Conformations of Disaccharides by Empirical Force-field Calculations: Part IV. β-Galactobiose

Kjeld Rasmussen

Chemistry Department A, The Technical University of Denmark, DK – 2800 Lyngby

Rasmussen, Kjeld. 1986. Conformations of Disaccharides by Empirical Force-field Calculations: Part IV. β-galactobiose. Acta Chem. Scand. A 40: 149–153.

Conformations of β-galactobiose are found by conformational energy minimisation in two well-documented potential energy functions, one of which includes modelling of hydrogen bonding. The most populated conformer in this function fits the active site of an anti-galactan immunoglubin.

In the previous papers[1-3] of this series, conformational properties of disaccharides of α- and β-D-glucopyranose were investigated. The third paper dealt with the very flexible β-gentiobiose, 6-O-β-D-glucopyranosyl-β-D-glucopyranose; further work on this was reported in a review paper[4]. In connection with studies of the binding of galactosides to anti-galactan[5,6] it was of interest to calculate plausible conformers of galactobiose.

Force fields. – Two force fields, or rather potential energy functions, were used: PEF300 and PEF400. They were both used in our previous studies, and their development and application are described[4,7,8,9] extensively.

Nomenclature. – In the following, galactobiose connotes 6-O-β-D-galactopyranosyl-β-D-galactopyranose.

The constitution is shown in Fig. 1; the three inter-ring torsional angles are defined as follows: φ, H(C1′)–C1′–O6–C6; ψ, C1′–O6–C6–C5; ω, H(C5)–C5–C6–O6.

Experimental studies. – No references to this particular disaccharide were found; a number of crystal structures of galactoses and galactosides have been solved[10-13].

Calculations

Program. – The Consistent Force Field system was used, in the version developed by Niketić and Rasmussen[14]. One of its main characteristics is that energy minimisation is performed using relaxation in all atomic coordinates, which is imperative to obtain meaningful equilibrium conformations[1-4].

Initial conformations. – 24 initial conformations were constructed by inverting the configuration at C4 and C4′ of the gentiobiose conformers[3].

Energy minimisation. – The same procedure as in our earlier work was followed: after up to 50 steepest descent iterations 10–20 modified Newton iterations would usually bring the conformation to an energy minimum with a scaled gradient norm less than 10^{-6} kJ mol^{-1} $Å^{-1}$.

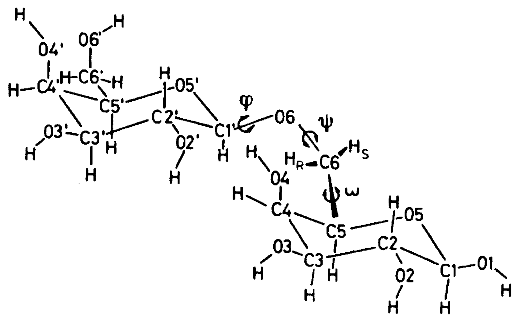

Fig. 1. Constitution and atom numbering of galactobiose (6–O–β-D-galactopyranosyl-β-D-galactopyranose).

Results and discussion

The minima. – The absolute and relative conformational energies and the inter-ring torsional and valence angles are shown in Tables 1 and 2, together with absolute and relative free enthalpies and Boltzmann distributions of all and of the more populated conformers. In both potential energy functions, two of the initial conformations minimised to the same. The spread in ΔE and ΔG is small, particularly when PEF300 is used.

From Fig. 2 it is seen that φ and ω cluster somewhat more in PEF300 than they do in PEF400, and that ψ does not cluster at all. This behaviour is analogous to that found for gentiobiose[3] and reflects that PEF300 follows a more conventional concept than PEF400 does[4]: the non-bonded interactions in PEF300 are modelled with traditional exp-6 functions[7,8] whereas Lennard-Jones functions overlayed by strong electrostatic interactions are used in PEF400[9].

There is no correlation between the positions of a conformer on the energy scales in the two potential energy functions. This is due to the fact that the particular non-bonded interaction between H and O is not given special significance in PEF300, whereas a modelling of the hydrogen bond is achieved in PEF400 through the electrostatic terms[4,9].

The distribution on conformers is much more even in PEF300 than in PEF400 which again reflects the extensive, probably exaggerated[4], intramolecular hydrogen bonding caused by PEF400 and not modelled at all by PEF300. An analogous difference was found for gentiobiose[3,4,15], though the predominance of just two conformers in PEF400 is not so pronounced as for galactobiose.

On the other hand, the geometric details of a conformer are rather similar in the two functions, with only a few exceptions: ω of no. 11; φ and ψ of nos. 13 and 14 (in PEF300 no. 13 is like no. 12 except for the torsion around one exocyclic C–O bond); φ of no. 21. In PEF400, nos. 18 and 19 coincide identically; in PEF300 they almost do, the difference being just one exocyclic torsion.

Table 1. Galactobiose in PEF300.

Conformer	E	ΔE	φ	ψ	ω	C5C6O6	C6O6C1′	G	ΔG	n_{23}	n_{12}	n_5
01	6.886	2.696	53	110	−175	111	114	889.254	3.763	0.022		
02	8.442	4.252	56	−132	−164	110	113	889.234	3.743	0.022		
03	10.691	6.501	162	132	−172	111	115	893-776	8.285	0.004		
04	8.519	4.329	170	−130	−174	111	115	889.461	3.970	0.020		
05	5.758	1.568	−1	2	−177	112	114	892.999	7.508	0.005		
06	8.547	4.357	−17	−161	−166	110	114	889.906	4.415	0.017		
07	5.838	1.648	46	128	51	110	113	889.618	4.127	0.019		
08	7.745	3.555	41	−91	65	111	113	887.155	1.664	0.051	0.065	
09	7.745											
10	8.262	4.072	160	148	59	110	115	890.343	4.852	0.014		
11	7.513	3.323	162	−96	−19	110	115	889.737	0.164	0.094	0.119	0.210
12	8.386	4.196	−12	103	55	110	114	889.799	0.226	0.092	0.116	0.205
13	8.982	4.792	−12	103	55	110	115	891.251	1.678	0.051	0.065	
14	4.190	0.000	54	134	58	110	113	887.325	1.834	0.048	0.061	
15	7.852	3.662	60	103	−43	110	113	887.213	1.722	0.050	0.063	
16	8.719	4.529	42	171	−51	109	113	885.876	0.385	0.086	0.109	0.192
17	5.863	1.673	17	−91	−47	110	114	887.721	2.230	0.041	0.052	
18	10.245	6.055	166	126	−54	109	115	887.574	2.083	0.043	0.055	
19	10.282	6.092	166	126	−54	109	115	888.567	3.076	0.029		
20	6.972	2.782	162	−96	−20	110	115	886.834	1.343	0.058	0.074	
21	5.964	1.774	26	66	−73	111	114	886.180	0.689	0.076	0.096	0.170
22	7.183	2.983	29	67	−68	111	114	891.684	6.193	0.008		
23	9.167	4.977	−12	−170	−52	109	113	885.491	0.000	0.100	0.127	0.224
24	9.084	4.894	−15	−161	−52	109	113	888.599	3.108	0.029		

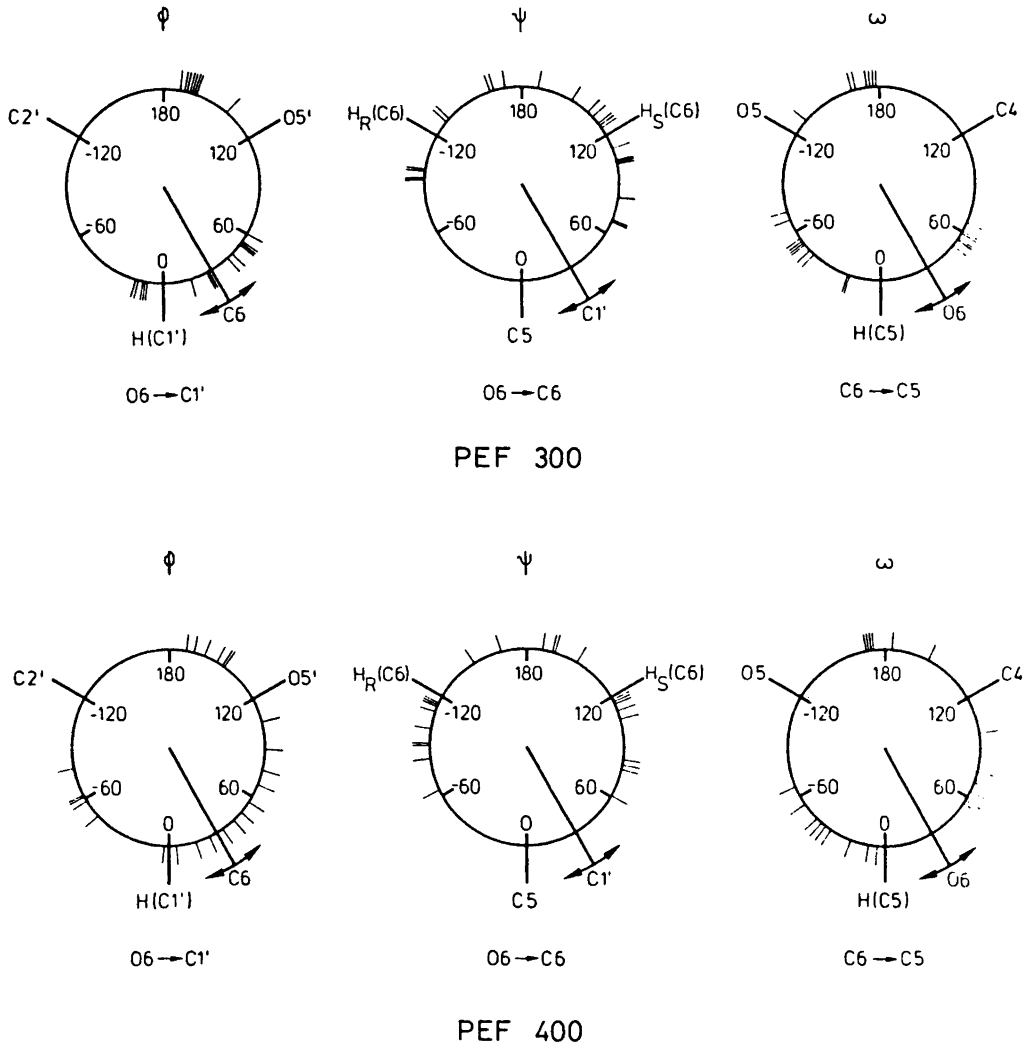

Fig. 2. Values of φ, ψ and ω for 23 local minima.

Conformer no. 4 in PEF400 was selected for modelling[6] the binding of galactan to immunoglobulin A J539. This conformer is shown in Fig. 3 in both potential energy functions. It is the most populated conformer in PEF400.

In the reducing galactose unit, the conformation around C5–C6 is *ga* (O6 *gauche* to 05, *anti* to C4) in conformer No. 4. The same conformation was found in β-D-galactose[10], methyl-β-D-galactopyranoside[11,12], and 2-deoxy-β-D-galactose[13].

Conclusion

For the two comparatively stiff disaccharides β-maltose[1,4] and β-cellobiose[2,4] it was possible to calculate all possible "main" conformers and to estimate the path of interconversion between two conformers. For the very flexible β-gentiobiose[3,4], many minima were found; with some confidence probably all those which will be of interest in modelling. For galactobiose this also seems to be

Table 2. Galactobiose in PEF400.

Conformer	E	ΔE	φ	ψ	ω	C5C6O6	C6O6C1′	G	ΔG	n_{23}	n_2
01	−382.732	12.747	67	106	153	113	115	534.601	10.416	0.007	
02	−351.530	43.949	56	−114	−170	111	115	557.480	33.291	0.000	
03	−360.642	34.837	171	117	176	111	118	554.590	30.405	0.000	
04	−390.125	5.354	159	−115	−173	112	117	524.185	0.000	0.492	0.642
05	−395.479	0.000	4	77	−168	114	118	525.636	1.451	0.274	0.358
06	−364.185	31.294	−61	170	−171	110	117	540.447	16.262	0.001	
07	−378.330	17.149	47	118	71	110	117	538.003	13.818	0.002	
08	−377.332	18.147	88	−64	64	113	116	533.770	9.585	0.010	
09	−358.968	36.511	42	−99	57	110	115	546.666	22.481	0.000	
10	−379.254	16.225	150	149	56	110	116	530.383	6.198	0.040	
11	−380.031	15.448	146	−82	99	112	116	531.172	6.987	0.029	
12	−376.782	18.697	15	111	77	110	121	540.590	16.405	0.001	
13	−344.481	50.998	−58	163	59	109	116	558.844	34.659	0.000	
14	−350.783	39.342	−51	−109	70	111	118	555.147	30.962	0.000	
15	−382.350	13.129	105	82	−11	111	116	530.320	6.135	0.041	
16	−370.354	25.125	76	−163	−41	109	114	532.966	8.781	0.014	
17	−384.040	11.439	24	−89	−55	110	116	529.477	5.292	0.058	
18	−375.312	20.167	165	116	−21	110	117	536.432	12.247	0.004	
19	−375.312										
20	−383.522	11.957	146	−90	−7	111	116	531.468	7.283	0.026	
21	−353.827	41.652	−78	78	−34	113	121	557.748	33.563	0.000	
22	−368.549	26.930	33	60	−66	113	116	548.617	24.432	0.000	
23	−356.607	38.872	−61	165	−46	108	116	549.994	25.809	0.000	
24	−352.549	42.930	−5	−147	−38	108	119	554.859	30.674	0.000	

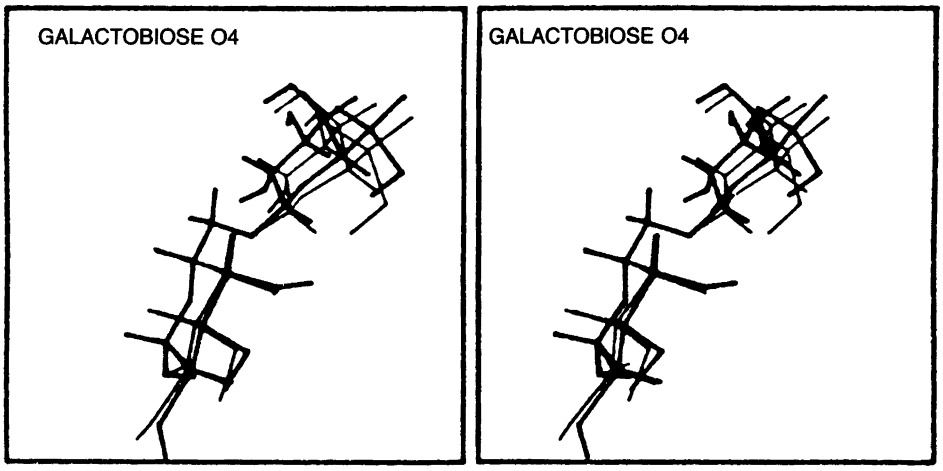

Fig. 3. Conformer no. 4; thin lines: PEF300; thick lines: PEF400.

the case. As pointed out above, two minima may differ in just an exocyclic torsion. This emphasizes again[7] that each "main" conformer, here represented by a set of (φ,ψ,ω), has a range of conformers differing widely in exocyclic torsions but only slightly in intercyclic torsions.

It is also demonstrated here that relaxation in all degrees of freedom is necessary in conformational calculations. This means that not only torsional, but certainly valence angles must also vary, and, though not so important in saccharides, bond lengths as well. Such an approach, though imperative, is often neglected even in contemporary work[16].

Supplementary material

Coordinates of all conformers found can be obtained on a tape, 600', 6250 bpi, NL, EBCDIC, card images, from RECKU, Vermundsgade 5, DK-2100 København Ø, telex 15069 recku dk. Ask for DANDOK-0003-85 and refer to this paper. The handling will cost Dkr 500.

References

1. Steen Melberg and Kjeld Rasmussen, *Carbohydr. Res., 69* (1979) 27–38.
2. Steen Melberg and Kjeld Rasmussen, *Carbohydr. Res., 71* (1979) 25–34.
3. Steen Melberg and Kjeld Rasmussen, *Carbohydr. Res., 78,* (1980) 215–224.
4. Kjeld Rasmussen, Disaccharide conformations: A step towards modelling Lipid A, Molecular Structure and Dynamics (M. Balaban, ed.), *Balaban, Jerusalem, 1980*, p. 171–210.
5. Y. Ittah and C. P. J. Glaudemans, *Carbohydr. Res., 95* (1981) 189–194.
6. Cornelis P. J. Glaudemans, Pavol Kovać and Kjeld Rasmussen, *Biochemistry, 23* (1984) 6732–6736.
7. Klavs Kildeby, Steen Melberg and Kjeld Rasmussen, *Acta Chem. Scand., A31* (1977) 1–13.
8. Steen Melberg and Kjeld Rasmussen, *Acta Chem. Scand., A32* (1978) 187–188.
9. Steen Melberg and Kjeld Rasmussen, *J. Mol. Struct., 57* (1979) 215–239.
10. B. Sheldrick, *Acta Crystallogr., B32* (1976) 1016–1020.
11. B. Sheldrick, *Acta Crystallogr., B33* (1977) 3003–3005.
12. S. Takagi and G. A. Jeffrey, *Acta Crystallogr., B34*(1978) 2006–2010.
13. R. Puliti, C. A. Mattia and G. Barone, *Carbohydr. Res., 95* (1981) 47–52.
14. Svetozar R. Niketić and Kjeld Rasmussen, The Consistent Force Field: A documentation, Lecture Notes in Chemistry 3, *Springer-Verlag,* 1977.
15. Kjeld Rasmussen, Potential Energy Functions in Conformational Analysis, Lecture Notes in Chemistry 37, *Springer-Verlag,* 1985, p. 54–58.
16. R. U. Lemieux and K. Bock, *Arch. Biochem. Biophys., 221* (1983) 125–134.

Received September 9th, 1985.