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NMR AND DFT STUDY OF CHONDROITIN SULPHATE

Michal Hricovíni*[1] and Miloš Hricovíni[1]

[1]Institute of Chemistry, Slovak Academy of Sciences, SK-845 38, Bratislava, Slovakia, chemmike@savba.sk

INTRODUCTION

Chondroitin sulphate is a sulphated glycosaminoglycan (GAG), abundantly present in connective tissues, particularly articular cartilage. There, it plays a critical role in maintaining structural integrity and elasticity. As a key component of the extracellular matrix, it is involved in various biological processes, including cellular signalling pathways, tissue hydration, and matrix organisation [1,2]. Furthermore, the therapeutic potential of chondroitin sulphate as an agent in joint-related disorders such as osteoarthritis has been studied due to its anti-inflammatory and cartilage-protective properties [3,4]. The therapeutic potential of chondroitin sulphate lies in its ability to reduce cartilage catabolism by inhibiting extracellular matrix degradation [5].

METHOD

The combination of NMR spectroscopy and density functional theory (DFT) provides valuable insights into the structure, dynamics, and solubility of glycosaminoglycans [6].

The geometry optimisation of the GAG has been performed by Gaussian 16 using the MN15/6-311++G(2d,2p)//SMD approach to determine the 3D structures of chondroitin 4-sulphate and chondroitin 6-sulphate tetrasaccharides. The proton-proton coupling constants were calculated using DFT method utilising MN15 functional and DGTZVP basis set. The investigated structures of GAG tetrasaccharides are shown in Fig. 1.

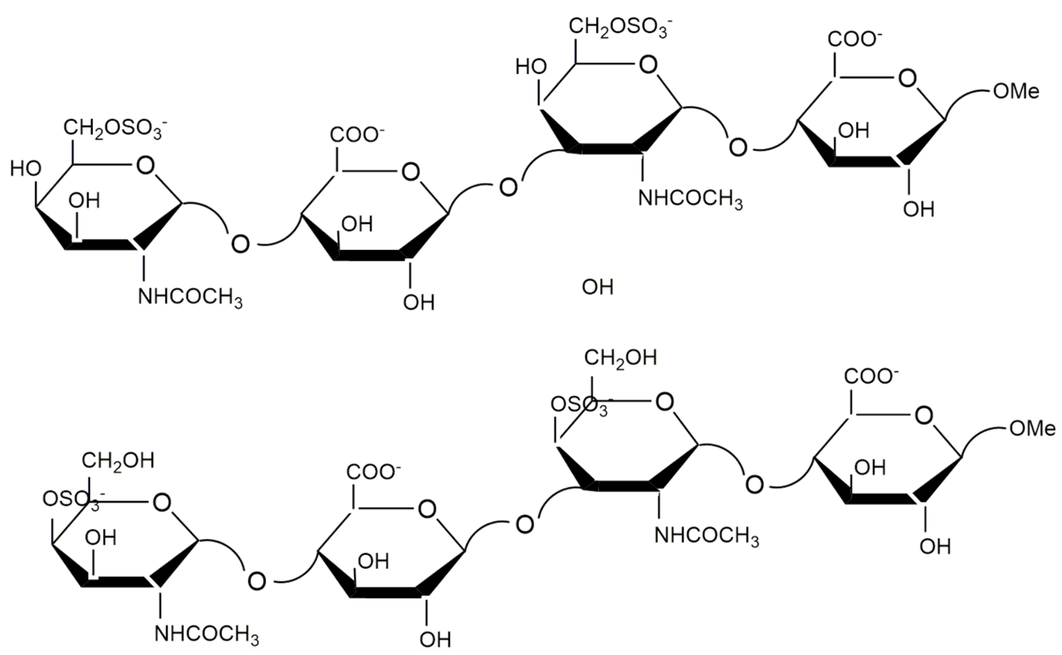

Fig 1. Scheme of studied chondroitin 4-sulphate and chondroitin 6-sulphate tetrasaccharides.

RESULTS AND DISCUSSION

The selected computed torsion angles for chondroitin 4s and 6s are listed in Tab. 1. Furthermore, the DFT-computed one-bond proton-carbon coupling constants were also calculated from fully optimised geometry and are summarised in Tab. 2.

Table 1. The dihedral angles of chondroitin 4s and 6s across glycosidic linkages obtained by geometry optimization using DFT method (MN15/6-311++G(2d,2p) using the implicit SMD solvent model (Fig. 2 and 3).

Dihedral angles / deg		ϕ_1	ψ_1	ϕ_2	ψ_2	ϕ_3	ψ_3
$^4C_1$	4s	53.5	85.5	-146.2	47.8	46.8	-179.9
	6s	167.1	33.6	37.2	60.6	50.9	-168.8

Table 2. The selected computed one-bond proton-carbon coupling constants for chondroitin 4s and 6s obtained by DFT method using MN15/DGTZVP approach.

$^nJ_{C\text{-}H}$ / Hz		$^1J_{C1H1}$ (Gal_{NR})	$^1J_{C4\text{-}H4}$ (Gal_{NR})	$^1J_{C1\text{-}H1}$ (Glc_{NR})	$^1J_{C5\text{-}H5}$ (Glc_{NR})	$^1J_{C1\text{-}H1}$ (Gal_R)	$^1J_{C4\text{-}H4}$ (Gal_R)	$^1J_{C1\text{-}H1}$ (Glc_R)	$^1J_{C5\text{-}H5}$ (Glc_R)
$^4C_1$	4s	176.5	173.4	179.2	161.9	174.7	178.6	181.9	162.3
	6s	179.9	164.4	178.4	162.7	178.4	169.6	182.7	155.1

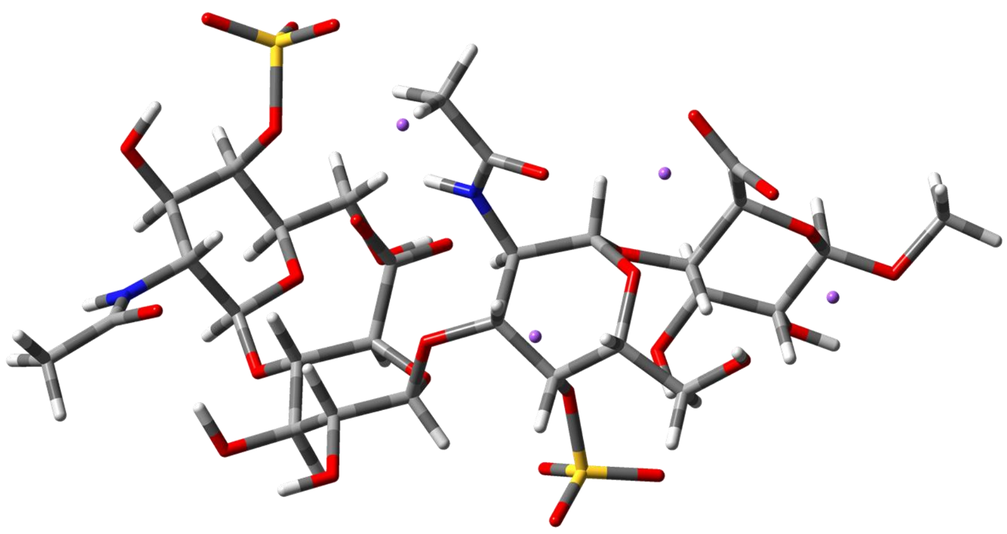

Fig 2. The optimised geometry of chondroitin 4-sulphate.

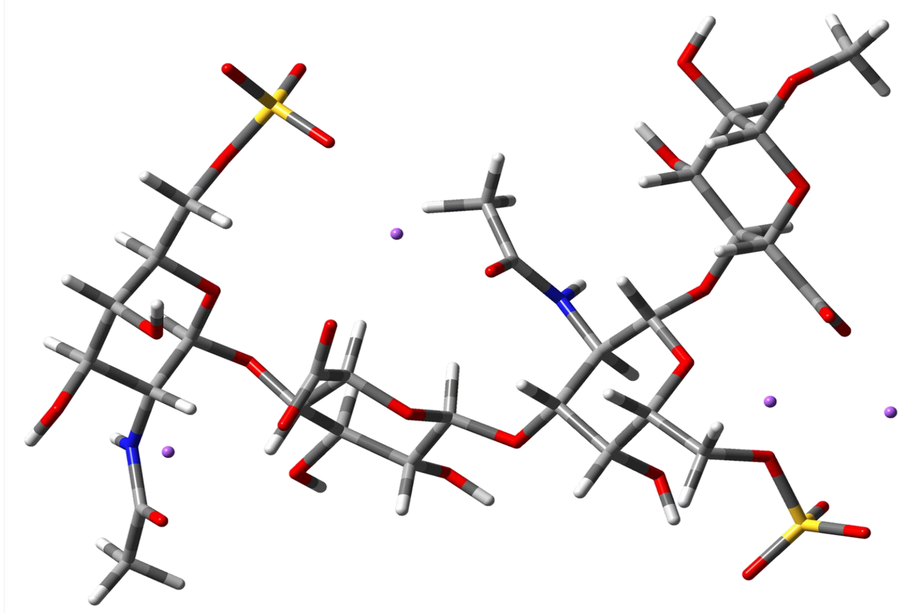

Fig 3. The optimised geometry of chondroitin 6-sulphate.

CONCLUSION

Computed proton–proton and proton–carbon coupling constants revealed that the one-bond proton–carbon coupling constants ($^1J_{C\text{-}H}$) depend strongly on the substitution position (C-6 vs. C-4). However, substitution also affects the $^1J_{C\text{-}H}$ and $^3J_{C\text{-}H}$ magnitudes in the neighbouring atoms. The $^1J_{C\text{-}H}$ values were consistent with the experimental NMR values. The $^3J_{C\text{-}H}$ values also revealed differences in the glycosidic linkage conformations in chondroitin tetra-saccharides. These findings demonstrate that the position of sulphate groups on the chondroitin backbone significantly affects electronic distribution, geometry, and $^nJ_{C\text{-}H}$ magnitudes, thereby highlighting the role of hydrogen bonding and ionic interactions in the 3D structure of chondroitin tetrasaccharides.

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