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The effects of protecting and acyl groups on the conformation of benzyl α-L-rhamnopyranosides: An in silico study

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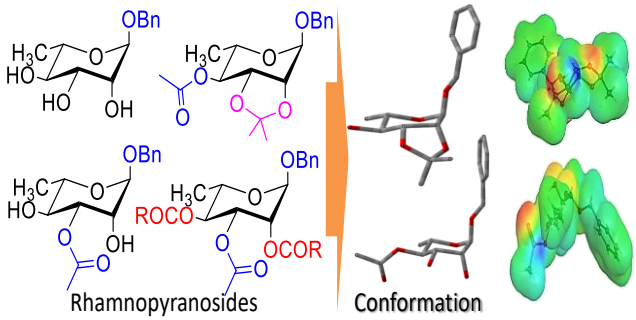
Abstract:

Carbohydrate fatty acid (CFA) esters especially rhamnopyranoside esters having both the hydrophilic and lipophilic nature showed broader applications including anticancer activities. It was reported that appropriate conformation is needed for better activities and conformational distortion reduced antimicrobial functionality. In this context, two different esters series of benzyl α-L-rhamnopyranosides, one with 2,3-O-acetonide group and the other one without acetonide group, were subjected for the density functional theory (DFT) optimization. The optimized structures with 2,3-O-acetonide rhamnopyranoside clearly showed distortion from the regular $^1C_4$ chair conformation while rhamnopyranoside esters without 2,3-O-acetonide functionality exhibited almost regular $^1C_4$ chair conformation. Also, the number and position of acyl group(s) present in the benzyl rhamnopyranoside imposes a small effect on their pyranose chair conformation. Thermodynamic properties including frontier molecular orbitals (FMO) and molecular electrostatic potential (MEP) of both the series of rhamnopyranosides are also discussed which indicated that 4-O-acyl rhamnopyranosides are more reactive than the 3-O-acyl analogues.

Keywords: *Conformational study; DFT optimization; MEP; Rhamnopyranoside; Sugar esters (SEs); Thermodynamic properties.*

Graphical Abstract



Highlights

- Acetonide protected rhamnopyranosides are highly distorted from $^1C_4$ chair conformation.
- Acyl group at C-4 position of rhamnopyranoside imposes more electrophilicity than at C-3 position.
- The number and chain length of acyl group(s) in rhamnopyranoside affect very little on its chair conformation.

1. Introduction

The most ubiquitous biomolecules named carbohydrates play the pivotal role in many biological processes. However, many natural carbohydrate compounds showed poor binding affinities [1] which led their structural modification to improves applicability in various fields including drug candidates [2-4]. Structural modification with

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one or more acyl group(s) led to the formation of sugar esters (SEs) [5-6] having diverse applications in different industries [7-10]. However, stereocontrolled i.e. site selective synthesis of SEs has long been recognized as a significant challenge in carbohydrate chemistry [11-12]. The presence of several secondary hydroxyl groups with almost similar reactivity imposes a barrier on selective esterification [13]. In this respect various methods were developed and employed successfully [14-19].

Among the SEs, synthetic rhamnopyranosides were reported to show promising activities like neuroprotective [20], antidepressant [21-22], anticarcinogenic [23], antimicrobial [24-26], and pharmacological properties [27] as well as in bioremediation of pollutants. For example, rhamnopyranose 4-*O*-, 2,3-di-*O*- and 2,3,4-tri-*O*-acyl esters isolated from roots of *Scrophularia buergeriana* were found to reduce glutamate-induced neurotoxicity [20]. Rhamnose esters bearing various plant extracts have long been used in Oriental medicine as a treatment for fever, constipation, swelling, neuritis and laryngitis [28-29]. Recently, the synthesis and interfacial properties of rhamnopyranoside derived bolaamphiphile type biosurfactant materials (e.g. **1**, Figure 1) are reported [30]. Although having effects for immunological activities there have no precise correlations been made between a particular constituent of these compounds and an observed pharmacological activity [31].

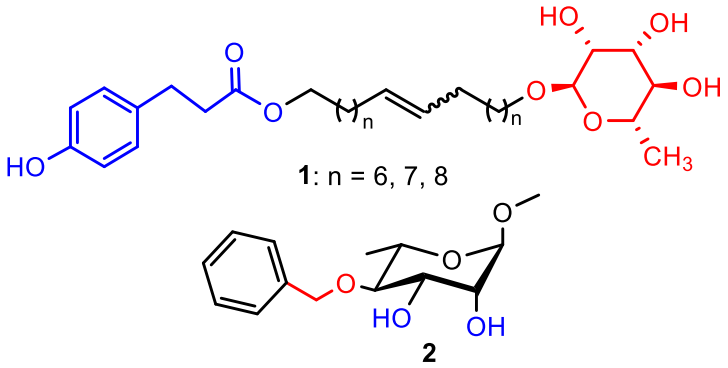

Figure 1. Structure of compound **1**, and **2**.

The shape or conformation of a molecule greatly influences its rates of reaction and other properties. The spatial shape of branched sugar molecules (oligosaccharides) depends mainly on the conformational features of the branch points. The conformational properties of such branched oligosaccharides may cause considerable anomalies in NMR spectra with chemical shift values [32]. The proximity of the conformational states of the disaccharide units in branched oligosaccharides has been described by analyzing both the nOe experimental data and theoretical conformational analysis [33]. Thus, many workers reported X-ray crystallographic data for appropriate assignment of conformation. For example, Pendril et al. established the structure of methyl 4-*O*-benzyl-α-L-rhamnopyranoside (**2**) which structurally exists in $^1C_4$ chair conformation with some H-bonding [34]. Now a days, density functional theory (DFT) approach with the B3LYP functional with both the 6-31G (d,p) and 6-311+G (d,p) basis sets are used for the investigation of the structural (conformational) and energetic parameters which provide information on the potential biological activity [35]. Hence, the present work is designed to investigate the stable conformation(s) of acylated benzyl α-L-rhamnopyranoside derivatives with the aid of quantum mechanical DFT approaches.

Our previous publications presented synthesis, characterization and biological activities of different protected and un-protected rhamnopyranoside esters [36-40]. Here, basically we report an investigation related to the effect of acetonide protecting group and acyl group(s) on the conformation of benzyl α-L-rhamnopyranoside (**3**) on the basis of quantum mechanical DFT studies.

2. Computational Method

2.1. Materials

For the present study we have considered two series of esters of benzyl α-L-rhamnopyranoside (**3**). The first series (**4-6** and **7a,b**) were prepared via 2,3-*O*-acetonide protection of compound **3** (Figure 2) [41]. The second series (**8** and **9a-d**) were prepared using

dibutyltin oxide method (Figure 2) [42]. All these benzyl rhamnopyranosides **4-9** were characterized by spectroscopic technique and elemental analyses, and their antimicrobial activities were also reported [27, 41].

2.2. Methods

Initially, the structure benzyl α-L-rhamnopyranoside (**3**) with appropriate geometry was taken from available structure database namely ChemSpider. The rest of the rhamnopyranoside structures for **4-9** were drawn in the GaussView (5.0) program [43] keeping this standard stereochemistry of the molecules. These rhamnopyranoside molecules were optimized with Gaussian 09 program at DFT (B3LYP) computing method [44-45] with 6-31G basis set [46-47] of DFT at 298 K and 1 atm without any solvent.

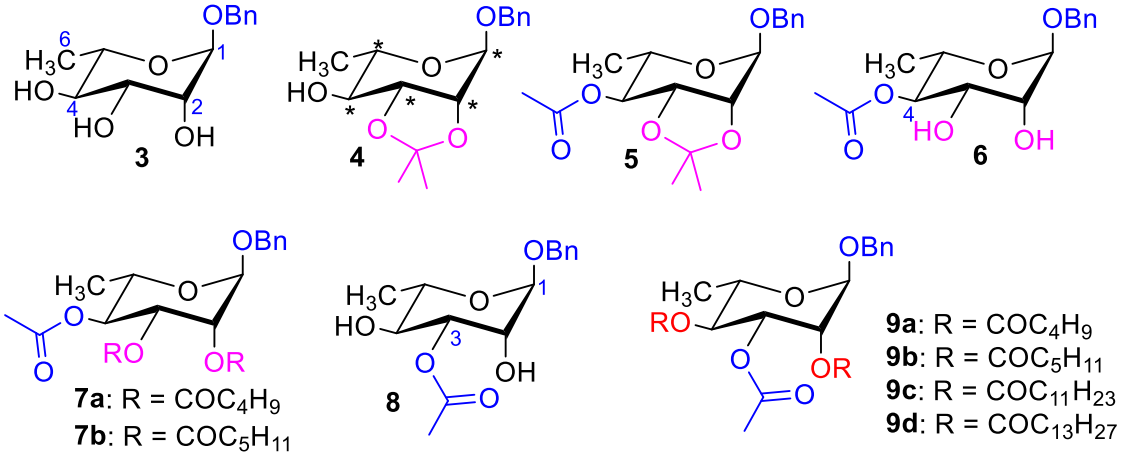

Figure 2. Structure of rhamnopyranosides **3-9** (* indicates stereocentre).

FMO (frontier molecular orbital) energy like HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and HOMO-LUMO gap were calculated from the optimized structures using GaussView (5.0) program. DOS plots were obtained from GaussSum 3.0. Molecular electrostatic potential (MEP) was also calculated at the same level of DFT, and MEP visualization was conducted by online WebMO demo server [16, 39].

3. Results and discussion

3.1. Conformations of rhamnopyranosides 3-9a-d

The structural shape and conformation of biologically active compounds immensely influenced their interactions with receptor proteins [48]. In this respect many researchers conducted conformational study of methyl α-L-rhamnopyranoside (**10**) [49], methyl 4-*O*-benzyl-α-L-rhamnopyranoside (**2**) [34] and methyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (**11**) [50]. From their X-ray crystal structures of compounds **2**, **10-11** they found that these exist in regular $^1C_4$ conformation (Figure 3). In the past few decades development of quantum mechanical and spectroscopic techniques made it easier to study the structure and conformation of bioactive molecules [51-52]. Thus, in the present study quantum mechanical DFT (B3LYP) optimization was used for the conformational study of several derivatives of benzyl rhamnopyranoside **3**.

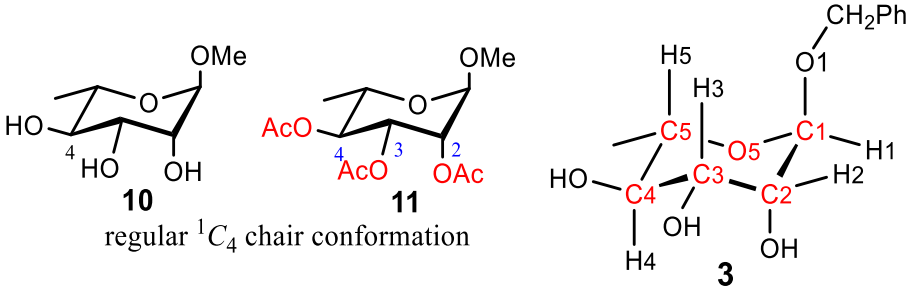

Figure 3. Regular chair conformation of **10** and **11**.

Initially, we considered first series of rhamnopyranosides **4-7a,b** (Figure 2). In compound **4** and **5**, one five-membered isopropylidene ring is fused with the six-membered pyranose ring at C-2 and C-3 position. Necessary bond angle and dihedral angle of the optimized rhamnopyranoside **3-7a,b** are presented in Table 1.

It is clear from Table 1 that incorporation of acetonide ring at C-2 and C-3 position as in **4** of rhamnopyranoside **3** increased bond angles at ∠O5-C1-C2, ∠C1-C2-C3 and ∠C2-C3-C4, and decreased at ∠C4-C5-O5.

Table 1. Bond angle and dihedral angle of rhamnopyranoside **3-7a,b**.

Molecule	Bond angle in degree					
	O5-C1-C2	C1-C2-C3	C2-C3-C4	C3-C4-C5	C4-C5-O5	C5-O5-C1
3	113.7	111.3	110.8	110.4	107.3	115.3
4	114.3	115.6	113.6	110.8	106.1	115.1
5	114.0	116.0	112.0	111.4	105.7	114.8
6	113.2	111.3	110.6	110.8	107.1	115.5
7a	112.0	110.7	110.9	111.1	109.0	115.3
7b	112.0	110.7	111.0	110.9	109.0	115.2
	Dihedral angle, in degree					
	H1-C1-C2-H2	H2-C2-C3-H3	H3-C3-C4-H4	H4-C4-C5-H5		
3	76.12	49.26	-177.54	-177.44		
4	83.93	32.40	-163.87	-174.68		
5	82.11	35.00	-162.59	-176.92		
6	75.44	49.43	-173.96	178.64		
7a	68.10	53.99	-170.24	173.40		
7b	68.27	53.88	-170.20	176.65		

*All these values were calculated from DFT (B3LYP) method and 6-31G basis set.

Also, huge increase of dihedral angle at ∠H1-C1-C2-H2 (~8°) and ∠H3-C3-C4-H4 (~15°), and decrease at ∠H2-C2-C3-H3 than the compound **3** created huge deviation in the pyranose ring conformation. This ultimately caused deviation of chair conformation and compound **4** exist as distorted $^1C_4$ chair conformation as shown in Figure 4. Further incorporation of acetyl group at C-4 position of compound **4** formed the compound **5** which was found almost similar distorted $^1C_4$ chair conformation. Removal of 2,3-*O*-acetonide group from **5** created compound **6** with the elimination of extra distortion and found to exist in regular $^1C_4$ chair conformation (Table 1, Figure 4). Again, addition of further acyl groups at C-2 and C-3 positions of **6** formed **7a,b**. The presence of extra acyl groups at these positions caused very small bond angle change and conformationaly found almost similar to the regular $^1C_4$ chair conformation (Figure 4).

Interestingly, it was observed that in all the compounds **3-9a,b** the glycosidic benzyl group at C-1 position located *exo*-orientation with respect to pyranose ring (Figure 4). The bond angle between ∠C1-O1-CH2 was found 114.6° for **3**, 114.4° for **4**, 114.5° for **5**, 114.5° for **6**, and 114.9° for **7a** supported the above observation.

Knowing conformational structures of **4-7a,b**, we were interested to know the effect acyl groups at other position and different chain lengths as in **8-9a-d** (Figure 2).

It is evident from Table 2 that addition of acetyl group at C-3 position of rhamnopyranoside **3** formed 4-*O*-acetate **8** and bond angles increased small amount at ∠C2-C3-C4 and ∠C4-C5-O5, and decreased very small in other positions.

Also, its dihedral angle increased little amount (3°) at ∠H2-C2-C3-H3 and remains almost same to compound **3** at other positions. Although both the 3-*O*-acetate **8** and 4-*O*-acetate **6** seem to exist in $^1C_4$ chair conformation (Figure 4 and 5), their bond angles and dihedral angles differs slightly. This clearly indicated that the position of acyl group imposes a small effect on their pyranose chair conformation.

Again, we checked effect of chain length (5C to 14C) at C-2 and C-4 positions of **8** (as in **9a-d**) on conformations. Addition of five-carbon (5C) acyl groups at C-2 and C-4 positions as in **9a** didn't alter bond angles considerably as compared to **8**. However, dihedral angles decreased at ∠H1-C1-C2-H2 (14°) and ∠H3-C3-C4-H4 (7°), and increase at ∠H2-C2-C3-H3 (10°) as compared to the compound **8**.

As shown in Figure 5, its conformational structure remains in conformity with $^{1}C_{4}$ chair conformation although bond and dihedral angle change must impose little change in conformation.

Elongation of chain length to 6C-14C at these C-2 and C-4 positions indicated almost similar bond angles and dihedral angles. All these observations indicated that addition of more acyl groups might have little change on the conformation structure but chain elongation at the same position didn't affect conformation too much of rhamnopyranoside.

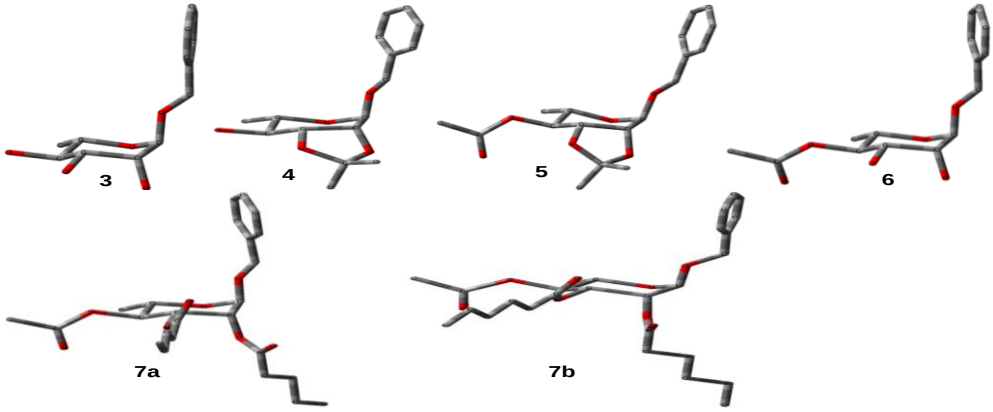

Figure 4. DFT optimized conformation of **3-6** and **7a,b** (H atoms are not shown).

Table 2. Bond angle and dihedral angle of rhamnopyranoside **8-9a,d**.

Molecule	Bond angle in degree					
	O5-C1-C2	C1-C2-C3	C2-C3-C4	C3-C4-C5	C4-C5-O5	C5-O5-C1
3	113.7	111.3	110.8	110.4	107.3	115.3
8	112.6	111.2	112.7	109.7	110.5	114.9
9a	111.4	109.7	110.7	110.4	109.0	115.0
9b	111.4	109.8	110.8	110.5	108.9	115.0
9c	111.4	109.8	110.8	110.3	109.0	114.9
9d	111.0	109.2	110.6	110.3	108.2	117.8
	Dihedral angle, in degree					
	H1-C1-C2-H2	H2-C2-C3-H3	H3-C3-C4-H4	H4-C4-C5-H5		
3	76.12	49.26	-177.54	-177.44		
8	77.89	46.03	-168.93	176.55		
9a	65.68	56.19	-175.40	175.78		
9b	65.91	55.80	-175.02	175.74		
9c	65.82	55.98	-175.12	175.82		
9d	66.29	56.70	-175.69	174.76		

*All these values were calculated from DFT (B3LYP) method and 6-31G basis sets.

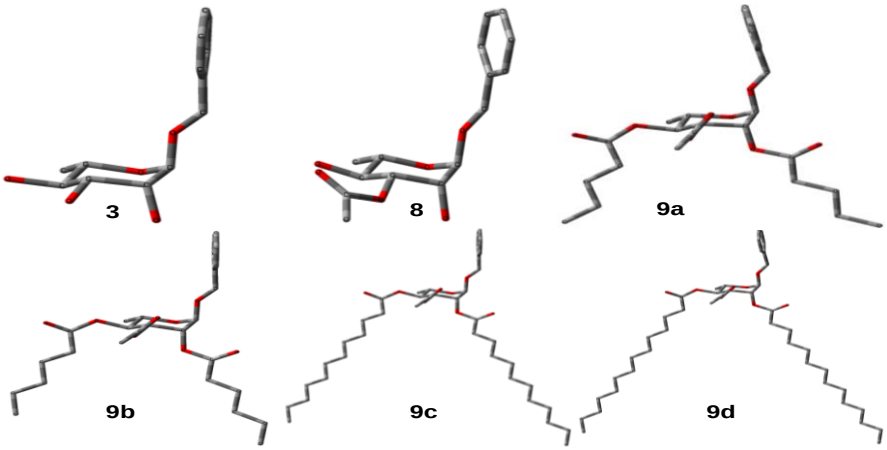

Figure 5. DFT optimized conformation of **8** and **9a-d** (H atoms are not shown).

3.2. Thermodynamic properties

Some thermodynamic properties like electronic energy (EE), enthalpy, Gibb's free energy (GFE), entropy and dipole moment (DM) of all the rhamnopyranosides **3-9a-d** are predicted from their DFT optimized structures (Table 3). With the increase of molecular size and atoms their EE increased as usual [53]. It was noticed that positional change of acetyl group as in 4-*O*-acetate **6** and 3-*O*-acetate **8** affect their entropy and dipole moment. The lower entropy and dipole moment of **8** (156.4 cal/mol-K and 3.64 Debye) than **6** (158.5 cal/mol-K and 4.28 Debye) clearly indicated more stability of 3-*O*-acetate **8** than 4-*O*-acetate **6**. On the contrary, compound **8** should be less reactive than compound **6**.

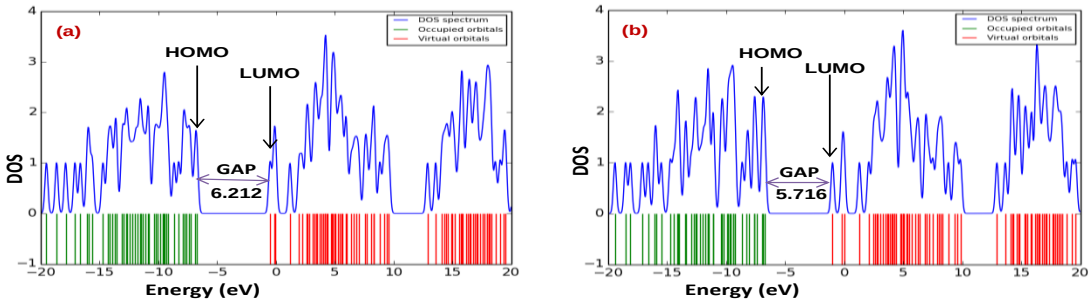

Figure 6. DOS plot of compound (a) **6** and (b) **8**.

Table 3. Some thermodynamic properties of **3-9a-d**.

Compound	MF	EE (Hartree)	Enthalpy (Hartree)	GFE (Hartree)	Entropy (cal/mol-K)	DM (Debye)
3	$C_{13}H_{18}O_5$	-882.0556	-881.7352	-881.7998	135.972	2.7199
4	$C_{16}H_{22}O_5$	-998.7613	-998.3750	-998.4466	150.750	1.3104
5	$C_{18}H_{24}O_6$	-1151.3750	-1150.9471	-1151.0282	170.713	2.5949
6	$C_{15}H_{20}O_6$	-1034.6679	-1034.3061	-1034.3814	158.461	4.2776
7a	$C_{25}H_{36}O_8$	-1575.7204	-1575.0949	-1575.2084	238.959	2.0085
7b	$C_{27}H_{40}O_8$	-1654.3286	-1653.6429	-1653.7638	254.434	2.0449
8	$C_{15}H_{20}O_6$	-1034.6689	-1034.3072	-1034.3815	156.418	3.6457
9a	$C_{25}H_{36}O_8$	-1575.7093	-1575.0840	-1575.1986	241.089	4.6646
9b	$C_{27}H_{40}O_8$	-1654.3174	-1653.6320	-1653.7530	254.501	4.6841
9c	$C_{39}H_{64}O_8$	-2125.9663	-2124.9197	-2125.0825	342.707	4.7308
9d	$C_{43}H_{72}O_8$	-2268.2713	-2267.0324	-2267.2043	361.783	5.5791

* EE indicates RB3LYP energy

3.3. Molecular orbital properties of 3-9a-d

The molecular orbital related HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) energy levels [54], HOMO-LUMO gap, hardness [55-57] and softness of rhamnopyranosides are mentioned in Table 4 (Figure 6). Here, η = Gap/2 and S = 1/ η. For most of these rhamnopyranosides (except **9d**) HOMO, LUMO and HOMO-LUMO gap was found almost similar. Hence, addition of acetonide group or acyl group(s) has not considerably changed their hardness and softness. However, 4-*O*-acetate **6** (~3.1) has greater hardness than the 3-*O*-acetate **8** (~2.9). To our surprise compound **9d** has lower HOMO-LUMO gap (5.0 eV) and hence lower hardness and higher softness than the other rhamnopyranosides.

3.4. MEP of synthesized rhamnopyranosides

Molecular electrostatic potential (MEP) correlates with dipole moment, electronegativity, and partial charges. It is a very useful property for analyzing the relative polarity, and predicting molecular reactive behavior especially to forecast the reactive sites for electrophilic and nucleophilic attack. MEP can be determined experimentally as well as computationally. Here, MEP of all the molecules are predicted from their DFT optimized structures using WebMo server [39] and shown as three dimensional diagrams of molecules in Figure 7.

In the MEP red zone indicates the lowest and blue zone as the highest electrostatic potential energy value (Figure 7). Also, red color represents maximum negative area and favorable site for electrophilic attack, blue color represents the maximum positive area and favorable site for nucleophilic attack, and green color indicates zero potential area. It is clear from Figure 7 that with the addition of acetonide group, as in **4**, decreases both electrophilicity (-0.1377) and nucleophilicity (+0.1136) than non-acetonide **3** (-0.1506 to +0.1645). While, in general, with the incorporation of acyl group(s) to the rhamnopyranoside skeleton (as in **6**, **7a,b**, **8**, **9a-d**) intensity of red color is increased and hence indicating the favorable site for electrophilic attack of these compounds. An important observation is that 4-*O*-acetate **6** has higher red value (-0.212) than the 3-*O*-acetate **8** (-0.1760) which is in conformity with our previous observation on the basis of entropy and dipole moment (Table 3) that **6** is more reactive than **8**. Overall, rhamnopyranoside esters are more favorable for electrophilic reaction than nucleophilic attack.

Table 4. Energy (eV) of HOMO, LUMO, energy gap, hardness, and softness of **3-9a-d**.

Compound	ε_{HOMO}	ε_{LUMO}	Gap	Hardness (η)	Softness (S)
3	-6.608	-0.0376	6.570	3.285	0.304
4	-6.660	-0.120	6.540	3.270	0.306
5	-6.730	-0.191	6.539	3.270	0.306
6	-6.704	-0.492	6.212	3.106	0.322
7a	-6.691	-0.358	6.333	3.167	0.316
7b	-6.681	-0.357	6.324	3.162	0.316
8	-6.697	-0.981	5.716	2.858	0.350
9a	-6.652	-0.497	6.155	3.078	0.325
9b	-6.652	-0.491	6.161	3.081	0.325
9c	-6.654	-0.490	6.164	3.082	0.325
9d	-8.920	-3.909	5.011	2.501	0.400

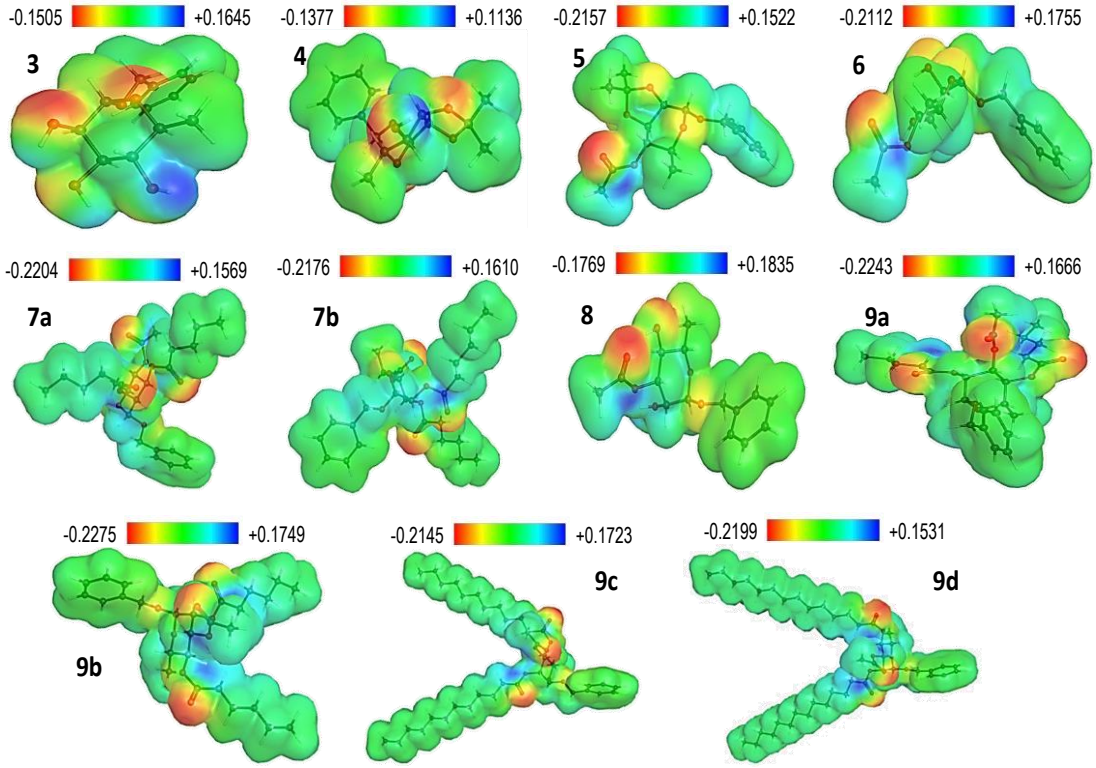

Figure 7. Molecular electrostatic potential map of **3- 9a-d**.

4. Conclusion

As most of the SEs is syrupy in nature their structure can't be elucidated by X-ray crystallography. Hence, the current work presents the DFT optimized structures of two ester series of benzyl α-L-rhamnopyranosides. Detailed conformational study of compound **3-9a-d** importantly indicated that the fusion of a five-membered acetonide ring with the six-membered pyranose ring of benzyl rhamnopyranoside molecule created huge distortion in its $^1C_4$ chair conformation. The number, position and length of ester chain(s) as added to the rhamnopyranoside ring also caused a very minor distortion in $^1C_4$ chair conformation with respect to bond angles and dihedral angles. Several thermodynamic, molecular orbital and molecular electrostatic potential properties are also discussed with respect to the structural modification of the synthetic benzyl α-L-rhamnopyranosides.

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