Carbohydrate Polymers 78 (2009) 10–15

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Structure and conformation of α-, β- and γ-cyclodextrin in solution: Theoretical approaches and experimental validation

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ARTICLE INFO

Article history:
Received 9 August 2008
Accepted 18 February 2009
Available online 3 March 2009

Keywords:
^{13}C NMR chemical shift surface
Anomeric carbon
GIAO
Glycosidic bond
Cyclodextrin
ONIOM methods

ABSTRACT

The anomeric carbon chemical shifts of α-, β- and γ-cyclodextrin in solution were studied experimentally and theoretically by NMR and two-layer ONIOM2 (B3LYP/6-31G*-GIAO: HF/6-31G*-GIAO) variant. The dependence between the anomeric carbon chemical shift and the glycosidic bond φ and ψ dihedral angles in D-Glcp-D-Glcp disaccharides with and (1 → 4) linkages in α-configurations were computed by Gauge-Including Atomic Orbital (GIAO) ab initio and ONIOM in water solvent using PCM methods. Complete chemical shift surfaces versus φ and ψ for this disaccharide were computed. We also present empirical formulas of the form $^{13}C\ \delta = f(\varphi,\psi)$ obtained by fitting the ab initio data to trigonometric series expansions. The results are consistent with experimental observations and show the applicability of chemical shift surfaces in the conformational behavior of oligosaccharides.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides built up from α-D-glucopyranose units connected with a α-1,4 glycosidic linkage. The CD molecule comprise 6 glucopyranose units, while β- and γ-CD comprise 7 and 8 units, respectively, arranged in a ring-shape manner and presenting a conical shape, Fig. 1. They have ability to form hydrogen bonds with the surrounding water molecules or intermolecular ones (Hesek, Hembury, Drew, Borovkov, & Inoue, 2001) and inclusion complexes with a large variety of organic and inorganic guests (Prabaharan & Mano, 2006; Uekama, 2002).

One of the most remarkable applications of CDs is its use as drug carriers in controlled release systems. For example as drug carriers, β-CD allows the solubilization, stabilization, and transport of hydrophobic drugs together with several pharmacological benefits such as the reduction of unwanted side effects (Hedges, 1998; Uekama, Hirayama, & Irie, 1998). During the complex formation with drug molecules, no covalent bonds exist between the CD and its guest, thus complexation can be considered as a dynamic process. The drug molecules included within the CD cavity therefore may be dissociated upon dilution, displaced by a more suitable guest, or transferred to a matrix for which it has a higher affinity, such as a biological membrane (Loftsson & Brewster, 1996). Therefor reveal the structural details of cyclodextrin could be so benefit.

Between different methods to study of carbohydrate especially oligosaccharide conformation, theoretical calculation of NMR properties, in combination with NMR experimental data, can produce lots of information about the structure details of such molecules (Adeyeye et al., 2003; Brien & Moyana, 2004; Wormald et al., 2002). In most of these approaches, estimation of internuclear distances between oligosaccharide proton pairs is obtained using 1D or 2D nuclear Overhausser enhancement (NOE) experiments, and structural information is derived from homo and hetero nuclear vicinal (^3J) and geminal (^2J) coupling constants.

Carbohydrate ^{13}C chemical shifts have been employed as another valuable source of structural information that could be used instead of NOE and *J*-coupling data. In particular, the anomeric carbon chemical shift is depended on the glycosidic bond; φ and ψ dihedral angles (Jarvis, 1994).

There are many uses for applying computational chemistry to the study of CD, especially in the structural characterization of host–guest complexes by ab initio (Dobado & Benkadour, 2004) molecular mechanics (MM) (Momany & Willett, 2000) molecular dynamics (MD) (Choi, Yang, Kim, & Jung, 2000), and semiempirical methods (PM3, MNDO AM1, etc.), (Lipkowitz, 1998). To our knowledge, due to the size of these systems quantum-mechanical calculations consist of DFT and ONIOM (Svensson et al., 1996) methods on CDs including solvent effect have not been reported. Thus, the aim of the present work is to evaluate the applicability of these computational approaches in characterizing the structural details and predicting the NMR chemical shifts in α-, β- and γ-CDs by comparison with experimental data.

As pointed out in a recent review by Imberty and Pérez (2000) the conformational dependence of chemical shifts in oligosaccharides has been poorly understood. Since in this report we examined

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doi:10.1016/j.carbpol.2009.02.020

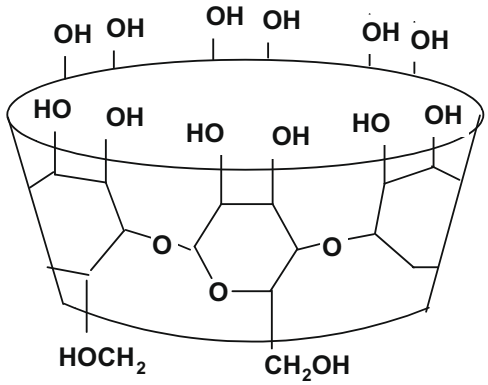

Fig. 1. Structures of the cyclomaltooligosaccharides α-CD ($n = 6$), β-CD ($n = 7$) and (c): γ-CD ($n = 8$).

applicability of ^{13}C chemical shift to study the carbohydrate conformation, using the surface corresponding to the D-Glcp α (1 → 4) linkage with α-, β- and γ-cyclodextrin as model systems. The results show that ^{13}C data obtained from theoretical chemical shift surfaces reproduce experimental observation in solution and serve as a useful model.

Therefore we present structural (geometries) and spectroscopic (NMR chemical shifts) characterizations for a series of modified α-, β- and γ-cyclodextrin, that can help synthetic chemists in assigning of the NMR spectra of the CD derivatives and inclusion complexes.

2. NMR measurements

^{1}H NMR, ^{13}C NMR, COSY, HMQC and HMBC of α-, β- and γ-CD were obtained at 298 K in D_2O (99.99% D) on a Bruker DRX500 operating at 500.133 MHz for ^{1}H and 125.770 MHz for ^{13}C, using 5 mm broad band inverse probe with sufficient digital resolution. Sodium 4,4-dimethyl-4-silia-[2H4] pentanoate was used as internal standard. ^{1}H NMR and ^{13}C NMR spectra were acquired using a spectral width of 3255 and 22,123 Hz, respectively, and a 90° pulse (10.3 μs). All 2D NMR spectra were acquired by pulsed field gradient-selected methods. 2D correlation spectroscopy (COSY) was used to confirm ^{1}H assignments. Heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) were used for ^{13}C assignments, Fig. 2. HMQC and

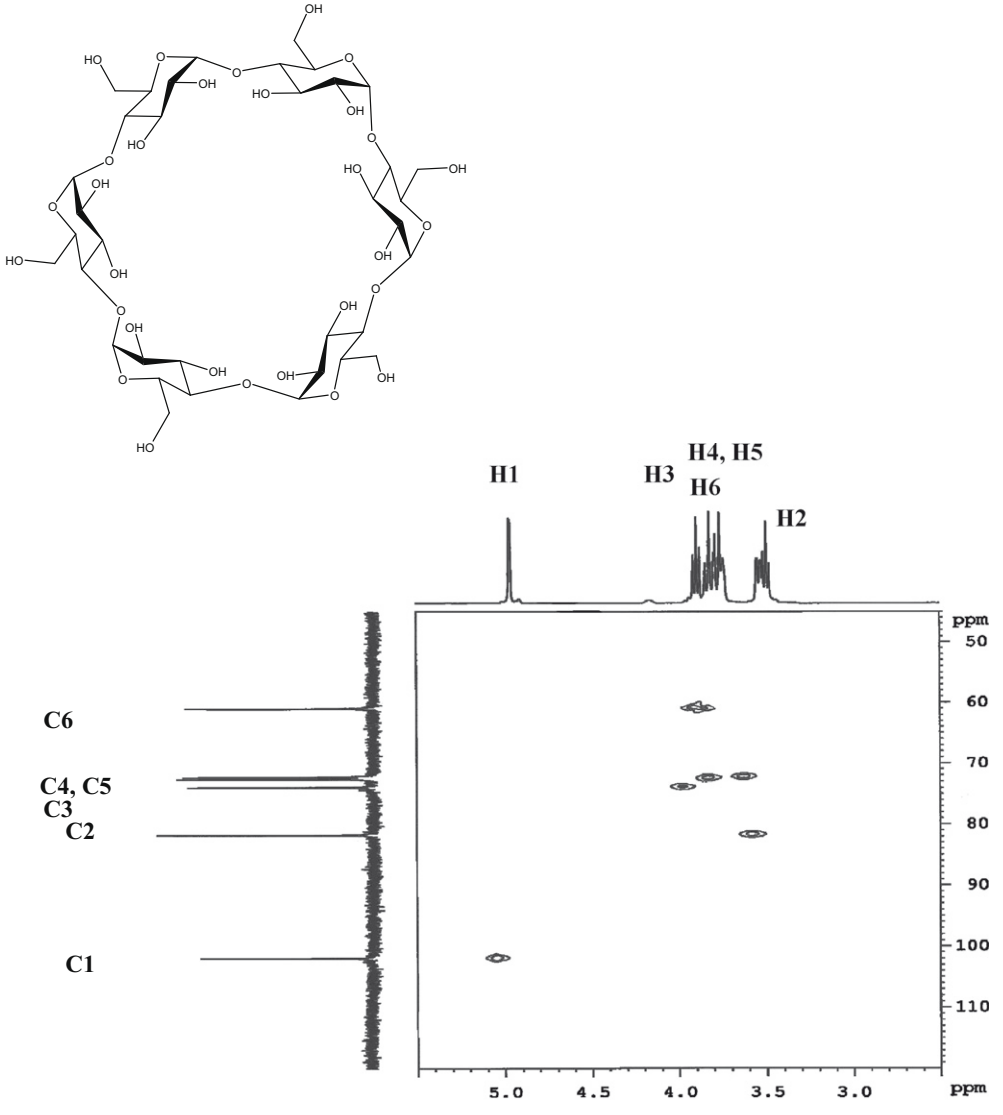

Fig. 2. HMQC spectrum of α-cyclodextrin.