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# Molecular dynamics simulations of matrix assisted laser desorption ionization: Matrix–analyte interactions

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ABSTRACT

There is synergy between matrix assisted laser desorption ionization (MALDI) experiments and molecular dynamics (MD) simulations. To understand analyte ejection from the matrix, MD simulations have been employed. Prior calculations show that the ejected analyte molecules remain solvated by the matrix molecules in the ablated plume. In contrast, the experimental data show free analyte ions. The main idea of this work is that analyte molecule ejection may depend on the microscopic details of analyte interaction with the matrix. Intermolecular matrix–analyte interactions have been studied by focusing on 2,5-dihydroxybenzoic acid (DHB; matrix) and amino acids (AA; analyte) using Chemistry at HARvard Molecular Mechanics (CHARMM) force field. A series of AA molecules have been studied to analyze the DHB–AA interaction. A relative scale of AA molecule affinity towards DHB has been developed.

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## 1. Introduction

In the past decades, the MALDI technique has become an important analytical tool for studying the chemistry of bio-molecules such as peptides and proteins [1–8]. MALDI is an experimental technique that was introduced in mid-1980s by Karas and Hillenkamp [9], and provides the means to volatilize the analyte molecules (mainly bio-molecules) from the matrix (crystalline molecular solid) during an ablation process. The matrix acts as a support for the analyte molecules and prevents them from being destroyed during laser excitation. The lasers are targeted on a sample which results in a plume of analyte and matrix organic molecular ions [10]. These resulting ions are then studied through mass spectroscopy. The bio-molecules tend to be fragile and may fragment, so to avoid the thermal decomposition of these analyte molecules they are co-crystallized with the matrix that absorbs the majority of the laser irradiation [2,3].

Even though MALDI is a popular technique, clear understanding of ionization process and the chemistry involved in matrix–analyte interactions is still under investigation and an area of research [11]. Molecular dynamics simulations of MALD (without ionization) have been done by Zhigilei, Garrison, Vertes and co-workers [12–18]. In the simulation set-up, experimental conditions are simulated to understand the matrix–analyte interactions and the ejection of analyte molecules from the matrix [14,17,19–22]. These calculations showed that the analyte molecules are ejected within matrix clusters after ablation and hence remain solvated at all laser fluences [12–14,17,20–22]. These simulations are especially important when their lies a discrepancy between experimental results and the understanding behind it is unclear. The experimental data show a molecular ion peak showing that the analyte molecules free themselves from the matrix.

## 2. Methods

To address the discrepancy it is important to understand the nature of intermolecular interactions between the matrix molecules and the analyte molecules. A popularly used matrix is DHB. Since the analyte molecules are essentially composed of combinations of AA molecules, it is useful to classify the AA molecules on a relative scale of matrix affinity.

We evaluated the potential energy between DHB and various AA molecules using CHARMM [23] force fields to study the matrix–analyte chemistry. The primary reason to use CHARMM force field is that it is well established for studying most bio-molecules. In the CHARMM program, the internal structure of the building blocks of bio-molecules is defined by the molecule's topology and its parameters. The topology of a molecule describes the bond connectivity, angle, dihedral angle and improper dihedral angle, charge distribution, hydrogen-bond donors and acceptors and internal coordinate information.

Although, the CHARMM force field is well established, there are specific challenges related to our application for matrix–analyte system. The challenges include setting up the topology and parameters for matrix molecule DHB, shown in Fig. 1. The matrix

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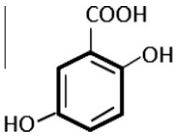


**Fig. 1.** Structure of 2,5-dihrydoxybenzoic acid (DHB).

molecule DHB is an organic molecule and is not included in standard CHARMM program. Another challenge is to include the non-zwitterionic forms of the AA molecules.

We developed the topology and force field parameters for DHB in CHARMM by modifying the existing standard AA molecules phenylalanine (PHE) and tyrosine (TYR) due to similar structural components as shown in Fig. 2a and b, respectively. This was done by determining the already known parameters from PHE and TYR. The common part being the benzene rings with a –OH group in both DHB and TYR. The topology and parameters for the second –OH group in DHB were replicated. For the unparameterized part, we integrated pre-existing topology/parameter for the –COOH group (pre-defined in CHARMM for AA molecules as side groups in acidic AA such as glutamic acid, Fig. 3). This idea was intuitive but from a chemical standpoint it is important to note that –COOH group is now connected directly to the phenyl ring. The next step was to carefully assign the atom type, partial charges, equilibrium bond lengths and angles, bond and angle force constants for -COOH with respect to its connectivity with benzene ring. Figure 4 shows the DHB molecule that was included in CHARMM database. Overall, the molecule should be neutral with zero charge (highlighted in blue). The molecule is divided into various subgroups (which also should have a zero charge). In the figure, column 2 is the atom name, column 3 is the atom type (determined from the pre-defined database in CHARMM). The last column is the partial charge. This is followed by the definition of bond connectivity.

Changes in partial charges were made in the –COOH group (highlighted in red in Fig. 4). The carbon atom named CC (of type CC in CHARMM) was modified to 0.71 (CHARMM value: 0.55) and the hydrogen atom named HI (of type H in CHARMM) was modified to 0.47 (CHARMM value: 0.31) so that net charge for −COOH group is zero. This is in the spirit of acidic AA molecules that have neutral –COOH group as side chain. The modified equilibrium bond lengths and angles, bond and angle force constants of atoms have been listed in Tables 1 and 2 according to the CHARMM nomenclature (atom types pre-defined in CHARMM).

Following the DHB setup, the second challenge of generating the non-zwitterionic forms of AA molecules was addressed. The

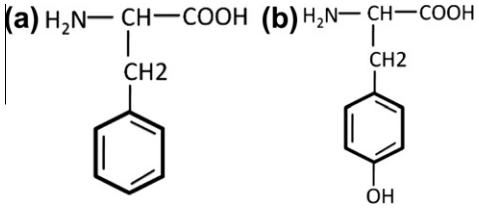


**Fig. 2.** Structure of (a) PHE in non-zwitterionic form and (b) TYR in non-zwitterionic form.

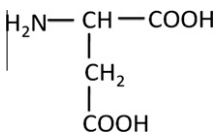


**Fig. 3.** Structure of glutamic acid (GLU), an acidic AA.

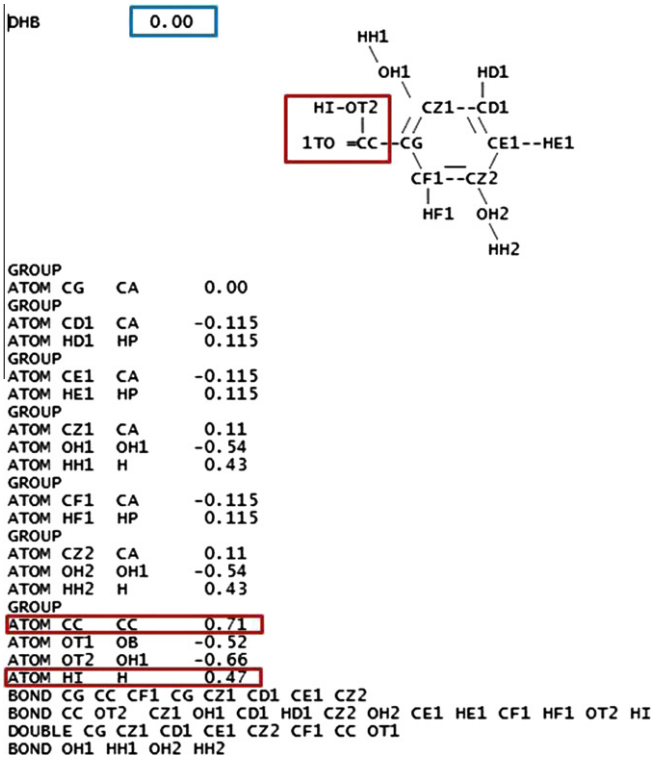


**Fig. 4.** Structure and topology details of DHB in CHARMM.

**Table 1**
Bond length: potential is given as $V_b = K_b(R - R_0)$; $K_b$ is the force constant, $R$ is the bond length (Angstroms) and $R_0$ is the equilibrium bond length.

| Atom types | $K_b$ (kcal/mol/Å$^2$) | $R_0$ |
|---|---|---|
| CC CA | 305.0 | 1.36 |
| CC OH1 | 305.0 | 1.25 |
| OC H | 525.0 | 0.97 |

**Table 2**
Angle: potential is given as $V_{angle} = K_\theta(\theta - \theta_0)$; $K_\theta$ is the force constant, $\theta$ is the angle and $\theta_0$ is the equilibrium bond angle.

| Atom types | $K_\theta$ (kcal/mol/radian$^2$) | $\theta_0$ (deg) |
|---|---|---|
| CA CC OH1 | 40.0 | 120.0 |
| CA CC OB | 40.0 | 120.0 |
| OB CC OH1 | 1100.0 | 120.0 |
| CC OH1 H | 120.0 | 107.4 |
| CA CA CC | 45.8 | 122.3 |

non-zwitterionic forms are not standard in the CHARMM program since the majority of the calculations for bimolecular systems are performed in presence of solvent. In general, the AA molecules exist in their zwitterionic forms as shown in Fig. 5a. In our case, however, after the laser irradiation on the solid sample the simulations are performed in the gas phase where the AA molecules exist

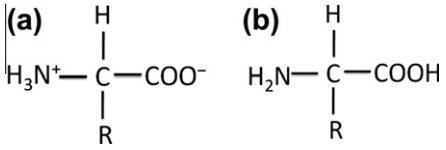


**Fig. 5.** Schematic of amino acid, (a) zwitterionic form and (b) non-zwitterionic form, where R is an alkyl side chain.