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Computational Raman spectrum of Alitame

Berguzar Yilmaz[1], Ozan Unsalan[2,*]

[1]Department of Biotechnology, Graduate School of Natural and Applied Science, Ege University, Izmir, Turkey

[2]Department of Physics, Faculty of Science, Ege University, Izmir, Turkey

*Correspondence: physicistozan@gmail.com (Ozan Unsalan)
ORCIDs Berguzar Yilmaz: https://orcid.org/0000-0001-7873-9743
Ozan Unsalan: https://orcid.org/0000-0001-5736-7530

Abstract: Alitame is an artificial sweetener. It is used in food and beverages to give a sweet taste as many other sweeteners. These sweeteners exhibit different sweetness scale based on their molecular structure and functions. Furthermore, since many artificial sweeteners lack detailed vibrational spectra, there is a need to obtain and gather both experimental and computational data on this kind of compounds. In this work, Raman spectra was computed using Gaussian09 software with the DFT/B3LYP functional with 6-311 ++ G(2df,2p) basis set. Assigned vibrational modes and computational Raman spectrum of alitame in the 100-3600 cm^{-1} range is presented for the first time. This way, revealing vibrational data and making robust connections between molecular vibrations and structure to activity of such a compound paves the way to better understand the nature of sweet taste of sweeteners by constructing a possible future spectroscopic sweetness scale.

Keywords: DFT; Raman spectroscopy; Alitame; Artificial sweetener; Spectroscopic sweetness scale.

1. Introduction

With accelerated population growth and developing technology, many chemical products are found in almost every aspect of our lives. Many additives are used for the cheap production and sale of many products we use, and for extending shelf life. One category of such additives are artificial sweeteners. Sweeteners can be obtained from natural sources such as fruit, vegetables, and milk, or they can be obtained artificially by chemical synthesis. Sweeteners can be classified as natural sweeteners and artificial sweeteners, as well as sweetener with high nutritional value and low nutritional value. Natural sweeteners may be high or low calorie such as maltose (4 kcal/g), saccharose (4 kcal/g), lactose (4 kcal/g), sorbitol (2. 6 kcal/g), stevia (calorie-free) (Edwards et al., 2016; İşgören & Sungur, 2019; Oktavirina et al., 2021). Other artificial sweeteners are acesulfame-K (0 kcal/g), cyclamate (0 kcal/g), saccharin (0 kcal/g), aspartame (4 kcal/g), alitame (0 kcal/g), neotame (0 kcal/g), sucralose (0 kcal/g), stevioside, neohesperidin (0 kcal/g), dihydrochalcone (Edwards et al., 2016; İşgören & Sungur, 2019; Oktavirina et al., 2021). Artificial sweeteners are also known as low-nutrient value sweeteners. Artificial sweeteners such as aspartame, saccharin, neotame, alitame have high sweetening power and low energy value (Edwards et al., 2016; İşgören & Sungur, 2019; Oktavirina et al., 2021). Artificial sweeteners are produced as an alternative to sugar. They contain less energy than the same amount of sugar. Artificial sweeteners are included in

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many foods such as low-calorie drinks, chewing gums, biscuits, breakfast cereals, chocolates, mints, low-calorie foods, jam, halva, milk desserts, fruit yoghurts, ice creams, cough syrups, diabetes products and sports drinks.

Alitame is easily absorbed in the gastrointestinal tract (Chattopadhyay et al., 2014). Alitame is 2,000 times sweeter than sugar and its caloric value is negligible (Kroger et al., 2006). It is also soluble in most polar solvents, highly stable at elevated temperatures and over a wider pH range (Chopra et al., 2020). JEFCA (The Joint FAO/WHO Expert Committee on Food Additives) reviewed safety data on alitame in 2002 and the committee concluded that there was no evidence that alitame is carcinogenic (Kroger et al., 2006). This compound (L-aspartyl-D-alanine 2,2,4,4-tetramethyl- thietanylamide) has 47 atoms ($C_{14}H_{25}N_3O_4S$), and consists of one CH_2, three C = O, one OH, one NH_2, two single CH groups, two NH, five methyl (CH_3), two single CH groups and one S atom. Thus, alitame has 135 vibrational wavenumbers. Computational IR spectrum of alitame was recently published (Altunayar-Unsalan & Unsalan, 2021) together with first time reported experimental spectra. In a review on non−nutritive sweeteners in different foodstuffs (wine, beer, orange juices, apple juices, herbal tea, candied fruits, canned peaches, canned mangos, cakes, fish) non−nutritive sweeteners were determined simultaneously by HILIC-MS/MS (Hydrophilic Interaction Liquid Chromatography coupled with Tandem Mass Spectroscopy), HPLC/ESI-MS (High-Performance Liquid Chromatography Electrospray Ionization coupled with Mass Spectrometry), RP-HTLC-MS/MS (Reverse Phase High Performance Liquid Chromatography coupled with Tandem Mass Spectrometry) analytical methods (Núñez et al., 2017; Ordoñez et al., 2015; Yang & Chen, 2009). Using NMR, the most compatible conformational structures were revealed by studying the sweet L, D stereoisomer, the bitter L, L stereoisomer and the tasteless D, D stereoisomer. In that study, the taste properties of conformers of each stereoisomer were figured out (Feinstein et al., 1991). Molecular properties of alitame have been deduced using theoretical studies using the PM3 (Parametric Method 3) method embedded in the Argus Lab program (Chopra et al., 2020).

In another theoretical study, the geometric structure of alitame was optimized with the 6-311++G(2df,2p) DFT/B3LYP method using Gaussian09 software. This theoretical work was carried out by anharmonic approach. Electrostatic potential (ESP) was mapped determine the electrophile and nucleophile attack sites and chemical reactivity of alitame. IR spectroscopic calculations were performed and the vibrational motions of the molecule were revealed for the first time (Altunayar-Unsalan & Unsalan, 2021). Although there are many experimental and theoretical studies on artificial sweeteners, we observed a big gap on alitame and its vibrational spectra, particularly Raman spectrum. Alitame has been investigated using analytical techniques such as NMR, HILIC–MS/MS, HPLC/ESI–MS, and RP-HTLC–MS/MS. Theoretically, its geometric properties were calculated, the ESP map was created and IR spectra were acquired. However, no practical or theoretical Raman investigations have been conducted. The studies theoretically methods in computer environment, can be obtained quickly chemical information. With this methods can be calculated many properties (such as optimized geometries, transition states and energies, thermodynamic properties) for any molecules (organic or inorganic). In addition, many measurements can be made theoretically spectroscopically. Although the theoretical methods have many deficiencies, the theoretical methods developed with related convergence and neglects can give results very close to the experimentally obtained data but the relevant theoretical methods should be chosen very carefully. The obtained theoretical and experimental data are associated, is provide more reliable information. In this theoretical study, Raman spectra of alitame were obtained and in order to was carry out to aid future experimental studies (such as on food or medicine). To the best of our knowledge, our work is the first effort to compute the Raman spectrum of alitame. We believe that this work could fill this gap on alitame.

2. Materials and methods

All quantum chemical computations on alitame were performed by Gaussian09 quantum chemistry software using DFT/B3LYP functional with 6-311 ++ G(2df,2p) basis set. Optimized geometry has been visualized with Chemcraft software (Zhurko, 2005). With anharmonic approach and at 298 K has been simulated Raman spectrum of alitame. The theoretically calculated Raman results of Alitame were opened in the Chemcraft software. The results obtained from the Chemcraft software were loaded into the Spectragryph software. Without any scaling, Alitame's Raman spectra were visualized with the Spectragryph software (Menges, 2021).

3. Results and discussion

Up to our knowledge, there is no theoretical Raman spectrum on alitame. The DFT-B3LYP/6-311 ++ G(2df,2p) set was used to compute Raman spectra. Data obtained in this study are given in Figures 2-4 and Table 1.

The taste receptors on our tongue detect sweetness, which is a psychobiological signal. The sweetener must have the correct molecular structure and electrical configuration to attach to the receptor. The AH-B (Shallenberger & Acree, 1967) and B-X (Kier, 1972) theories are used to try to explain sweetness. To have a sweet taste, a molecule must have a pattern that displays an electronegative atom (B), a polarized system (A-H), and a third hydrophobic part (X). The distance between the AH and B regions should be in the range of 2.4 to 4 Å. HOMO-LUMO calculations can reveal electrophile and nucleophile attack sites on a molecule. ESP (Electrostatic potential) calculations can also reveal electrophile and nucleophile attack sites, as well as the chemical reactivity of the molecule. Molecule parameters such as alitame's heat of formation, dipole moment and single point energy were computed theoretically, and HOMO-LUMO surfaces were generated (Chopra et al., 2020). In 2021, Altunayar-Unsalan and Unsalan created an electrostatic potential map (ESP) for alitame. When this map was examined, three AH regions were identified. The AH regions of alitame consist of NH_x (X = 1 and 2) and it has been revealed to have low electron density, whereas the B regions consist oxygen atoms and have a high electron density. The bond lengths of NH_x were measured as 2.664 and 2.236 Å for NH bonds and 3.591 Å for the NH_2 group. These calculated bond lengths are compatible with the molecular theory of sweet taste. It has been suggested that the symmetrical single NH and C=O units in Alitame may be related to the sweetness of alitame as well as other possible artificial sweeteners that may have such symmetrical units. The symmetrical NH and C=O units in alitame's ESP regions have been linked to the sweetness of the compound (Altunayar-Unsalan & Unsalan, 2021).

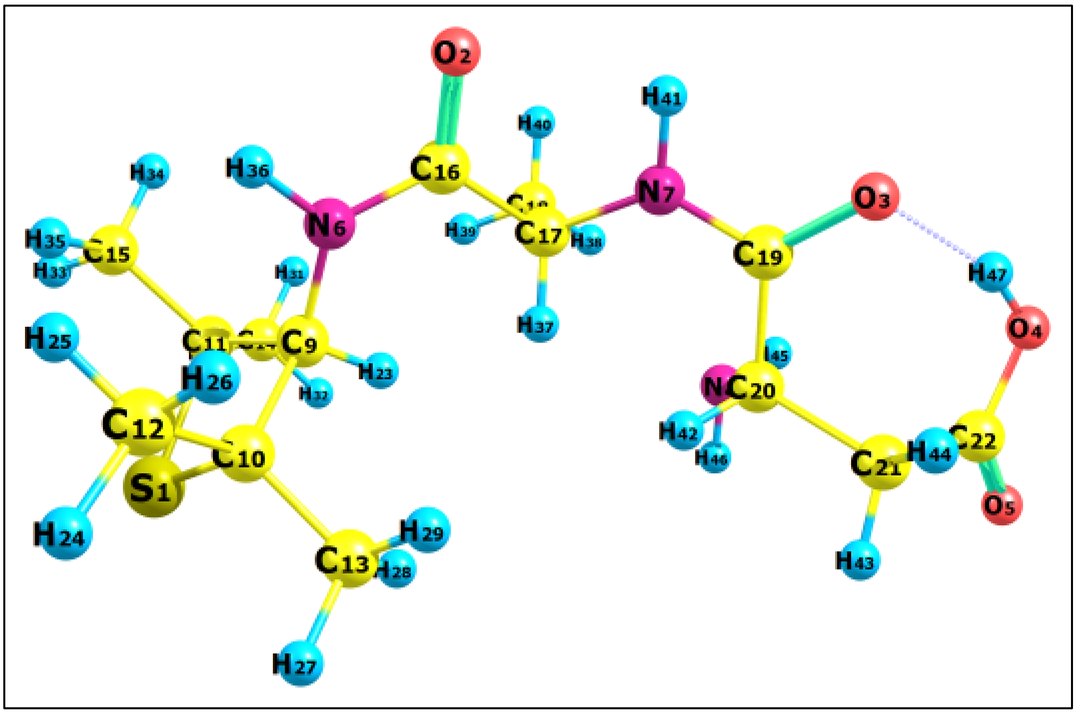

Figure 1. Optimized geometric structure of alitame.

In this work the DFT-B3LYP/6-311 ++ G(2df,2p) set was used to compute Raman spectra also the computed wavenumbers are given together with the peak assignments in Table 1. Vibrational modes are assigned to all bands between 100- 3600 cm^{-1} range. NH stretching vibrations were computed between 3578 cm^{-1} and 3487 cm^{-1}, whereas OH stretching vibrations are at 3325 cm^{-1}. Antisymmetric CH stretching vibration were assigned between 3142 cm^{-1} and 3080 cm^{-1} while the bands observed between 3055-3022 cm^{-1} were attributed to symmetric CH stretching vibrations in alitame. In addition, the C=O stretching vibration was assigned to the 1814 cm^{-1} and 1732 cm^{-1} wavenumbers. CC stretching vibrations were calculated between 1128 and 551.7 cm^{-1} whereas C=N stretching vibrations were calculated at 831.2 cm^{-1}. NC stretching vibrations of alitame were allocated to the bands detected at 1123 cm^{-1} and 621.7 cm^{-1} whereas CN stretching vibrations of alitame were assigned to the bands recorded at 386.1 and 180 cm^{-1}. In addition, 337.4 cm^{-1} was assigned to the CS stretching vibration. In-plane bending, out of plane bending, and torsion have been attributed to other bands. All computed Raman spectra can be seen in Figure 2, 3, 4.

The functional groups of the molecule are determined by using IR and Raman spectroscopic methods. Although the vibrational movements of the functional groups of the molecule are detected by IR spectroscopy, some groups are not included in the IR spectra due to the working principle, so information that cannot be obtained with IR can be revealed by Raman spectroscopy. IR and Raman spectroscopy are complementary methods. The results obtained with both methods can be similar. This obtained similar energy shifts are actively interpreted for both methods. When the data obtained the Altunayar-Unsalan and Unsalan study on Alitame in 2021 is examined, it is observed that many vibrational movements are active for both IR and Raman. However, as a result of the examination, it was observed that are vibrational movements specific both methods. These results are given in Table 2. This theoretical research, we hope, will benefit future alitame research.

Table 1. Calculated vibrational wavenumbers and assignments of alitame based on DFT B3LYP/6-311 ++ G(2df,2p).

Raman shift (cm^{-1})	Assignments*	Raman shift (cm^{-1})	Assignments
3578	ν_{s}NH (100)	1125	νNC (25)
3561	ν_{as}NH (100)	1097	τNCCH (42)
3543	νNH (97)	1081	νNC (23)
3487	νNH (96)	1080	νCC (19)
3326	νOH (98)	1046	τCCCH (28)
3142	ν_{as}CH (97)	1019	τCCCH (35)
3134	ν_{as}CH (94)	1010	νCC (31)
3124	ν_{as}CH (97)	1004	νCC (15)
3113,6	ν_{as}CH (82)	980	νCC (15)
3113,5	ν_{as}CH (97)	953	νCC (26)
3112	ν_{as}CH (86)	945	νCC (36)
3110	ν_{as}CH (96)	942	νCC (36)
3107	ν_{as}CH (96)	932	τHCCO (13)
3105	ν_{as}CH (88)	918	νCC (16)
3095	ν_{as}CH (92)	888	δCCC (19)
3093	ν_{as}CH (93)	868	νNC (26)
3084	ν_{as}CH (95)	859	νCC (27)
3080	ν_{as}CH (85)	831	νC=N (29)
3055	ν_{s}CH (95)	813	νC=O (26)
3048	ν_{s}CH (89)	801	τCCOH (24)
3033	ν_{s}CH (89)	790	νCC (24)
3030	ν_{s}CH (73)	756	τCCOH (64)
3022.9	ν_{s}CH (83)	733	δCCN (11)
3022.7	νCH (86)	694	τCCNH (22)
3018	ν_{s}CH (95)	669	τCCNH (51)
1814	νC=O (77)	651	τCCNH (26)
1732	νC=O (63)	623	νNC (17)
1684	δHNH (66)	618	τCCNH (15)
1667	νC=O (63)	602	δOCN (18)
1517	δHCH (62)	597	δO=C−O (45)
1516	δHCH (62)	567	νCC (18)
1510	δHCH (61)	551	νCC (28)
1509	δHCH (65)	489	δO=CN (22)
1504	δHCH (58)	463	δCCN (55)
1503.9	δHCH (52)	457	δCCC (14)
1501	δHCH (43)	423	δCCN (21)
1490	δHCH (67)	412	νNC (23)
1489.3	δHCH (52)	387	νCN (25)
1488.8	δHCH (68)	366	νNC (16)
1484	δHCH (73)	354	δCCC (17)
1481	δNCH (43)	338	νCS (18)
1478	δNCH (49)	322	δCCC (26)
1457	δHCH (62)	319	δCCC (38)
1438	δHCH (78)	297	δCCN (10) + τCCNH (10)
1430	δHCH (69)	285	δCCC (12)
1425	δNCH (39)	282	δCCN (13)

1415	δHCH (72)	277	τCCCH (34)
1411	δHCH (75)	259	δCCC (10)
1406	δNCH (51)	252	τCCCO (13)
1396	τNCCH (30)	241	τCCCH (28)
1388	τHCCO (22)	235	τCCCH (34)
1360	δNCH (56)	228	τNCCH (32)
1358	δCOH (55)	226	δCCC (29)
1344	τCNCH (59)	216	τCCCO (13)
1313	τNCCH (25)	203	γCN (15)
1302	δCCH (35)	199	δCCC (29)
1285	τHCCO (18)	180	νCN (15)
1264	τNCCH (27)	154	δCCC (31)
1252	δHCH (10)	114	τCCCN (14)
1226	τCCCH (31)	104	δCNC (23)
1220	νNC (11)	86	τCNCC (28)
1191	νNC (11) + τNCCH (14)	75	τNCCN (37)
1186	δCNH (30)	68	νCO (52)
1185	νC−O (13)	55	τCCNC (39)
1176	δNCH (12)	37	τCCCO (43)
1136	τCCCH (21)	27.4	τCCNC (31)
1127	νCC (16)	26.8	τCNCC (51)
		22	τCNCC (72)

*ν_s: stretching; δ: in−plane bending; γ: out−of−plane bending; τ: torsion. **Potential energy distribution (PED) (≥10).

Table 2. IR and Raman specific peaks of Alitame

Alitame-specific IR peaks		Alitame-specific Raman peaks	
Vibrational wavenumbers (cm^{-1})	Corresponding modes	Vibrational wavenumbers (cm^{-1})	Corresponding modes
566,6	CC stretching	551,7	CC stretching
599,2	O=C-O in plane bend	621,7	NC stretching
617,8	CCNH torsion	651,5	CCNH torsion
789,3	CC stretching	800,5	CCOH torsion
918,9	CC stretching	944,8	CC stretching
1283	HCCO torsion	1303	CCH in-plane bending
1358	COH in-plane bending	1360	NCH in-plane bending
1358	COH in-plane bending	1438	HCH in-plane bending
1419	HCH in-plane bending	1506	HCH in-plane bending
1440	HCH in-plane bending	3033	CH symmetric stretching
1513	HCH in-plane bending	3139	CH symmetric stretching
3027	CH symmetric stretching	3325	OH stretching
3325	OH stretching		

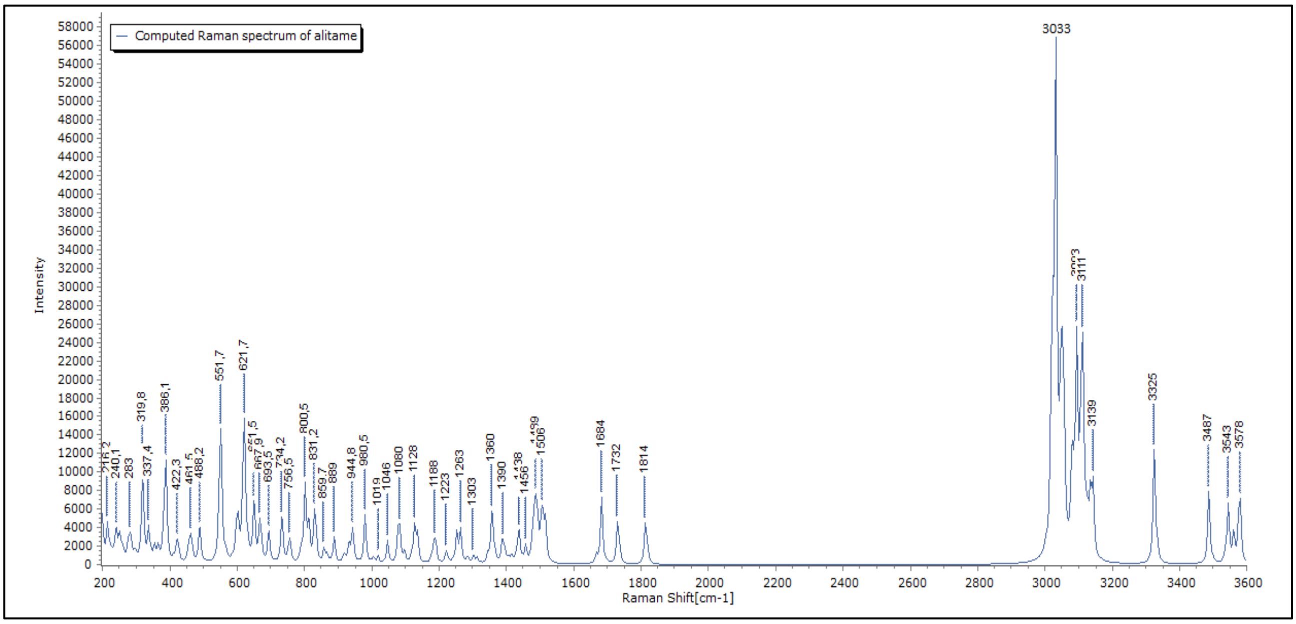

Figure 2. Computed Raman spectrum of alitame between 200-3600 cm^{-1}.

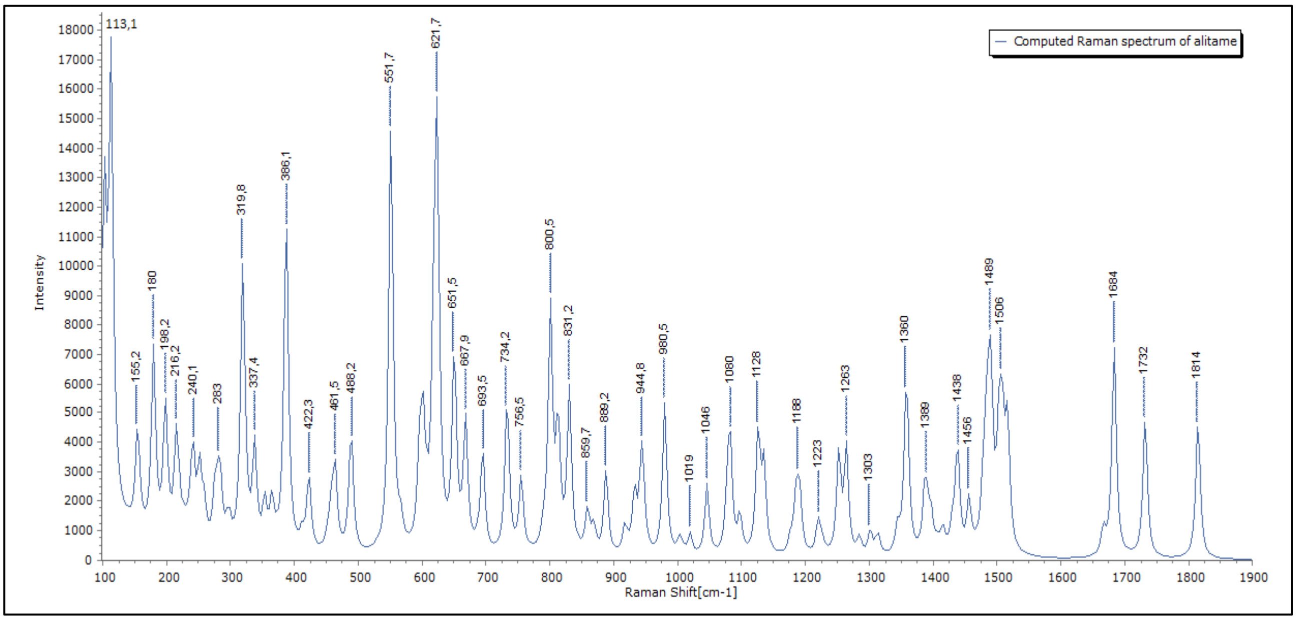

Figure 3. Computed Raman spectrum of alitame between 100-1900 cm^{-1}.

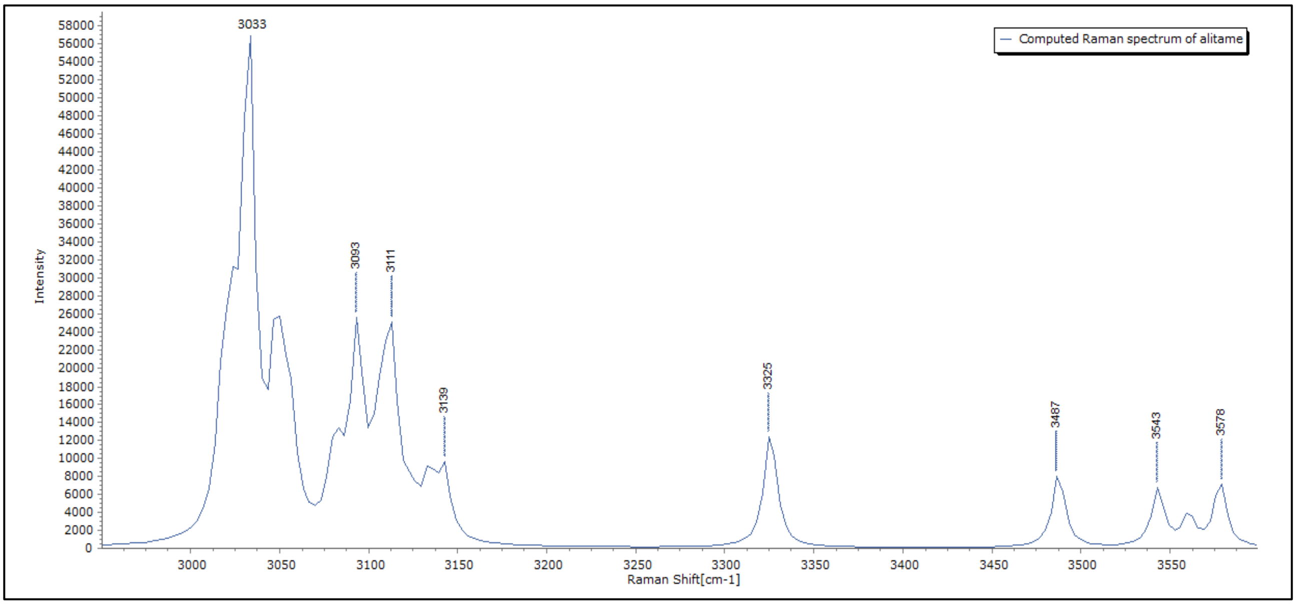

Figure 4. Computed Raman spectrum of alitame between 2950-3600 cm^{-1}.

4. Conclusion

Theoretical Raman spectrum of alitame have not been published previously, thus there is a major gap in terms of Raman spectroscopy of various artificial sweeteners, including alitame. Anharmonic Raman vibrational wavenumbers of alitame were computed and assignment of the bands were performed for the first time in this study. Modes were assigned to all bands between 100 and 3600 cm^{-1}. Our research will aid future investigations using vibrational spectroscopy properties of alitame and similar artificial sweeteners. In sweetness determination based on theoretical descriptors (dihedral angles), it was reported that the dihedral angle of –19.4° between H_{36}-N_6-N_7-H_{41} and the two adjacent C=O groups might be responsible for the sweetness of the compound (Altunayar-Unsalan & Unsalan, 2021). This finding should be further investigated by means of theoretical computations, and also be applied on other artificial sweeteners, then comparing the results. Consequently, it is clear that there still is no consensus on the origin of the sweetness of a compound, particularly an artificial one. This is why there is a strong need to define the descriptive molecular parameters which might explain the sweetness of a compound.

Conflict of interest

Authors declare that there is no conflict of interest.

CRediT Author Statement

Berguzar YILMAZ: Formal analysis, Resources, Data Curation, Writing - Original Draft, Editing.
Ozan UNSALAN: Conceptualization, Supervision, Review and editing, Methodology.

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