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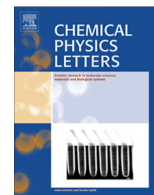

How acidic are monomeric structural units of heparin?

Milan Remko [a,b,*], Ria Broer [c], Piet Th. Van Duijnen [c]

[a] Department of Pharmaceutical Chemistry, Comenius University in Bratislava, Odbojarov 10, 832 32 Bratislava, Slovakia
[b] Center for Hemostasis and Thrombosis, Hemo Medika Bratislava, 851 04 Bratislava, Slovakia
[c] Department of Theoretical Chemistry, Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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ABSTRACT

Density functional theory methods with the B3LYP functional have been used to letter the acidity of carboxyl, *O*-sulfo and *N*-sulfo groups in six basic monomeric structural units of heparin (1-OMe ΔUA-2S, 1-OMe GlcN-S6S, 1,4-DiOMe GlcA, 1,4-DiOMe GlcN-S3S6S, 1,4-DiOMe IdoA-2S, and 1,4-DiOMe GlcN-S6S). The predicted gas-phase acidity of the acidic functional groups in the monomeric structural units of heparin is: *O*-sulfo > *N*-sulfo > carboxyl. The computed pK_a values provide the same order of acidity as was observed in water solution. This implies that hydration does not change ordering of acidity of major acidic groups of monomeric structural units of heparin.

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1. Introduction

Heparin is a linear polysaccharide macromolecule containing of variable proportion of disaccharide sequences consisting of either uronic acid or glucuronic acid and glucosamine residues. Few hydroxyl groups on each of these monosaccharide residues may be sulfated giving rise to a polymer that is highly negatively charged. The average negative charge of individual saccharide residues is about 2.3 [1,2]. This complex organic acid, that is found especially in lung and intestinal tissue, has a mucopolysaccharide as its active constituent, prevents blood clotting, and is used in the form of its sodium salt in the treatment of thrombosis and in heart surgery [3,4]. The heparin polysaccharide chain is not orally bioavailable and must therefore be administered intravenously or subcutaneously (it is not degraded in stomach acid). Its antithrombotic activity is explained by its ability to potentiate the activity of the serine protease inhibitor antithrombin (AT), which inactivates a number of serine proteases (such as thrombin and factor Xa) in the coagulation cascade [1,5]. It was found that a unique pentasaccharide fragment constitutes the minimal binding domain for AT [6,7]. It contains *O*-sulfo, *N*-sulfo groups and carboxyl moieties, which are in the antithrombin–pentasaccharide complex completely ionized and interact with the complementary (Arg, Lys, Glu and Asn) side chains on the protein [7–12]. It was shown experimentally, that Arg and Lys residues of proteins are clearly in position to have hydrogen bond interaction with the negatively charged sulfo and carboxyl groups of heparin pentasaccharide [8,13–17]. The bulk of these hydrogen bonds are sulfo group-mediated interactions. Therefore, determination of important physicochemical properties such as acidity of sulfo and carboxyl groups of heparin can provide more insights into the nature of the protein–heparin interactions. With regards to experimental studies, the pK_a values of carboxyl moieties of heparin-derived glycosaminoglycans have been determined using nuclear magnetic resonance spectroscopy [18–20]. Experimental gas-phase acidities have not been reported so far for basic monomeric structural units of heparin.

In this Letter we have used large-scale theoretical calculations for the determination of the gas-phase acidities and pK_a values for *O*-sulfo, *N*-sulfo and carboxyl functional groups of six monomeric structural units of heparin: 1-OMe ΔUA-2S (**1**), 1-OMe GlcN-S6S (**2**), 1,4-DiOMe GlcA (**3**), 1,4-DiOMe GlcN-S3S6S (**4**), 1,4-DiOMe IdoA-2S (**5**), and 1,4-DiOMe GlcN-S6S (**6**) (Figure 1: GlcN is glucosamine, IdoA is iduronic acid, GlcA is glucuronic acid, S is sulfo, and Me is methyl). The results of this letter are analyzed and compared with the available experimental data for structurally related systems. They are also discussed in the context of the present theories of action of these glycosaminoglycans.

2. Computational details

The geometry of the six monomeric structural units of heparin (1-OMe ΔUA-2S (**1**), 1-OMe GlcN-S6S (**2**), 1,4-DiOMe GlcA (**3**), 1,4-DiOMe GlcN-S3S6S (**4**), 1,4-DiOMe IdoA-2S (**5**), and 1,4-DiOMe GlcN-S6S (**6**)), respectively and their anionic forms (Figure 1) has been completely optimized with the GAUSSIAN 09 program system [21], using density functional theory [22–24], employing the B3LYP/6-311++G(d,p) method [25–27]. Calculations of gas-phase acidities of model acids $CH_3–NH–SO_3H$ and $CH_3–O–SO_3H$ were also carried out by means of the more accurate CBS-QB3 approach [28]. The CBS-QB3 method uses B3LYP coupled to the CBSB7 defined basis set for all geometry optimizations and frequency calculations.

* Corresponding author at: Department of Pharmaceutical Chemistry, Comenius University in Bratislava, Odbojarov 10, 832 32 Bratislava, Slovakia.
E-mail address: remko@fpharm.uniba.sk (M. Remko).

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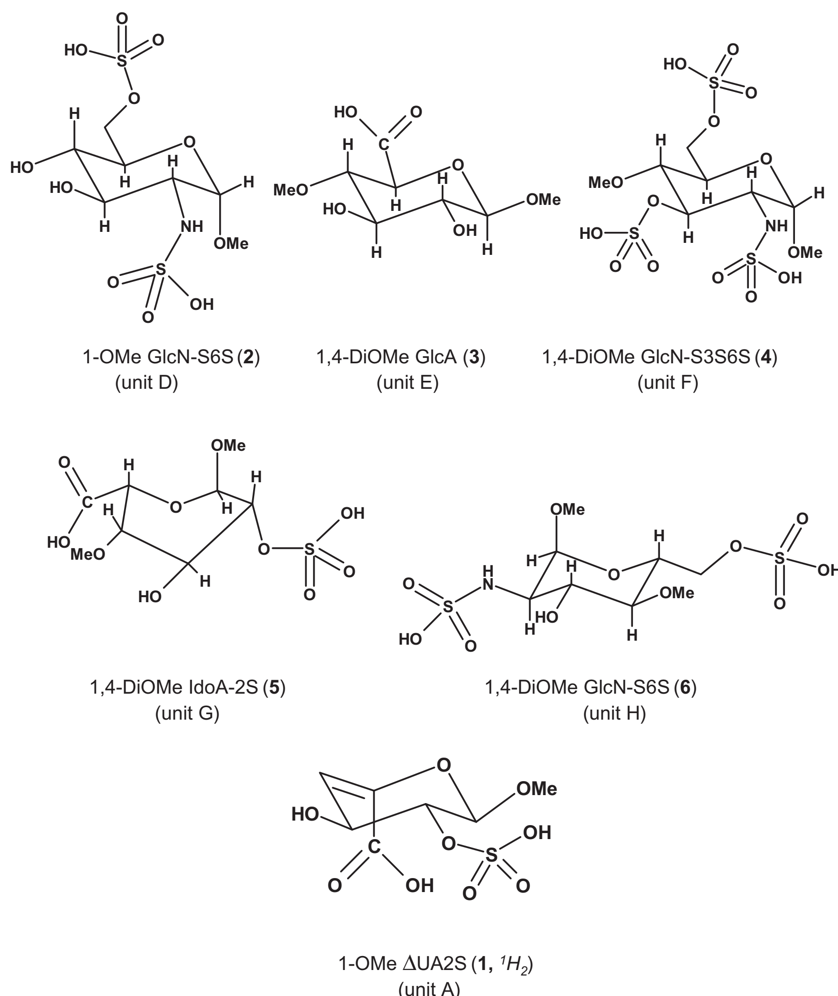

Figure 1. Structure of the acids studied.

The gas-phase acidity ΔE(A) was defined as the energy of deprotonation ΔE for reaction (A):

$$\mathrm{AH(g)} \rightarrow \mathrm{A^-(g)} + \mathrm{H^+(g)} \tag{A}$$

The enthalpy of deprotonation, ΔH^{298}, was computed using Eqs. (1) and (2):

$$\Delta H^{298}(\mathrm{A}) = \Delta E^{298}(\mathrm{A}) + \Delta(pV) \tag{1}$$

$$\Delta E^{298} = [E^{298}(\mathrm{A^-}) + 3/2\ RT] - E^{298}(\mathrm{AH}) \tag{2}$$

where E^{298} stands for the total energies of the stable conformations of the acids and their anions (including the thermal energy correction at T = 298.15 K). In Eq. (1) we substituted $\Delta(pV) = RT$ (1 mol of gas is obtained in the reaction (A)). The gas-phase Gibbs energy, ΔG^{298}, of the proton abstraction reaction may be calculated from:

$$\Delta G^{298} = \Delta H^{298} - T\Delta S^{298} \tag{3}$$

The enthalpy of deprotonation was calculated using expression (1). The entropy contribution is given by:

$$-T\Delta S^{298} = -T[S(\mathrm{A^-}) + S(\mathrm{H^+}) - S(\mathrm{AH})] \tag{4}$$

For T = 298 K at the standard pressure, the second term $TS(\mathrm{H^+})$ = 32.5 kJ mol^{-1} [29]. Thus:

$$\Delta G^{298} = \Delta H^{298} - T[S(\mathrm{A^-}) - S(\mathrm{AH})] - 32.5 \tag{5}$$

Notice that there is an inverse relationship between the magnitude of ΔG and the strength of the acid. The more positive the value of the ΔG, the weaker the acid. The calculations of the macroscopic pK_a of the studied species were performed using the program SPARC developed by Carreira et al. [30–32]. The computer program SPARC uses computational algorithms based on fundamental chemical structure theory to estimate a variety of chemical reactivity parameters (such as ionization pK_a, kinetics, heat of vaporization, boiling point, diffusion coefficient, etc.). SPARC costs the user only a few minutes of computer time and provides greater accuracy than is possible with other conventional methods [33].

3. Results and discussion

3.1. Geometry

Although heparin is structurally often described in terms of its disaccharide structural units [1,2], the main monosaccharide 'building blocks' of this polymer were identified using current experimental methods [1,34]. It was shown [34,35] that degradation of heparin by heparinase produces at the non-reducing end a terminal uronate with an unsaturated 4,5 carbon bond (structure 1-OMe ΔUA-2S (**1**), Figure 1), which may exist in two different forms $^2H_1$ and $^1H_2$, respectively. According to the NMR solution conformation investigations the uronate (A) residue is

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