MOLECULAR STRUCTURE OF DERMATAN SULPHATE TETRASACCHARIDE

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INTRODUCTION

The knowledge of carbohydrate molecular structure is essential for understanding various processes in glycobiology. Dermatan sulphate (DS) belongs to the group of glycosaminoglycan (GAG) polysaccharides with biological importance [1]. DS is present in various tissues in higher organisms, e.g. in skin, blood vessels or lungs and plays important roles in various processes, namely intercellular and cell-matrix interactions, cell migrations and morphogenesis [2]. The investigation of DS solution properties and formation of their intermolecular complexes with proteins rely mainly on methods of theoretical chemistry as well as high-resolution NMR spectroscopy. In the present contribution, the results of calculations of molecular geometry of dermatan sulphate by density functional theory (DFT) are discussed and compared with experimental spectroscopic data.

METHODS

The structure of dermatan sulphate tetrasaccharide is shown in Fig. 1.

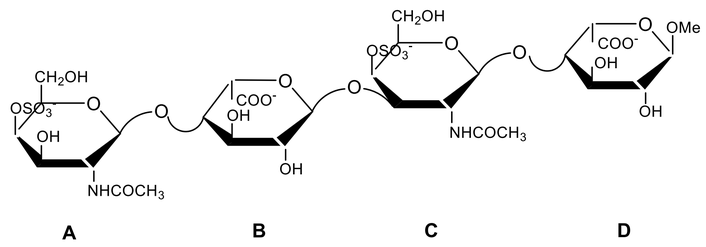

Fig 1. Scheme of dermatan sulphate tetrasaccharide.

In order to proper understanding the behaviour of dermatan sulfate in water environment, geometry optimisation of various forms of dermatan sulphate tetrasaccharides has been performed. Calculations were performed by Gaussian 16 software package [3] using density functional theory (DFT) method applying MN15 functional [4] and the 6-311++G(2d,2p) basis set. The cavity of 209 explicit water molecules has been used in order to mimic the hydration of studied dermatan sulphate molecules. The water cavity was optimised using molecular mechanics with UFF method [5].

RESULTS

The geometry optimization of three conformers ($^4C_1$, $^1C_4$ and $^2S_0$) are shown in Fig. 2-4. The data showed that the positions of sulphate groups at the pyranose rings significantly influenced the molecular structure of the investigated DS tetrasaccharide. The computed data also revealed that formation of a complex hydrogen bond network and strong ionic interactions influence the first hydration shell and plays important role in shaping the three-dimensional structure of DS tetrasaccharide. The energy differences are shown in Tab. 1. and selected geometry parameters are summarised in Tab. 2 and 3.

Table 1. DFT–computed (MN15/6–311++(2d,2p)) relative energies (left) and dihedral angles across glycosidic linkages (right) for three dermatan sulphate conformers.

Conformer	$^4C_1$	$^1C_4$	$^2S_0$
ΔE (kJ/mol)	13.1	0	9.7

Dihedral angle across glycosidic linkage (deg)	$^4C_1$	$^1C_4$	$^2S_0$
GalNAc (A)-IdoA (B) φ/ψ	52/44	-135/7	49/-15
IdoA-β (B)-GalNAc (C) φ/ψ	59/36	-59/-38	63/-12
GalNAc (C)-IdoA (D) φ/ψ	26/95	48/-13	47/2

Table 2. The selected proton-proton distances for three dermatan sulphate conformers obtained by geometry optimization using DFT method (MN15/6-311++G(2d,2p) in the presence of implicit solvent (Fig. 2-4). The values are compared with results published in [6] calculated by AMBER force field method. (N. c. = not calculated).

Conformer	$^4C_1$		$^1C_4$		$^2S_0$	
Method	DFT	MM/AMBER [6]	DFT	MM/AMBER [6]	DFT	MM/AMBER [6]
β-GalNAc						
A1-A3	3.13	n. c.	2.73	2.68	2.82	2.63
A1-A5	2.86	n. c.	2.12	2.40	2.77	2.42
A2-A4	3.66	n. c.	3.82	3.83	3.75	3.81
A3-A4	2.55	n. c.	2.36	2.45	2.52	2.49
β-IdoA						
B1-B2	3.00	n. c.	2.60	2.54	3.03	3.09
B2-B5	3.54	n. c.	3.75	4.04	2.45	2.39
B3-B4	2.99	n. c.	2.67	2.57	3.04	3.08
B4-B5	2.24	n. c.	2.27	2.50	2.36	2.37
β-red-GalNAc						
C1-C3	2.33	n. c.	2.53	2.53	2.39	2.53
C1-C5	2.14	n. c.	2.49	2.40	2.17	2.42
C3-C4	2.41	n. c.	2.53	2.45	2.53	2.46
C3-C5	2.25	n. c.	2.38	2.50	2.58	2.40

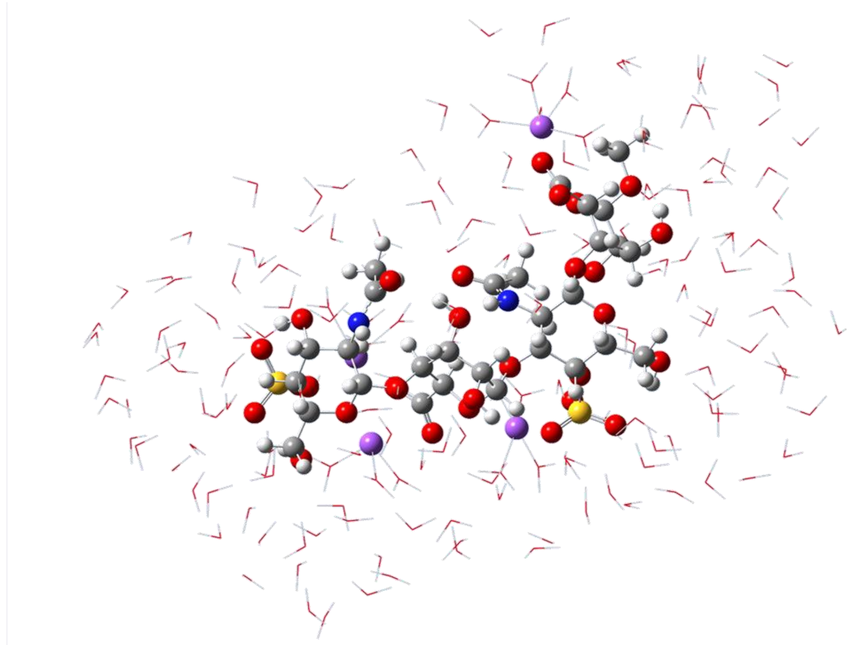

Figure 2. The optimised geometry of conformer $^4C_1$.

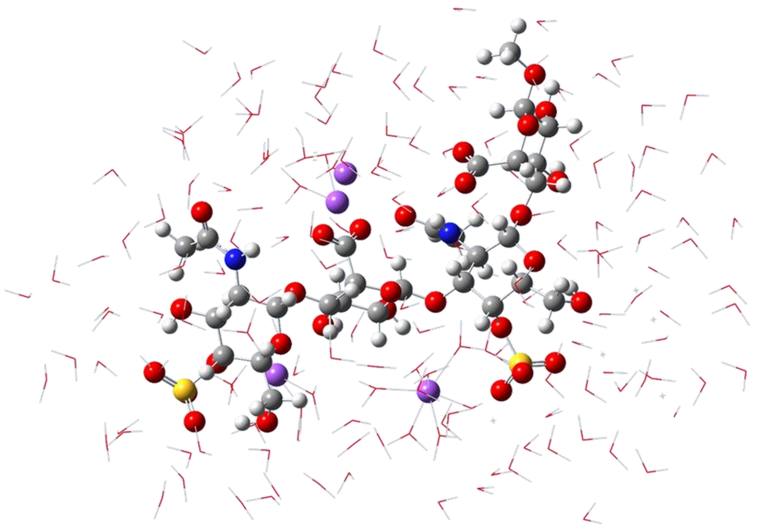

Figure 3. The optimised geometry of conformer $^1C_4$.

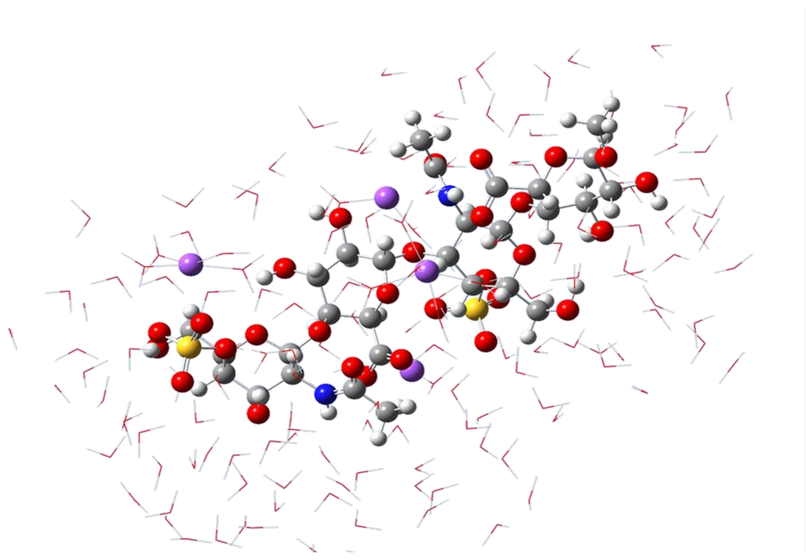

Figure 4. The optimised geometry of conformer $^2S_0$.

CONCLUSIONS

In summary, DFT calculations provided detailed analysis of molecular structures of the dermatan sulphate tetrasaccharide in aqueous solution. As each form ($^1C_4$, $^4C_1$ or $^2S_0$) had a unique hydrogen bond configuration, interconversion among these forms was accompanied by breaking and forming new inter-residue hydrogen bonds. This was illustrated by energy differences explaining the stability of each conformer. Additionally, DFT–computed geometries indicated a several differences in bond lengths, angles and dihedral angles among intra-ring atoms or at the glycosidic linkages, obtained by DFT method compared to the published results using the AMBER method.

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