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CONFORMATIONS OF DISACCHARIDES BY EMPIRICAL FORCE-FIELD CALCULATIONS: PART I, β-MALTOSE

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ABSTRACT

Conformations of β-maltose have been studied by using convergent energy minimisation in a simple force field. Parameters for the force field were taken from similar studies on α- and β-D-glucopyranose. Four local minima are found on the ϕ,ψ-map; the free enthalpy differences are 2.8, 3.4, and 5.6 kJ.mol^{-1} above the lowest, corresponding to a distribution of 59:19:15:7. These minima are surrounded by a manifold of minimum conformers differing only in exocyclic torsions. Conformations of the two lowest minima are close to X-ray structures, and (ϕ,ψ) of the lowest minima are very close to what can be derived from n.m.r. experiments. The path on the ϕ,ψ-map of conformational interchange between the two lowest minima has been investigated, and barrier heights and rates of conversion estimated. Conversion is fast on the n.m.r. time-scale. The distribution-weighted average of a crucial H---H distance agrees with n.m.r. measurements. The possible existence of several minima for maltose can explain known irregularities in some amylose conformations.

INTRODUCTION

In an attempt to describe conformations and conformational interchange of carbohydrates, we present here a conformational analysis of maltose through energy minimisation in which all internal degrees of freedom are allowed to relax. In earlier work[1,2], we developed a force field for α- and β-D-glucopyranose, which we now apply to the considerably more-flexible disaccharides.

Nomenclature. In the following, β-maltose connotes 4-*O*-α-D-glucopyranosyl-β-D-glucopyranose. The constitution of β-maltose, giving atom numbering and the torsional angles ϕ and ψ, are shown in Fig. 1; ϕ and ψ are defined by atoms H(C-1′)–C-1′–O-4–C-4 and H(C-4)–C-4–O-4–C-1′, respectively. Our definition of a torsional angle follows the IUPAC convention[3]: a torsional angle A–B–C–D is defined through a Newman projection; it 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

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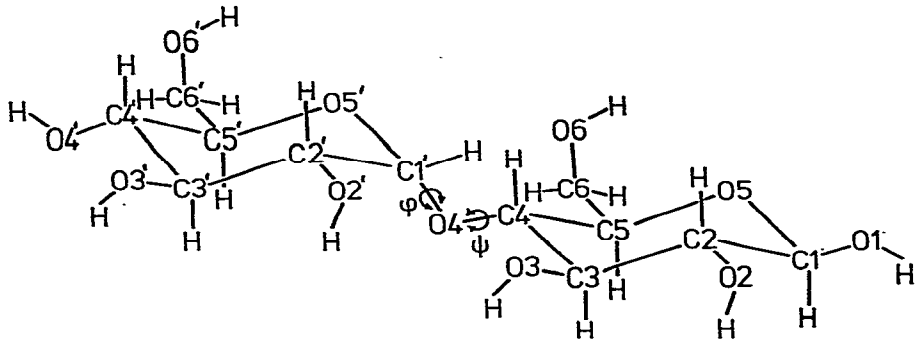

Fig. 1. Constitution and atom numbering for β-maltose (4-*O*-α-D-glucopyranosyl-β-D-glucopyranose).

positive if the sense of rotation is clockwise. In our former paper[1], we used the opposite sense.

Earlier calculations. Empirical calculations of the potential energy of non-bonded interactions indicate that α-maltose has a number of conformations which correspond to minima on the potential-energy surface. Rao *et al.*[4] found a minimum around $(\phi,\psi) = (-30,-10)$, and Blackwell *et al.*[5] found minima located at $(\phi,\psi) = (20,20)$, $(-20,-15)$, and $(-80,-45)$. Also, semi-empirical calculations have been performed on β-maltose. Giacomini *et al.*[6], using the PCILO method, found minima at $(\phi,\psi) = (-12,-5)$, $(-33,-22)$, and $(-42,-9)$. Saran and Govil[7], with the extended Hückel method, found minima at $(\phi,\psi) = (-40,0)$, (0,50), (50,40), (0,0), (10,20), (70,20). The minimum at (50,40) corresponds to their Fig. 2, but not to their text. They did not give relative energies. Within the last five years, Brant[8] and Rees and Smith[9] have performed empirical calculations on α-maltose. With only non-bonded interactions taken into account, Brant found a deep minimum at $(\phi,\psi) = (-20,-20)$ and another at $(-40,-160)$. Rees and Smith found a minimum at $(\phi,\psi) = (-35,-15)$ which changes to $(\phi,\psi) = (-70,-40)$ when a special function for hydrogen bonding is excluded.

Although the above-mentioned calculations are basically different, they have one common feature: no allowance was made for energy minimisation in the space of all atomic co-ordinates; they are simply mappings over a two-dimensional space.

Experimental studies. Two X-ray structures are relevant for comparison with calculated conformations of maltose, after proper transformation. The fractional co-ordinates taken from the X-ray diffraction structures of methyl β-maltoside monohydrate[10] ($R = 0.056$) and β-maltose monohydrate[11] ($R = 0.103$) were transformed to cartesians, from which we calculated the internal co-ordinates; (ϕ,ψ) and the glycosidic angle C-1′–O-4–C-4 were $(-9.2,9.1)$ and 117.6° for methyl β-maltoside, and (3.2,10.3) and 117.0° for β-maltose. In general[12], the glycosidic angle for a (1→4)-linked disaccharide lies in the range 115.7–117.6°, with an average value of 116.5°.

Some n.m.r. studies of maltose in solution should be mentioned. Vicinal ^{13}C–^{1}H coupling constants have been used to study torsions around the glycosidic bonds[13,14].

Preliminary results from Bock *et al.*[15], based on the same coupling constants and on ^1H relaxation-times, indicate that (ϕ,ψ) for methyl β-D-maltoside in D_2O are in a region around (−30,−40).

It seems evident that the *intra*-molecular hydrogen bond O-2′–O-3, which is observed in the solid state[10,11], is not broken in solution; this means that ϕ and ψ are mainly determined by *intra*-molecular forces. This is supported by n.m.r. studies[16] of maltose, cyclohexa-amylose, cyclohepta-amylose, and amylose in Me_2SO-d_6.

CALCULATIONS

The computational methods and programmes used here were developed from the CFF system of Lifson and Warshel[17] by Niketić and Rasmussen[18]. The main difference between our calculations and earlier ones is that we perform energy minimisation, which means that all degrees of freedom are allowed to relax; *i.e.*, no internal co-ordinate is kept fixed. We then relate minima on the potential-energy surface to equilibrium conformations.

Force field. In previous work[1,2], we developed a force field for α- and β-D-glucopyranose. This reproduces structure and anomer distribution very satisfactorily, although it is a very simple and conventional force field. Harmonic functions are used for bond and angle deformations, Pitzer terms for torsional motions, and Buckingham potentials for non-bonded interactions, which here are all interactions separated by three or more bonds.

The force field and parameters are given in Table I. It is seen that the contribution from E_ϕ to the total energy E_T is very small, because of the very low value of K_ϕ. This situation is a consequence of an attempt to treat interactions between charge clouds on vicinal sigma-bonded atoms as pure non-bonded interactions[2].

Initial conformations. All initial conformations of β-maltose, where nothing else is stated, were produced by coupling the crystal structures for α- and β-D-glucopyranose[19,20] followed by suitable rotations around ϕ and ψ.

Energy minimisation. All initial conformations produced in this way had a high energy-gradient and thus were far from a minimum. The gradient was lowered very efficiently by a steepest descent algorithm[18a], and at this point we switched to a modified Newton algorithm[18b] which uses second partial derivatives in the search for a minimum. The disaccharides are much more flexible than the monosaccharides and, when subjecting β-maltose to energy minimisation, we found that our modified Newton algorithm refused to work, most probably because the potential surface is shallow and puckered. This situation was overcome by choosing a much shorter initial step length in the linear search along the search direction. Minimisation was considered finished when the norm of the gradient became less than 10^{-6} kJ.mol^{-1}.Å^{-1}.

The strategy for minimisation of an initial conformation was to use 10–20 iterations with the steepest descent algorithm, followed by 10–40 iterations with the

TABLE I

FORCE FIELD FF300[a]

Bond deformations: $E_b = \sum_{\text{bonds}} \frac{1}{2}K_b(b - b_o)^2$

	K_b	b_o
C–C	3012	1.52
C–O	3611	1.42
C–H	3012	1.09
O–H	3372	0.97

Valence-angle deformations: $E_\theta = \sum_{\text{angles}} \frac{1}{2}K_\theta(\theta - \theta_o)^2$

	K_θ
C–C–C	602.1
C–C–O	602.1
C–C–H	391.2
C–O–C	602.1
C–O–H	337.2
O–C–O	602.1
O–C–H	391.2
H–C–H	313.0

Torsional deformations: $E_\phi = \sum_{\text{torsions}} \frac{1}{2}K_\phi(1 + \cos 3\phi)$

	K_ϕ
X–C–C–Y	0.02
X–O–C–Y	0.02

Non-bonded interactions: $E_{nb} = \sum_{i>j} \{A_{ij} \exp(-B_{ij} r_{ij}) - C_{ij}/r_{ij}^6\}$

	$A \times 10^{-4}$	B	C
C---C	98.74	4.32	1246.4
C---O	88.62	4.44	1020.5
C---H	13.13	4.20	505.4
O---O	77.99	4.55	836.8
O---H	11.74	4.32	415.5
H---H	2.76	4.08	205.4

[a]Units are such that energy is in kJ.mol^{-1}; distances are in Å; $\theta_o = 1.911$ rad. For torsions, X and Y may be C, O, and H.

modified Newton algorithm, depending on how far the conformation was from a minimum.

Conformational interchange. The modified Newton algorithm is designed to follow the bottom of a valley on the potential-energy surface, and this feature makes it suitable in a search for saddle points. It is thus possible to find relevant paths for the conformational interchanges between two minima.

RESULTS AND DISCUSSION

The minima. Using molecular models and chemical intuition, one can exclude

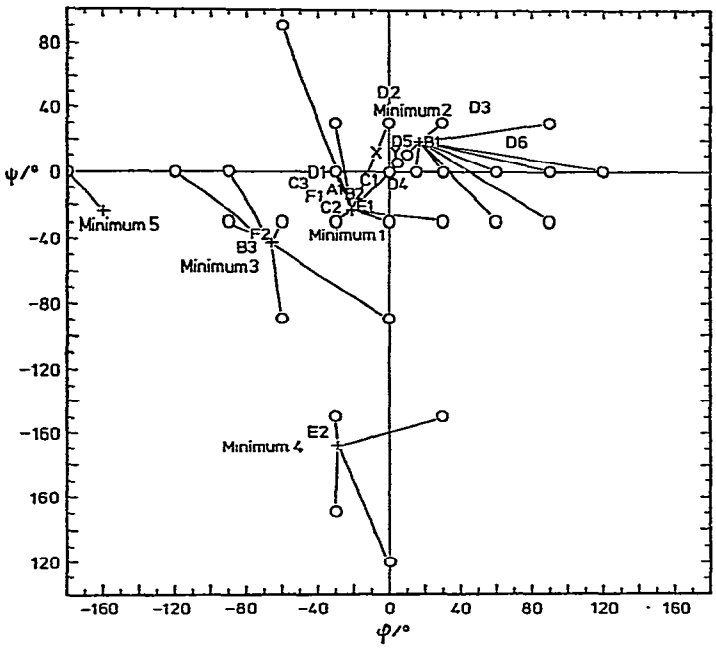

Fig. 2. Initial conformations (o) and final minima (+) of β-maltose on a φ,ψ-map. Results of Rao *et al.*[4] (A1), Blackwell *et al.*[5] (B1–B3), Giacomini *et al.*[6] (C1–C3), Saran and Govil[7] (D1–D6), Brant[8] (E1–E2), and Rees and Smith[9] (F1–F2). X-ray results of Chu and Jeffrey[10] (X) and Quigley *et al.*[11] (Y).

on the φ,ψ-map a great number of initial conformations as irrelevant, because of steric hindrance. In Fig. 2, all of the initial conformations are pictured on a φ,ψ-map. All 30 initial conformers are minimised to five different local minima which are listed in Table II. From these data, it is clear that the contributions to E_T from E_b and especially E_θ are not constant, which points out the importance of letting all degrees of freedom relax instead of keeping bond lengths and valence angles fixed.

The equilibrium conformation corresponding to minimum 5 is quite unrealistic and should be considered an artifact. The total potential-energy is very high due to strong bond-angle deformation and, from a steric point of view, it is almost impossible to reach minimum 5 from one of the others. In this connection, it should be mentioned that the value of K_θ for C–O–C is very important for the existence of minimum 5. If K_θ(C–O–C) is changed to 209.2 kJ.mol^{-1}.rad^{-2}, this minimum does not exist, and the conformer is minimised to minimum 3. No other change is seen. Therefore, it is relevant to speak of only four local minima for β-maltose. Evaluating statistical sums over the internal degrees of freedom[21], we find an equilibrium distribution based on differences in free enthalpy at 298 K of minimum 1 : minimum 2 : minimum 3 : minimum 4 = 59 : 19 : 15 : 7.

In this work, we have not attempted to find the global minimum, which would mean minimising a vast number of initial conformations differing only in one or

TABLE II

GLYCOSIDIC TORSIONAL AND VALENCE ANGLES, TOTAL ENERGY, AND ENERGY CONTRIBUTIONS FOR FIVE EQUILIBRIUM CONFORMERS OF β-MALTOSE; EXAMPLES OF THE MANIFOLDS OF MINIMA FOR EACH CONFORMER ARE SHOWN

	ϕ (deg.)	ψ (deg.)	C-1'–O-4–C-4 (degrees)	Energy (kJ.mol^{-1}) E_T	E_b	E_θ	E_ϕ	E_{nb}
Minimum 1	−21	−24	114.0	1.52	2.49	8.34	0.07	−9.38
	−23	−23	113.8	1.98	2.50	8.35	0.07	−8.94
	−21	−23	113.9	2.00	2.46	8.19	0.07	−8.72
	−23	−23	113.8	2.22	2.51	8.53	0.08	−8.90
	−20	−23	114.0	2.93	2.42	8.06	0.07	−7.62
Minimum 2	17	19	115.1	4.20	2.58	9.39	0.08	−7.85
	19	19	115.0	4.41	2.59	9.16	0.08	−7.42
	19	19	115.0	4.43	2.56	8.88	0.08	−7.09
	18	19	114.9	4.44	2.51	8.49	0.08	−6.64
	19	19	115.0	4.51	2.55	8.93	0.08	−7.05
	25	17	115.1	5.01	2.59	9.18	0.08	−6.84
	24	17	115.0	5.02	2.55	8.90	0.07	−6.50
	15	19	115.2	5.13	2.66	9.89	0.07	−7.49
Minimum 3	−66	−43	115.7	6.44	2.91	11.62	0.05	−8.14
	−66	−43	115.8	6.74	2.94	11.89	0.05	−8.14
	−66	−43	115.8	6.82	2.96	11.91	0.05	−8.10
	−69	−43	115.9	8.30	2.85	11.65	0.04	−6.24
Minimum 4	−29	−168	116.4	8.50	2.89	12.55	0.05	−6.99
	−32	−170	116.5	9.92	3.12	14.35	0.06	−7.61
	−32	−168	116.5	10.12	3.12	14.23	0.06	−7.29
Minimum 5	−160	−24	118.5	31.49	3.54	37.21	0.09	−9.35

two torsions around exocyclic C–O bonds. The main point for the subsequent applications is to find the skeletal minima.

In our previous work on glucopyranoses[1], we found that, with any local energy minimum, there is associated a manifold of minimum conformations corresponding to different values of exocyclic torsional angles. They lie close on the energy scale, characteristically within 2.5 kJ.mol^{-1}. An analogous statement applies to the four minima of β-maltose (see Table II). Here, we shall consider only different values of those torsional angles which determine the positions of the two -CH_2OH groups. In all of the conformers pictured in Fig. 2, the geometrical positions of the -CH_2OH groups correspond to C-4'–C-5'–C-6'–O-6' ~180° and C-4–C-5–C-6–O-6 ~60°, which is consistent with the crystal structures[10,11].

In Table III, some results concerning the three lowest minima are listed. From these data, it is evident that the orientations of the two -CH_2OH groups do not influence the total potential energy, except for minimum 3 where they are close to

TABLE III

INFLUENCE OF ORIENTATION OF THE $-CH_2OH$ GROUPS ON THE THREE LOWEST MINIMA OF β-MALTOSE

Initial		*Final*		*C-4'–C-5'–C-6'–O-6'*	*C-4–C-5–C-6–O-6*	E_T
ϕ *(degrees)*	ψ	ϕ *(degrees)*	ψ	*(degrees)*	*(degrees)*	*(kJ.mol^{-1})*
0	−30	−23	−23	−176	49	1.98
0	−30	−20	−23	−177	178	2.93
60	−30	17	19	−176	58	4.20
60	−30	18	19	−176	176	4.44
−60	−30	−66	−43	−175	63	6.44
−60	−30	−69	−43	63	−179	8.30

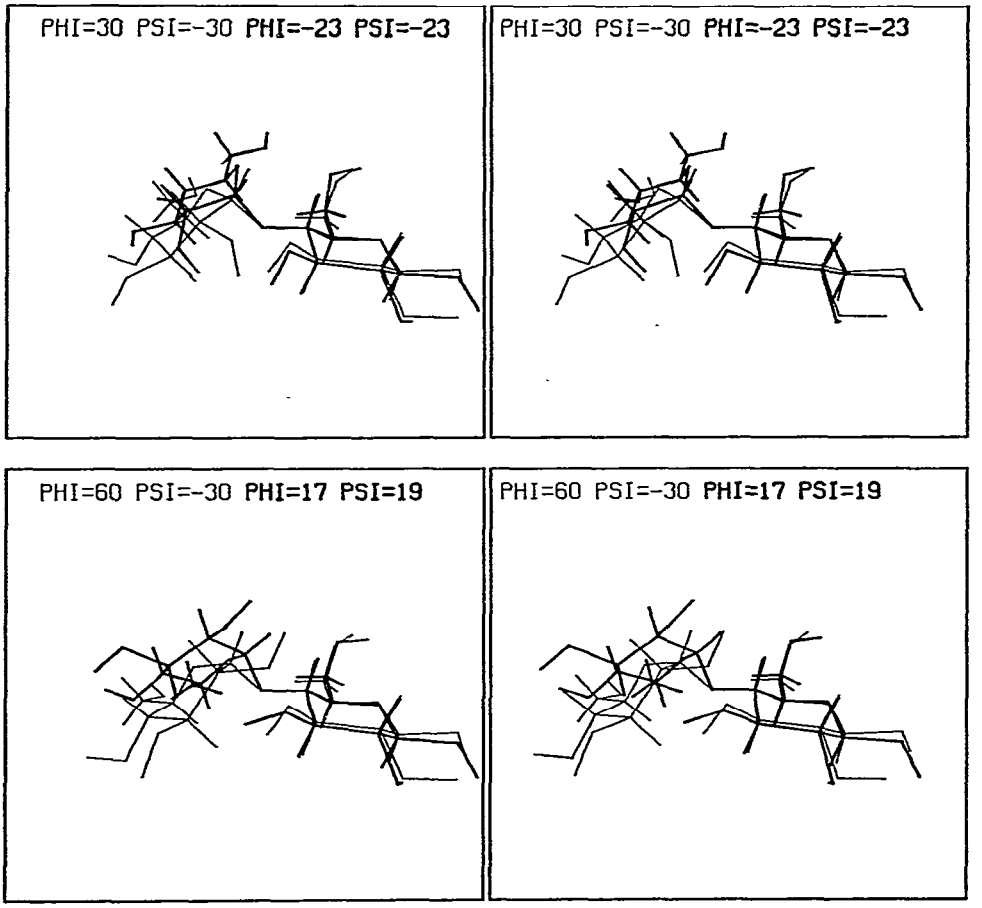

Fig. 3. Stereo-drawings of the two lowest minima of β-maltose. Initial (thin lines) and final (thick lines) conformations of minimum 1 (upper) and minimum 2 (lower).

each other in space. It is also seen that the "crystallographic positions" are to be preferred.

The ϕ,ψ-values are dependent on the exocyclic torsional angles (see Table III) of not only the CH_2OH groups but also the OH groups. From the calculations, there are examples where the ϕ,ψ-values of a specific local minimum may change by up to 5° due to different exocyclic torsional angles.

The stereo-drawings of β-maltose in Fig. 3 show two examples of minimisation. In both cases, the initial conformation is far from a minimum and it is seen that, during minimisation, not only ϕ and ψ, but all torsional angles, show changes.

Comparison with crystal-structure data. Although the crystal structure of β-maltose monohydrate is known[11] (R = 0.103), we have chosen the more-refined structure of methyl β-maltoside monohydrate[10] (R = 0.056) for comparison, because the methyl group introduced at O-1 does not effect any significant change in internal co-ordinates other than those involving O-1. Table IV shows a comparison of our results for minimum 1 with X-ray data from the crystal-structure determination of methyl β-maltoside monohydrate. Deviations (calculated minus measured values) of bond lengths and angles are shown, together with maximum, mean, and mean square-root deviations. These internal co-ordinates are reproduced very satisfactorily, as well as those we reported in previous work on α- and β-D-glucopyranose[1,2]. For endocyclic (containing only ring-atoms) and hybrid torsions (containing three ring-atoms and one side-atom), maximum and mean square-root deviations are listed; they are slightly larger than in our previous work. The deviations for the two exocyclic (containing two ring-atoms and two side-atoms) and the two intercyclic torsions (corresponding to ϕ and ψ) are also shown.

TABLE IV

DEVIATIONS OF CALCULATED FROM MEASURED[10] INTERNAL CO-ORDINATES FOR MINIMUM 1 OF β-MALTOSE

	Maximum	*Mean*	*Mean square-root*
Bond lengths (Å)	0.020	0.004	0.011
Valence angles (deg.)	−4.0	−0.1	1.7
Endocyclic torsions (deg.)	6.2		3.0
Hybrid torsions (deg.)	6.9		3.1
	$\lvert\phi_{calc} - \phi_{meas}\rvert$		
Exocyclic torsions (deg.)			
C-4–C-5–C-6–O-6	1.5		
C-4′–C-5′–C-6′–O-6′	6.0		
Intercyclic torsions (deg.)			
O-5′–C-1′–O-4–C-4	11.7		
C-3–C-4–O-4–C-1′	33.0		

Comparison with earlier calculations. In addition to our own results, Fig. 2 shows all equilibrium conformers found by mapping in a semi-empirical or empirical framework, as referred to in the Introduction. It is seen that all the empirical calculations taken together depict the same equilibrium conformers as those found in the present work, although one (or more) minimum is missed by each of the previous investigations. The PCILO and the extended Hückel methods suggest the existence of more minima around our minima 1 and 2 than are found by other methods. We consider the EHM results to be particularly misleading.

Path of conformational interchange. As mentioned previously, our modified Newton algorithm can be used to explore the potential-energy surface. In this way, we can find the way in which a conformational change between two equilibrium conformers may occur in the chosen force-field. Here, we shall be concerned with the path for conformational change between minima 1 and 2.

Fig. 4 shows a section of the ϕ,ψ-map in the region containing minimum 1 and minimum 2. Some exploratory calculations are performed on initial conformations produced in the same way as reported for Fig. 2; these show the paths along which the conformers were minimised. At selected points, the total energy and (in parentheses) the norm of its gradient are given. Also included in Fig. 4 are the relevant initial conformers of Fig. 2, shown by a circle and an arrow pointing in the direction of the

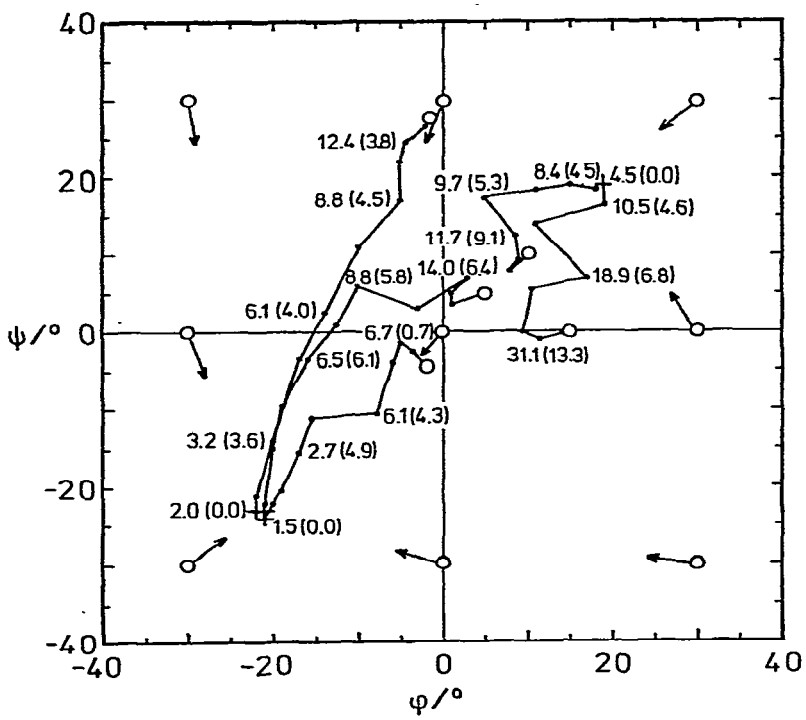

Fig. 4. ϕ,ψ-Map of β-maltose around minima 1 and 2. Total energy in kJ.mol^{-1}, and energy-gradient norm in kJ.mol^{-1}.Å^{-1} (in parentheses) of intermediate and final conformations.

actual minimum. From these calculations, it was evident that the path of interchange from minimum 1 to minimum 2 must resemble ϕ constant at $-20°$ and ψ changing from $-20°$ to $20°$, followed by ϕ changing from $-20°$ to $20°$ and ψ kept fixed at $20°$.

At this stage, we rotated the monomers of minimum 2 around ϕ and ψ, to get initial conformers in the ϕ,ψ-region where the saddle point was expected. The result is shown in Fig. 5. It seems as if the location of the minima is quite insensitive to the type of calculation and the chosen force-field. However, the form of the potential surface is very sensitive to the energy parameters, and therefore the height of the barrier between the two minima of Fig. 5 should only be taken as an approximation to the real barrier. With this reservation, the barrier height from minimum 1 to minimum 2 may be given as ~ 5 kJ.mol^{-1} and in the reverse direction as ~ 3 kJ.mol^{-1}.

Rates of conformational interchange. From the barriers, the rates of conformational interchange between minima 1 and 2, may be calculated, assuming an Arrhenius expression with a frequency factor corresponding to a glycosidic torsional frequency of the order of 100 cm^{-1}: $k_{12} = 100\ \text{cm}^{-1} \times (3 \times 10^8\ \text{cm.sec}^{-1}) \times \exp(-5000/8.3143/300) \approx 4$ GHz; $k_{21} \approx 9$ GHz. Such rates are fast on the n.m.r. time-scale, being of about the same order of magnitude as the molecular tumbling or, probably, even faster. Therefore, the conformations of β-maltose which can be derived from

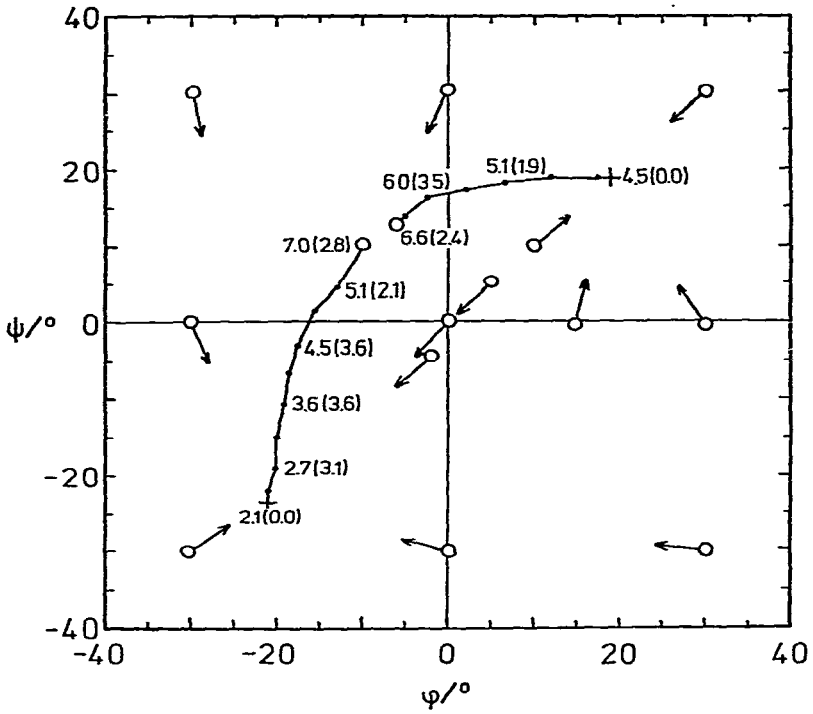

Fig. 5. ϕ,ψ-Map of β-maltose around minima 1 and 2. Path of conformational interchange.

n.m.r. experiments must be weighted averages of essentially four equilibrium conformations, modified by thermal vibrations.

Bock *et al.*[15] found the distance between H(C-1') and H(C-4) in C_6D_6 solution as 2.23 Å from ^1H T_1-measurements, and 2.28 Å from nuclear Overhauser enhancement, averaging 2.26 Å. Our calculations for β-maltose gave, for the same distance, 2.17, 2.15, 2.95, and 3.59 Å for minima 1, 2, 3, and 4. The weighted average, using the distribution calculated earlier, is 2.38 Å.

Rees and Thom[22] found that the optical rotation for maltose was strongly dependent on solvent and temperature, indicating the existence of different energy minima, and that the molecule was distributed within and between these minima. In aqueous solution, the optical rotation suggested that the molecule must spend a rather large part of its time around minimum 3. Vibrational spectra, on the other hand, would be superpositions of the spectra of the species present. Normal co-ordinate calculations[18c] showed that those spectra are very much alike, and a distinction would be impossible.

Material available. Internal and cartesian co-ordinates, and stereo-drawings, of all equilibrium conformers may be obtained from the authors.

CONCLUSION

We have shown that, given proper minimisation techniques and a reasonable force-field, it is possible to calculate realistic structures even for such flexible molecules as disaccharides. For β-maltose, there are four realistic minima on the ϕ,ψ-map which are surrounded by a manifold of minimum conformers differing only in exocyclic torsions. On comparison with other semi-empirical and empirical calculations, our study seems to include all minima previously found. The internal co-ordinates of the lowest minimum on the energy scale show a satisfactory agreement when compared with crystal-structure data.

We present a way of exploring the multidimensional energy-hypersurface, which enables intramolecular dynamics in a given force field to be predicted. In this work, the conformational interchange between minima 1 and 2 is studied, and the path on the ϕ,ψ-map is given together with approximate barrier-heights. It is very important that no internal co-ordinate is kept fixed during the interchange. If, for example, bond lengths and valence angles were fixed, this could introduce a very high and unpreferable, non-bonded, energy contribution around the transition-state conformation, because of very close interatomic distances, and thus cause a very high and unrealistic barrier-height. If, on the other hand, internal co-ordinates are allowed to change, small increases in bond lengths and valence angles will give rise to a slight increase in E_b and E_θ and avoid a larger increase in E_{nb}. All together, this entails a smaller value of E_T, lower barrier-heights, and higher conversion rates than would obtain with fixed bonds and angles.

In the crystal structure of cyclohexa-amylose hexahydrate[23], it is found that one of the six D-glucopyranosyl residues is rotated into a position nearly normal to

the ring axis. Optical rotation measurements in aqueous solution indicate the same distortion from hexagonal symmetry[22]. The suggestion of several energy minima for β-maltose does agree with such data for amylose and derivatives.

Considering the differences in internal geometry of various minima, it is questionable whether structures of oligo- and poly-saccharides should be constructed from a single set of monosaccharide co-ordinates, when the glycosidic linkages along the chain are not homoconformational. Our results on β-maltose do not contradict the scant experimental evidence available, and our methods therefore show some promise for future application to substituted saccharides and polymers.

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