. Millen, *Progr. Stereochem.*, 1962, **3**, 138.

conformational energy, **k** the Boltzmann factor, and T the absolute temperature.

Because a complete scan of the conformation space defined by all four angles would be a prohibitively large task, recourse was made to a random sampling technique, and furthermore, to increase the significantly contributing proportion of sampled conformations, the Markov chain method of Metropolis *et al.*[19] was used. This involves the generation of a sequence of conformations whose energies, being already distributed according to their Boltzmann weights, may be simply averaged to give a thermodynamically averaged energy. These conformations may be considered equally as being a representative sample of the conformational states existing at thermal equilibrium, or as the conformational states of a single molecule sampled at regular time intervals. Generation of the chain requires as a parameter an upper bound to the change in any conformation angle between successive steps, which affects the rate of convergence of the averaged energy to a stable value. A suitable value for this step-size was determined using the criterion that *ca.* 25% of the generated conformations should be ' rejected ' in the terms of Metropolis *et al.*[19] Observation of the progress of the chain showed that a 10° step-size met this criterion and gave convergence to *ca.* 0·1 kcal mol^{-1} after 5000 generated conformations, and further, that any effect caused by the arbitrary starting conformation being of atypically high energy could be eliminated by ignoring the first 100 cycles. The volume of calculation is



(I)

Atoms included in the energy calculations, and the four ' free ' rotation angles in a typical pentopyranose sugar

TABLE 3

Atomic co-ordinates (Å) derived from idealized bond lengths and bond angles [20]

	x	y	z
C(1)	0·0000	0·0000	0·0000
C(2)	1·5400	0·0000	0·0000
C(3)	2·0668	1·4470	0·0000
C(4)	1·3908	2·2536	−1·1243
C(5)	0·1383	2·0910	−1·0425
O(5)	−0·4856	0.7167	−1·1256
H(5A)	−0·6064	2·6349	−1·8630
H(5B)	−0·4978	2·5507	−0·0986
Hydroxy-groups equatorial			
O(1)	−0·4891	−1·3435	−0·0274
O(2)	2·0290	−0·6986	1·1479
O(3)	3·4854	1·4509	−0·1802
O(4)	1·7423	3·6354	−1·0143
H(1)	−0·3638	0·4686	0·9144
H(2)	1·9037	−0·5197	−0·8864
H(3)	1·8516	1·9126	0·9618
H(4)	1·7435	1·8957	−2·0915
Hydroxy-groups axial			
O(1)	−0·4891	0·5932	1·2057
O(2)	2·0290	−0·6986	−1·1479
O(3)	1·8093	2·0613	1·2654
O(4)	1·8627	1·8072	−2·3982
H(1)	−0·3638	−1·0268	−0·0378
H(2)	1·9038	−0·5197	0·8863
H(3)	3·1458	1·4413	−0·1544
H(4)	1·6506	3·3073	−1·0229

TABLE 4

Atomic co-ordinates (Å) derived from a survey of crystal structures for sugar residues having equatorial O(1) [21]

	x	y	z
C(1)	0·0000	0.0000	0·0000
C(2)	1·5230	0·0000	0·0000
C(3)	2·0565	1·4244	0·0000
C(4)	1·4407	2·2192	−1·1440
C(5)	−0·0795	2·1052	−1·1051
O(5)	−0·4733	0·7246	−1·1371
H(5A)	−0·5093	2·6298	−1·9712
H(5B)	−0·4595	2·5742	−0·1855
Hydroxy-groups equatorial			
O(1)	−0·4384	−1·3112	−0·1340
O(2)	1·9944	−0·7172	1·1388
O(3)	3·4756	1·4037	−0·1382
O(4)	1·7964	3·5962	−1·0405
H(1)	−0·3672	0·4791	0·9196
H(2)	1·8902	−0·5296	−0·8915
H(3)	1·8113	1·9082	0·9570
H(4)	1·8136	1·8309	−2·1033
Hydroxy-groups axial			
O(2)	1·9944	−0·7172	−1·1388
O(3)	1·7461	2·0514	1·2426
O(4)	1·9021	1·7230	−2·3988
H(2)	1·8901	−0·5296	0·8915
H(3)	3·1506	1·4067	−0·1123
H(4)	1·7321	3·2762	−1·0553

TABLE 5

Atomic co-ordinates (Å) derived from a survey of crystal structures for sugar residues having axial O(1) [21]

	x	y	z
C(1)	0·0000	0·0000	0·0000
C(2)	1·5230	0·0000	0·0000
C(3)	2·0551	1·4249	0·0000
C(4)	1·4465	2·2197	−1·1477
C(5)	−0·0743	2·1117	−1·1144
O(5)	−0·4652	0·7300	−1·1181
H(5A)	−0·4976	2·6154	−1·9960
H(5B)	−0·4572	2·5993	−0·2057
Hydroxy-groups equatorial			
O(2)	1·9943	−0·7166	1·1392
O(3)	3·4752	1·4052	−0·1288
O(4)	1·8071	3·5956	−1·0457
H(2)	1·8902	−0·5291	−0·8918
H(3)	1·8059	1·9099	0·9553
H(4)	1·8215	1·8283	−2·1049
Hydroxy-groups axial			
O(1)	−0.4384	0·5586	1·1938
O(2)	1·9943	−0·7166	−1·1392
O(3)	1·7395	2·0534	1·2405
O(4)	1·9107	1·7195	−2·3998
H(1)	−0·3672	−1·0352	−0·0587
H(2)	1·8902	−0·5291	0·8918
H(3)	3·1500	1·4079	−0·1051
H(4)	1·7416	3·2757	−1·0601

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[19] N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller, *J. Chem. Phys.*, 1953, **21**, 1087.

[20] W. J. Settineri and R. H. Marchessault, *J. Polymer Sci.*, *part C*, 1965, **11**, 235.

[21] S. Arnott and W. E. Scott, *J.C.S. Perkin II*, 1972, 324.

diminished by about two orders of magnitude compared with a systematic sampling procedure.

Two sets of stereochemical parameters were used for the calculations, one derived from idealised bond lengths and angles [20] and the other from a survey of crystal structures.[21] The co-ordinates are given in Tables **3**—**5**. With a Reeves *C*1 chair ring form, pentoses may have axial or equatorial hydroxy-groups at each of C(1), C(2), C(3), and C(4) giving sixteen possible isomers. Not all these exist naturally as free sugars in this chair form but all sixteen were taken for comparison purposes. Table **6** lists these isomers, their configurations, and the conventional names of the direct and mirror-image forms which will obviously have identical energies. Seven of these isomers have axial hydroxy-groups on next-to-adjacent carbon atoms, giving a strong repulsion between the two oxygen atoms involved. Since this might be expected to be partially accommodated by some distortion of bond angles these isomers will be denoted here ' strained,' and the remaining nine, ' unstrained.' Our potential functions make no allowance for bond angle strain and are therefore more reliably descriptive of the unstrained case.

TABLE 6

Nomenclature and configuration of all possible pentopyranoses

Configuration [a] at carbon 1	2	3	4	Conventional names Actual (C1)	Mirror image (1C)
A	E	A	E	α-D-ribose	corresponding L-sugars, *e.g.* α-L-ribose
E	E	A	A	β-D-ribose	
A	A	A	E	α-D-arabinose	
E	A	A	E	β-D-arabinose	
A	E	E	E	α-D-xylose	
E	E	E	E	β-D-xylose	
A	A	E	E	α-D-lyxose	
E	A	E	E	β-D-lyxose	
E	A	E	A	α-L-ribose	corresponding D-sugars, *e.g.* α-D-ribose
A	A	E	A	β-L-ribose	
E	E	E	A	α-L-arabinose	
A	E	E	A	β-L-arabinose	
E	A	A	A	α-L-xylose	
A	A	A	A	β-L-xylose	
E	E	A	A	α-L-lyxose	
A	E	A	A	β-L-lyxose	

[a] A ≡ axial, E ≡ equatorial.

The calculated energies were compared with free energies derived by Angyal.[5] The correspondence is not expected to be exact, as explained in the Introduction. The complete set of calculations was repeated for a series of values of the torsional energy parameter τ_i (see above) since this is the least well determined part of the potential. (It is based upon methanol which, as a primary alcohol, might not be a good model for the hydroxy-functions on the sugar ring.) It was found that a reduction of only *ca.* 20% from the original values gave the best agreement and these results are therefore cited here. The parameter used to evaluate the fit of a set of determinations was the root-mean-square deviation from Angyal's figures, denoted σ.

RESULTS AND DISCUSSION

Although for completeness we will present our results in parallel with those of earlier calculations,[11] the methods and objectives are different and the comparison should not be made too closely. In the earlier work, the minimum energy was calculated for each isomer whereas we have thought it more valid, for reasons given above, to calculate the thermodynamic average. The earlier investigators made several adjustments to improve agreement with the experimentally derived free energies, the most serious of which was the total omission of torsion potentials but also the modification of van der Waals functions involving oxygen and the addition of an extra energy term for the anomeric effect because they did not believe this to be implicit in their treatment. For some calculations they considered the possibility of changes in selected bond angles. In a later refinement, they attempted a crude estimate of the entropy term; we believe this to underestimate the proportion of conformational space that is accessible to axial relative to equatorial epimers, and therefore to overestimate the entropy difference. The calculations were extended to a wide range of compounds, including pentoses, hexoses, their methyl glycosides, and peracetates.[12]

TABLE 7

Conformational energies calculated for the ' unstrained ' pentoses (kcal mol^{-1})

Hydroxy configuration [a]	Fixed atoms (1)	Movable atoms (2)	Sum (3)	Zero mean (4)	Free energies from experiment (5)	Zero mean without EEEE and EEEA (6)	Zero mean experimental values without EEEE and EEEA (7)	Earlier calculation [b] (8)
EEEE	19·68	−13·64	6·04	0·06	−0·68			−0·72
AEEE	20·27	−14·67	5·60	−0·38	−0·33	−0·37	−0·46	−0·12
EAEE	21·75	−15·70	6·05	0·07	0·22	0·08	0·09	0·28
EEAE	20·53	−14·53	6·00	0·02	0·22	0·03	0·09	−0·16
EEEA	22·08	−16·13	5·95	−0·03	−0·23			−0·04
AAEE	19·29	−13·98	5·31	−0·67	−0·23	−0·66	−0·36	0·32
AEEA	21·37	−15·36	6·01	0·03	0·12	0·04	−0·01	0·41
EAAE	19·62	−12·87	6·75	0·77	0·62	0·78	0·49	0·31
EEAA	19·78	−13·69	6·09	0·11	0·32	0·12	0·19	−0·28

[a] Configuration at C(1) to C(4) respectively, using the convention defined in Table 4. [b] These are the calculations made without the consideration of angle strain and without the entropy term, as described in ref. 12.

We attempted to set up the basis of our calculations on the best evidence beforehand and then to avoid the subsequent use of adjustable parameters. Actually this ideal was compromised to the extent of optimising the height of the torsion barrier because C–O bond rotations are poorly characterised experimentally. The adjustment turned out to be rather small and otherwise our approach involves no fitting that might risk the introduction of circular arguments.

The results of the calculations for the nine unstrained pentoses are given in Table 7. These are for the co-ordinates given in Tables 4 and 5 but the results obtained with the other co-ordinates were similar. The first two columns give the energy contributions from the wholly fixed atoms (*i.e.*, those unaffected by the conformation angles), and the averaged contributions relating to the movable atoms, respectively The sum of these (column 3) is adjusted (by subtracting the column mean) to give a set with zero mean (column 4). This is compared with the free energies from experiment [5] and with earlier results [11] (columns 5 and 8), similarly adjusted. This procedure serves to estimate the discrepancy index, σ, given that the zero energies of the sets are not identically defined.

TABLE 8

Root-mean-square deviation of conformational energies calculated for the isomers listed in Table 7, from experimentally-derived free energies

Set	σ(kcal mol^{-1})
Complete set	0·32
EEEE and EEEA excluded	0·16
Complete set but calculations repeated with alternative co-ordinates [Table 3(a)]	0·31
EEEE and EEEA excluded	0·25
Previous calculations without allowance for angle strain	0·35
EEEE and EEEA excluded	0·39
Previous calculations with allowance for angle strain	0·50
EEEE and EEEA excluded	0·55

The values of σ are given in Table 8. Although it can be seen that the present method gives a fit that is only marginally superior to the better of the earlier values, the comparison is dramatically improved by a single further adjustment which is suggested by the observation that our calculations fail to predict the full stability of two particular isomers (EEEE and EEEA). These are expected [7-10] to have a source of stabilisation that was not included in our calculations, namely a favourable interaction with the structured component of liquid water. The spacing between oxygen atoms in all-equatorial pyranose sugars is believed to fit neatly into a ' cage ' of water molecules which are themselves hydrogen bonded together in their preferred, tetrahedral manner. These ordered arrays of water molecules have a dynamic rather than permanent existence and they make and break co-operatively. A mutual stabilisation of the water structure and the particular form of the sugar is to be expected when they are stereochemically compatible in this way. Such models were first proposed to account for the thermodynamic parameters associated with the mutarotation of all equatorial pyranose sugars.[7] In particular, the large entropy change could be explained if the β-anomers favour a greater degree of structure in the solvent water. These ideas are supported by the shift in equilibrium for certain sugars, from furanose to pyranose forms when the solvent is changed from dimethyl sulphoxide to water [8] and by a comparison of the rates of hydrolysis of methyl α- and β-glucopyranosides.[10] A variety of physical methods confirm that water molecules are indeed retarded in their motions by the presence of sugar solutes which have three or more hydroxy-groups that are disposed to fit the trydimite structure of water, *i.e.* which are all-equatorial.[9] This ' ordering effect ' decreases with increasing temperature, as expected.

It is consistent with the co-operative nature of this effect that our ' unexpected stabilization ' is largest (0·7 kcal mol^{-1}) for the isomer (EEEE) for which models can be built which show the simultaneous participation of all five sugar oxygens with the water structure, smaller (0·2 kcal mol^{-1}) when only four oxygens are available (EEEA), and undetectable for other isomers. If we now omit the two isomers which show this stabilization from the comparison with experimental free energies on the basis of a zero mean, most of the discrepancies disappear (Table 7, *cf.* column 6 with 7) and the discrepancy index, σ, drops from 0·32 to 0·16 kcal mol^{-1} (Table 8) which is almost within the radius of convergence of the Monte Carlo method. Perhaps it is significant that certain all-equatorial polysaccharides such as xylan [20,22] and hyaluronate in both the three- [23] and four-fold [24] forms can show a range of crystalline hydrates. Even though the packing mode changes, these examples conserve their conformations with changing water content, suggesting that particular polysaccharide conformations have a particular compatibility with water.

Our calculations are equally successful for axial and equatorial anomers and the so-called anomeric effect [25,26] is apparently included in the types of interaction that we have considered. It does not appear to be necessary to invoke a special hybridisation effect at C(1) [27-29] or the shape and disposition of the lone pair orbitals [30] to account for the main contributions to the relative energy. The anomeric effect has long been believed, from the influence of solvent and other evidence, to involve some form of polar interactions.[25] Our simple treatment represents the charge distribution of the molecule by a collection of point charges placed on the atoms in a way that is designed to approximate the experimentally observed bond dipoles. A similar conclusion, that a large contribution to the anomeric effect arises from interactions between bonded electrons through space, has been reached on the basis of *ab initio* quantum

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TABLE 9

Conformational energies calculated for all pentoses (kcal mol^{-1})

Hydroxy configuration	Fixed atoms (1)	Movable atoms (2)	Sum (3)	Zero mean (4)	Free energies from experiment (5)	Zero mean without EEEE and EEEA (6)	Zero mean experimental values without EEEE and EEEA (7)	Earlier calculation (8)
EEEE	19·68	−13·64	6·04	−0·14	−1·21			−1·11
AEEE	20·27	−14·67	5·60	−0·57	−0·86	−0·59	−0·99	−0·61
EAEE	21·75	−15·73	6·05	−0·12	−0·31	−0·14	−0·44	−0·11
EEAE	20·53	−14·53	6·00	−0·18	−0·31	−0·20	−0·44	−0·58
EEEA	22·08	−16·13	5·95	−0·23	−0·76			−0·43
AAEE	19·29	−13·98	5·31	−0·86	−0·76	−0·88	−0·89	−0·18
AEEA	21·37	−15·36	6·01	−0·17	−0·41	−0·19	−0·54	0·02
EAAE	19·62	−12·87	6·75	0·57	0·09	0·55	−0·04	−1·02
EEAA	19·78	−13·69	6·09	−0·09	−0·21	−0·11	−0·34	−0·69
AEAE	24·36	−17·93	6·43	0·26	0·64	0·24	0·51	0·80
EAEA	27·17	−19·85	7·32	1·14	0·74	1·12	0·61	1·19
AAAE	20·53	−14·03	6·50	0·32	0·39	0·30	0·26	0·45
AAEA	23·43	−17·53	5·95	−0·22	0·29	−0·24	0·16	0·70
AEAA	22·43	−16·41	6·02	−0·16	0·74	−0·18	0·61	0·57
EAAA	21·89	−15·63	6·26	0·08	0·79	0·06	0·66	0·30
AAAA	21·69	−15·17	6·52	0·35	1·09	0·33	0·96	0·75

[a] These are the calculations without the consideration of angle strain, and without the entropy term, as described in ref. 12.

mechanical calculations on model compounds.[28,31] To explain other differences between α- and β-anomers, especially in bond lengths, quantum mechanics show that it is necessary to invoke delocalisation of the lone pair electrons of the glycosidic oxygen.[28] This delocalisation must of course contribute to the energy difference between anomers but it would seem to be less important than the dipole–dipole interactions. Our ability to predict the anomeric effect on this investigation is therefore entirely in accord with other work.

When we extended our calculations to pentoses in which there were 1,3-diaxial oxygen substituents, the agreement with experiment was poor (Tables 9 and 10).

TABLE 10

Root-mean-square deviation of conformational energies calculated for the isomers listed in Table 9, from experimentally derived free energies

Set	σ(kcal mol^{-1})
Complete set	0·52
EEEE and EEEA excluded	0·43
Complete set but with calculations repeated with alternative co-ordinates [Table 3(a)]	0·66
EEEE and EEEA excluded	0·60
Previous calculations [12] without allowance for angle strain	0·37
EEEE and EEEA excluded	0·39
Previous calculations [12] with allowance for angle strain	0·44
EEEE and EEEA excluded	0·45

Obvious reasons for this are that the van der Waals and electrostatic repulsion would be severe in these structures and would occur in ranges in which our functions were not designed to cope accurately. The repulsions would likely be diminished by deformation of several bond and torsion angles,[32,33] with geometric and energetic consequences that would be complex and could differ from one example to another. Finally, the 'experimental free energies' themselves are probably less reliable for these particular compounds because of the rather circuitous way in which they have to be derived and we doubt whether it is worth while to refine our approach to cope with 'strained' structures until better experimental values are available for comparison.

The earlier calculations [12] do not predict the anomeric effect or the importance of co-operative hydration. Agreement with the experimental values is worse than ours for the unstrained pentoses but better than ours when strained pentoses are included. It is difficult to trace these differences to particular features of the calculations because there are so many differences in approach. For reasons given above, we believe our approach to be the more valid.

Included in Tables 8 and 10 are the results of our calculations with a less realistic set of co-ordinates, based upon idealised bond lengths and angles rather than on the ring geometries found in crystal structures. The results show trends that are qualitatively similar but which quantitatively are less convincing. We suggest that this is further evidence that the assumptions made about residue geometry require as much care and consideration as the choice of energy functions.[4,34]

Conclusions.—1. The agreement between calculation and experiment suggests that useful energy functions can be based on the approach that we have used here. 2. Such calculations are less reliable in structures in which atoms are squeezed significantly closer than their equilibrium distances. 3. There is some evidence that 'co-operative hydration' can contribute significantly to the conformational stability of structures which contain four or five suitably spaced oxygen functions. 4. It seems to be possible to account for the main features of the anomeric effect in terms of interactions between bond dipoles.

[4/1690 *Received*, 12*th August*, 1974]

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