

## TECHNICAL NOTE

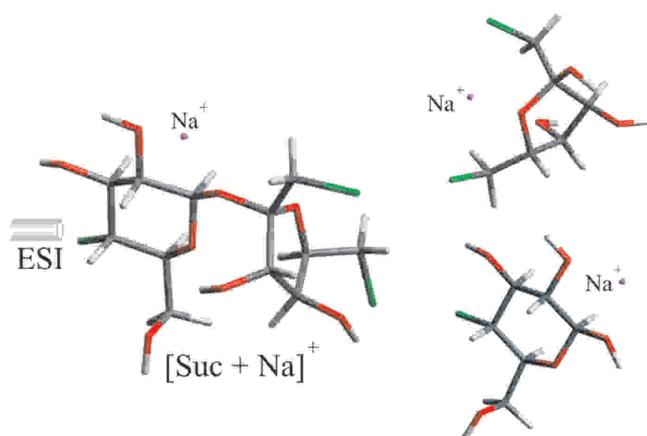
# How Sodiation Influences the Sucralose Behavior under Electrospray Ionization Mass Spectrometry

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Nowadays, the detection of sucralose sodium adduct under electrospray ionization in mass spectrometry analysis is a common analysis method, but its high chemical stability is not fully understood. In this work, we use quantum chemistry calculations and mass spectrometry data to understand why sodiated sucralose presents this behavior in mass spectrometry conditions. The potential energy and the position of sodium ions were evaluated using different basis sets in order to comprehend the importance of sodiation in sucralose properties. Quantum-chemical calculations show higher reliability to

explain the behavior of sucralose sodium adduct under mass spectrometry conditions, especially when its molecular geometry and potential energies are evaluated.

**Keywords:** DFT, Fukui functions, basis set, molecular geometry, potential energy.

## INTRODUCTION

Sucralose (C<sub>12</sub>H<sub>19</sub>Cl<sub>3</sub>O<sub>8</sub> – CAS 56038-13-2) is a synthetic organochlorine sweetener, sweeter than sucrose. Due to its wide use, and its environmental spreading, a higher sensitivity quantification method of sucralose sodium adduct was already reported,<sup>1</sup> that showed that it is interesting to evaluate sodiated compounds from different matrices in mass spectrometry (MS) studies. Nowadays, the use of MS for detection and quantitative analysis has been widely reported,<sup>2-4</sup> and today MS represents a conventional method for detecting several compounds. Although the detection of sodium adducts are reported for many pharmaceutical and organic compounds,<sup>5-8</sup> in studies using electrospray ionization (ESI) in mass

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spectrometry (ESI-MS) they are known to be difficult to fragment with tandem mass spectrometry (MS/MS) techniques.<sup>9</sup> However, it is unclear why some sodium adducts compounds presents higher chemical stability than the protonated ones in MS analysis. Moreover, Na<sup>+</sup> adduct formation is a quantitative and reproducible process which can be often used in ESI-MS.<sup>10</sup> In the present study, we evaluate the mass spectrum of sucralose sodium adduct in order to comprehend the position of the sodium ion, and why it is more stable ion in MS analysis, using quantum-chemical calculations (QCC).

A quantum-chemical theory was developed to investigate the structure of matter, and it is perceived as the density functional theory (DFT).<sup>11</sup> DFT is a worldwide accepted approach for modeling the ground state properties of molecules of interest,<sup>12</sup> and this function is a mixture of accurate (Hartree-Fock) exchange and local correction and gradient correction exchange and related terms, as first proposed by Becke (1996).<sup>13</sup> Thereby, this theory became a sophisticated tool for the semi-quantitative study of organic chemical reactivity.<sup>14</sup> To date, DFT has been used to calculate several reactive descriptors to predict molecular reactivity.<sup>15</sup> Exclusively B3LYP (Becke-3–Lee–Yang–Parr) has at present been used to show how halogenation of sucrose (sucralose) altered the electrostatic dipole moment of it,<sup>16</sup> and to calculate wavenumbers for the normal modes of vibration of sucralose.<sup>17</sup> Besides that, DFT calculations were used in MS studies to study the bond length, angle, and molecular geometry, which helps to understand their combination.<sup>18</sup>

## MATERIALS AND METHODS

### *Reagents and Solvents*

Sucralose was purchased from USP reference standard (Rockville, USA), acetic acid (Merck, Darmstadt, Germany), methanol (MeOH) was purchased from J.T Baker (USA). A Milli-Q-Plus ultrapure water system from Millipore (Milford, MA, USA) was used in stock solution of sucralose (1 µg mL<sup>-1</sup>).

### *Sample Preparation*

Acetic acid was added (0.1%) in 950 µL of methanol with 50 µL of a 1 mg mL<sup>-1</sup> standard solution. After stirring during 1 min in a vortex, the samples were filtered in membrane 0.2 µm pore-size syringe filter, then they were injected into a mass spectrometer.

### *MS conditions*

MS spectra were obtained either in the positive ion modes by direct infusion into Mass Spectrometer micrOTOF-QIII with Time-of-Flight and Electrospray Ionization (ESI-TOF) under the following conditions: Q-TOF (BrukerDaltonics, Massachusetts, USA); Electrospray positive mode; Scan Range (*m/z*): 50-600; Spray Voltage: 4.0 kV; Capillary temperature: 250 °C; Funnel: 200 Vpp. The samples were loaded into a 250 µL volume Hamilton gastight 7000 series syringe and introduced directly to the mass spectrometer, using Harvard Apparatus Pump 11 (Reno, NV) operating at a flow rate of 3 µL min<sup>-1</sup>. Desolvation and nebuliser gas (N<sub>2</sub>) flow rates were ~ 650 L h<sup>-1</sup>.

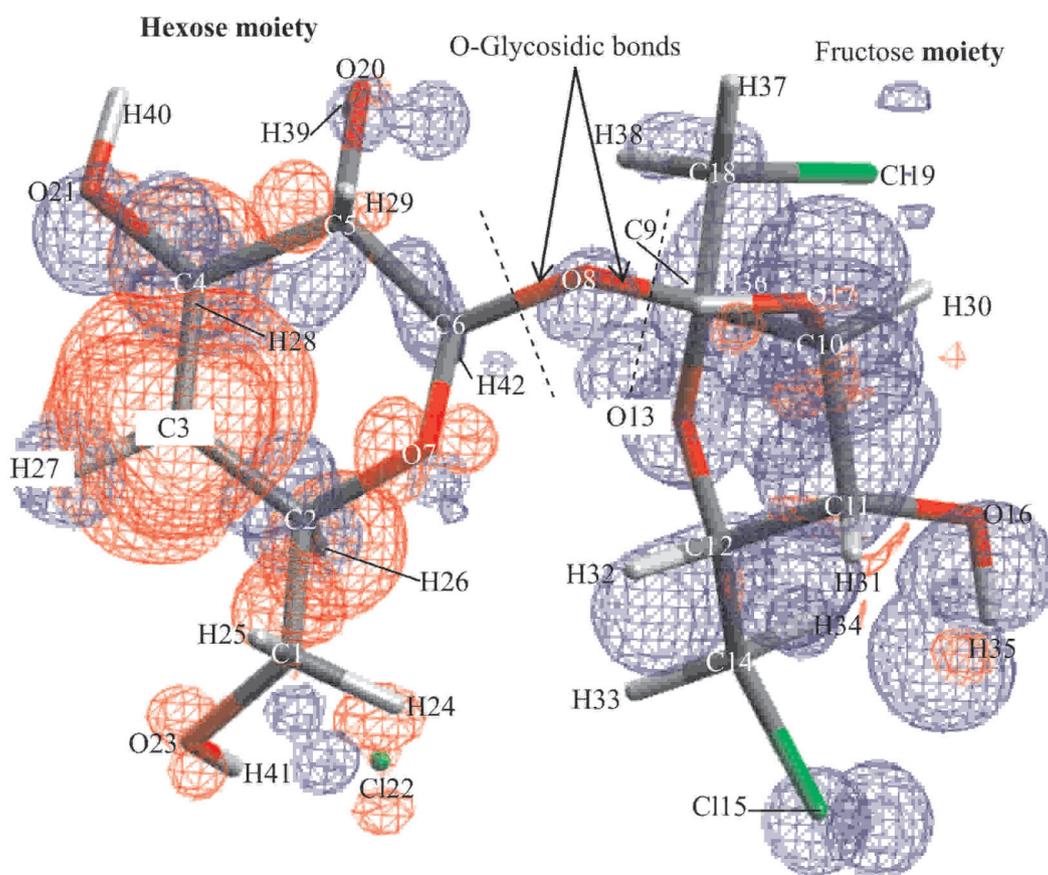
### *Computational Details*

The Gaussian 16 software revision A.03<sup>19</sup> used to perform the quantum chemical calculations. The molecular structures of all the species in-ground were optimized. Geometries were optimized to obtain local minimum energy. Molecular structures pictures were generated using Avogadro software, version 1.20.<sup>20</sup> The molecular 3D structure of transition states was visualized by using graphics software Molden 4. 2.<sup>21</sup> The descriptors based on the Fukui indices were generated by Multiwfn 3.2.1 program<sup>22</sup>, which is a multifunctional program function analysis.

## RESULTS AND DISCUSSION

### Theoretical Molecular Ionization

Here, MS data from a quadrupole time-of-flight mass spectrometer operating in with Time-of-Flight (TOF) QTOF-ESI-MS are reported and QCC from correlation-consistent, Pople and minimum basis to understand how sodium ion affects sucralose in ESI conditions. First, the sucralose ionization was studied, and it is well known that the peak-based signal is related to cation stability of precursor ion.<sup>23</sup> In the theoretical ionization study, the sucralose molecular geometry was optimized from DFT/B3LYP/6-31G(d) level, then the dual Fukui function descriptor (FFD) was calculated (Figure 1), but the C3-C12 bond brokedown. Although a lack of a proper description of London dispersion effects in mere B3LYP/6-31G\* calculations,<sup>24</sup> this level of calculation was chosen because of their popularity but deemed outdated in the theoretical community,<sup>25</sup> the intermolecular interactions of organic compounds,<sup>26</sup> and its cost effective factor.



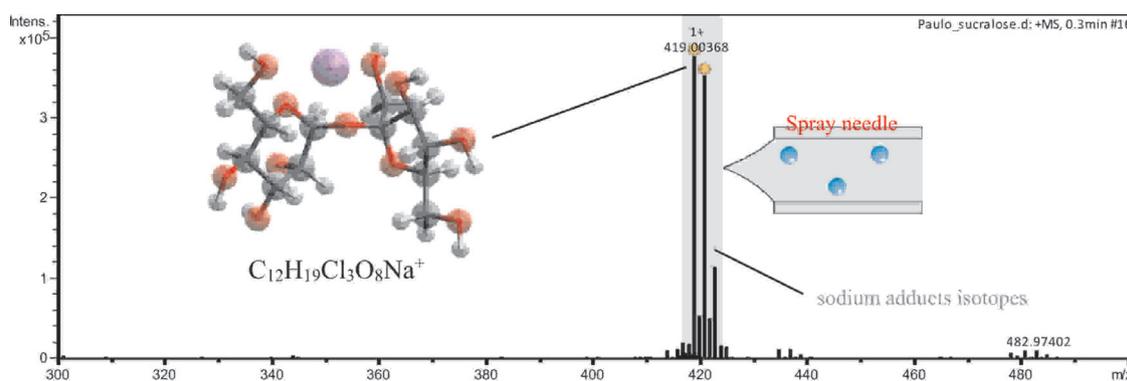
**Figure 1.** Map of the dual descriptor of the Fukui Function of the sucralose molecule from B3LYP/6-31G (d). Red and blue surfaces correspond to negative and positive regions, respectively. The atoms are numbered and labeled. The image was generated by the Avogadro program, and the descriptor was calculated by the Multiwfn program, from data generated by the Gaussian program 16.

According to the Figure 1, the FFD revealed that O17, O13, and O21 atoms presented the largest positive isosurfaces, as well the O20 atom. However, the O20, O8 and O17 atoms are able to coordinate the sodium ion, due to their spatial distribution. In order to study the potential energy involved in the molecular ionization, the theoretical protonation of sucralose molecule took place in oxygen atoms, and the sodium ion was added. After that, their molecular structures were optimized, and their potential ionization energies were calculated as the energy difference between the neutral molecule and its cation.

The equilibrium geometrical structures of sodium adduct of sucralose optimized from B3LYP/6-31G(d) presented the lowest potential energy (-2613,18 kcal mol<sup>-1</sup>), while the protonated sucralose species presented the highest ones (average -2451,36 kcal mol<sup>-1</sup>). Due to its lower potential energy, the base peak in the hypothetical mass spectra must be related to sucralose sodium adduct, even when an acidified solution is injected into a MS. The differences between ionization energies of protonated sucralose in O8, O13, and O21 atoms calculated from DFT/B3LYP/6-31G(d) were insignificant, which could not support us to certify the correct protonation site. In addition, the dual FFD indicates four nucleophilic groups with higher values, in both sites of the sucralose molecule and in O-glycosidic atom. We concluded that due to the exothermic nature of the sodium adduct formation, the dispersibility of sodium in the mobile phase, and the solubility in methanol, the ionization kinetics through the formation efficiency of the sodium adduct can be fully explained.<sup>27</sup>

### Sucralose behavior under MS conditions

To verify if the QCC was able to predict which specie presented the base peak in the mass spectra, an acidified sample was directly injected into the high-resolution mass spectrometer with TOF mass analyzer via flow injection analysis mode and electrospray ionization ion source (ESI+) (Figure 2).



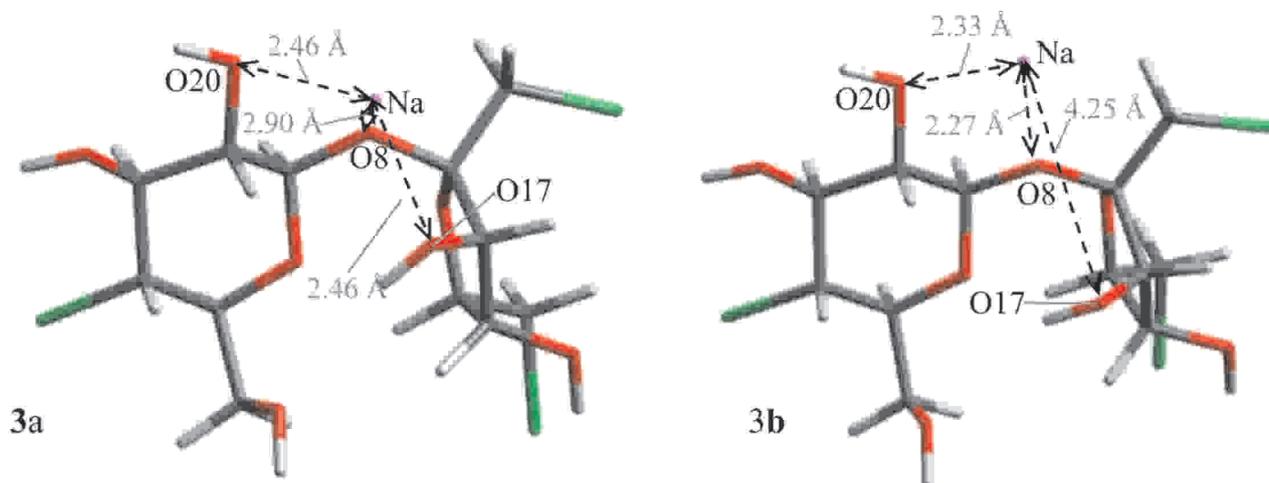
**Figure 2.** TOF-MS analysis of sucralose under positive ion mode, showing measured exact mass.

The mass spectra shows that sucralose sodium adduct at  $m/z$  419.00368 ( $C_{12}H_{19}Cl_3O_8Na^+$  – error 1.23 ppm) is the base peak, but the protonated sucralose was not observed. Furthermore, sucralose contains three chlorine atoms, and TOF analyses provided a valuable amount of isotopic accurate mass information for its detection of the sodium adducts isotopes ( $m/z$  421.000112, 420.00651, 422.00445 Da) and mass defect (422.99829 and 422.00445 Da). Although the acidified sample was injected into the mass spectrometer, the sodium adduct was more stable than protonated sucralose, which spectral data confirmed that. Ferrer et al. (2013)<sup>9</sup> also concluded that sucralose forms a strong sodium adduct, most of which could be detected in MS. Complementarily, Nilsson et al. (2017)<sup>29</sup> and Zhou et al. (2016)<sup>28</sup> also reported that the signal intensity produced by sodiated adducts was higher than the produced by protonated precursor ions. Hence, the evaluation of potential energies of ionized sucralose is a reliable tool to study its molecular ionization that was confirmed in mass spectral data. Owing to this particularity, the sodiated sucralose was used as a precursor ion to quantify sucralose with an acute sensitivity<sup>1,9,30</sup> and this method was interesting due to its application in environmental studies.

### Molecular geometry of sodiated sucralose

From a theoretical point of view, two different possible sites of sodium ion could take place to form the sodium adduct, and they are related to the interaction of O20, O8, and O17 and the sodium ion. Then, to study the interaction of sodium ion and the sucralose molecule, the sodiated sucralose structure was subjected to full QCC on different basis sets studies and a comparison of the bond lengths for the ion and

the potential energy were undertaken. Figure 3 shows the 3D molecular structure of  $[\text{Suc} + \text{Na}]^+$  calculated from cc-pvdz, and 6-31G(d) basis sets.



**Figure 3.** 3D optimized structure of the sodiated sucralose molecule, optimized from DFT level. The image was generated by the Avogadro program from data generated by the Gaussian program 16. Some atomic distances are shown. 3a - From RB3LYP/cc-pvdz. 3b - From B3LYP/6-31G(d).

Calculations from the thermodynamically most stable molecular structure of sodiated sucralose species were carried out, and the 3D models and the sodium ion position in a sodiated sucralose molecule are presented. According to the Figure 3, the oxygen atoms O20, O8 and O17 coordinated the approach of the sodium ion. The theoretical calculations using the basis sets 3-21G and cc-pvdz presented higher molecular geometry similarity, and they show an interaction of sodium ions and O8, O20 and O17 atoms. Otherwise, the basis sets LANL2DZ, 6-31G(d,p), 6-31G(d), STO-3G and cc-pvtz showed a specific interaction of the sodium ion and the O8 and O20 atoms. Analyzing the potential energy of sucralose sodium adducts, calculations from correlation-consistent basis sets presented lower values, while Pople and minimal basis sets revealed higher ones. Overall, the C9-O8 bond was longer than the C6-O8 one, but the addition of the sodium ion did not affect these bond lengths.

However, calculations from minimal basis sets presented longer bond lengths. The QCC from the basis set explored in this study showed that O8 atom presented highest negative atomic polar tensor (APT) charge in sodiated and neutral sucralose. Studying the electron density surfaces of molecules, Mohammad et al.<sup>31</sup> evaluated the equilibrium geometrical structures of sodium adducts optimized from pvdz basis, and observed higher accuracy of it which also explains our results. Moreover, evaluating different basis sets, the cc-pVDZ basis set was recommended as an acceptable balance between accuracy and computational cost.<sup>32</sup> Besides that, a deeper insight of non-covalent interactions were investigated and the cc-pVDZ basis set presented higher reliability to study the sodium coordination<sup>33</sup> due to its electron correlation level. However, augmented basis sets are computationally heavy, and outperformed by less computationally heavy options, but better results about energy are more significant.<sup>34</sup> Although Pople and minimal basis sets are a reasonable choice for exploration, they are not recommended when results require high accuracy or quantitative values. But the higher geometric correlation between 3-21G and cc-pvdz basis sets must be investigated. Differently, the basis sets LANL2DZ, 6-31G(d,p), 6-31G(d), STO-3G and cc-pvtz showed a specific interaction of the sodium ion and the O8 and O20 atoms.

To evaluate different basis sets, the cc-pvdz basis set is recommended as an acceptable balance between accuracy and computational cost,<sup>32</sup> and a deeper understanding of non-covalent interactions has also been studied, and due to its electronic correlation level, the cc-pvdz basis set has higher reliability

when studying sodium coordination<sup>33</sup> due to its electron correlation level. However, the enhanced basis set is computationally intensive, and the less computationally intensive option is better than the more computationally intensive one, but the better results regarding energy are more important.<sup>34</sup> Obviously, the position of Na<sup>+</sup> attachment is determined not only by the atomic charge, but also by spatial factors (the mutual position of the atomic interaction).<sup>35</sup>

## CONCLUSIONS

Overall, sucralose exhibits a oxygen-rich structure and the combination of threshold QTOF-MS measurements and QCC allowed us to understand why the sodiated sucralose is more stable than the protonated one. Comparing theoretical potential energy of protonated and sodiated sucralose, the [Suc + Na]<sup>+</sup> presented an incomparable lowest one. These results certified the superior chemical stability of sodiated sucralose and as the base peak in the mass spectra. From these data, sucralose sodium adduct must improve the sensitivity of quantification in MS analysis. Moreover, sucralose isotopic distribution enhances the selectivity of precursor ion and TOF-MS or ESI-MS/MS that provides exact masses, improving the method accuracy. Consequently, the mass spectral data showed that the most stable ion was [Suc + Na]<sup>+</sup>. Evaluating potential energy, bond lengths and sodium ion position of the sodiated sucralose from minimal (STO-3G), Pople (3-21G, 6-31G(d,p), and 6-31G(d)) and correlation-consistent (cc-pVDZ and cc-pVTZ) basis sets, the sodium position represented a remarkable difference. These basis sets did not present a more significant variance of APT charges and bond lengths, specially C9-O8 and C6-O8 bonds, but QCC presented that the oxygen atoms O20, O8 and O17 coordinated the approach of the sodium ion, and the basin sets 3-21G and cc-pvdz presented higher 3D geometry similarity due to the higher interaction of sodium ion and O8, O20 and O17 atoms.

## Conflicts of interest

All authors declare no conflicts of interest.

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