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Density Functional Theory Applied to Monitoring Pollutants Coupled with Molecular Imprinting Polymer

Teoria do Funcional da Densidade Aplicada à Monitorização de Poluentes Acoplada com Polímeros de Impressão Molecular

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Herein, quantum chemical calculations were performed to characterize the selective monomers interaction with glyphosate analyte to obtain a highly selective polymer with molecular recognition of glyphosate using Density Functional Theory (DFT) B3LYP method based on 6-31+g (d,p). The minimum energy state was evaluated by calculating the interaction of the glyphosate with 20 different monomers (16 functional and 4 structural monomers) for selective molecular imprinted polymer (MIP) in the molecular recognition of the analyte. Both the functional monomers and solvent play a key role in specific synthesis. The study reveals that ME2 (ethylene glycol dimethacrylate) is a structural monomer with the lowest interaction energy. Quantum calculations were performed for the vacuum and solvents like water, acetonitrile, toluene, methanol, and ethanol. Acrylic acid (MF3), methacrylic acid (MF10), and 2-acrylamido-2-methyl-1-propane sulfonic acid (MF15) interact with glyphosate effectively in some most solvents they had more favorable lower interaction energy. The result showed a complete set of information that allows selecting the most promising functional monomers with better interaction with the analyte. To avoid the expensive and time-consuming standard analytical determination methods, thus an alternative simple, rapid, green, and highly selective detection methods have been developed for MIP through computer simulation. It allows a good pathway in the experimental synthesis of MIP with high selectivity and efficiency. It also facilitates time optimization, and reagent helps make computational simulations a new environmentally friendly application.

Keywords: Molecular structures; molecular imprinted polymer; biosensor; density functional theory; glyphosate.

1. Introduction

Organic polymer refers to a type of polymer containing carbon atoms in its backbone. These polymers are often derived from natural sources or synthesized from organic compounds. Examples include plastics, proteins, carbohydrates, and nucleic acids.[1] The synthesis of molecularly imprinted polymers (MIPs) is characterized by a process involving the interaction of a functional monomer, analyte (or template molecule), and the medium in which the reaction occurs.[2] Functional groups present in the analyte structure facilitate interaction with the functional monomer, which can be of either a chemical or physical nature. This interaction enables the formation of the analyte-monomer complex.[3-5]

The thermodynamic stability of the complex is also influenced by the environment in which it is immersed. Thermodynamic stability relates to the overall energy state of a complex in a particular environment, considering factors such as temperature, pressure, solvent, and the presence of other molecules. Therefore, the selection and study of the solvent are crucial factors for achieving satisfactory results.[3] Hence, for the MIP to be more effective, the solvent should not disrupt this interaction, particularly when the bonding occurs via electrostatic forces or hydrogen bonding.[3-4] Solvents with low dielectric constants and non-polar characteristics are conducive to producing polymers with enhanced molecular recognition capabilities.[6]

The preparation techniques for Molecularly Imprinted Polymers (MIPs) primarily involveinvolves synthetic processes. The key components typically include a functional monomer, the analyte or template molecule, a crosslinking agent, initiators, and an organic solvent to dissolve these reagents.[7] The synthesis process of MIPs is typically divided into three steps. Firstly, complexation occurs, where functional monomers interact with the analyte in

a medium that may be aqueous or non-aqueous. Secondly, crosslinking takes place, which enhances the stability of the monomer-analyte complex and imparts rigidity to the polymer. This step is essential for creating stable cavities within the polymer structure.[8] The third step involves the removal of the specific and selective analyte, which forms the selective cavities within the polymer. This process allows the analyte to reoccupy these sites using the same interactions that occurred during synthesis.[9]

Recent literature underscores the increasing applications of MIPs, attributed to their straightforward preparation, chemical stability, and efficacy in environmental, biological, and food analyses.[10] Utilizing computational methods not only streamlines the acquisition of MIPs by minimizing trial-and-error stages in material selection but also conserves reagents and solvents. Computational chemistry assessments play a pivotal role in advancing molecular imprinted polymer (MIP) research and achieving its overarching goals. By leveraging computational techniques, researchers can gain invaluable insights into the design, synthesis, and performance of MIPs, thereby facilitating their optimization for various applications. This essay explores the significance of computational chemistry in MIP research and highlights notable examples of its success in advancing this field. Furthermore, it accelerates laboratory processes and diminishes environmental impact, particularly in assessing different organic solvents during synthesis optimization.[11-12]

The quantum calculations applied in MIPs involve various methods and mathematical models. These methods provide researchers with essential physicochemical insights into the system, including analyte-monomer interaction energies, spatial conformations, electronic density, and vibrational spectra.[13-14]

In this study, we utilized Density Functional Theory (DFT), a method previously employed to predict optimal conditions for MIP synthesis.[15-17] Additionally, it offers a lower computational cost compared to Hartree-Fock calculations.[5] The choice of this method provides reliable results and can directly use the experimental work, ensuring the most favorable energy interaction between the analyte and the monomers.[18-19]

The monomers depicted in Figure 1 have been widely used in various studies.[20-24] Among them, commercially available monomers such as methacrylic acid (MF10) and 4-vinyl pyridine (MF14) are particularly common in synthesizing MIPs with acidic and basic characteristics, respectively. This choice is because a monomer can serve as both a proton donor and a proton receptor for the analyte. However, other monomers, as illustrated in Figure 1, can be employed for different types of interactions with the analyte.[25]

In 1974, glyphosate (N-(phosphonomethyl) glycine) (Figure 2) was introduced into the agrochemical market, which shows a degree of toxicity III (moderately toxic).[26] Today, this compound is widely employed as a herbicide in industrial agriculture, underscoring its notable environmental repercussions. Thus, synthesizing materials with selective adsorption for this compound holds considerable scientific importance.[19-20] This work proposes to evaluate the interaction of each monomer as given in Figure 1 with glyphosate, in order or evaluate with lower energy interaction and greater stability in the Analyte- Monomer interaction necessary for the formation of a selective MIP. This selective synthesis process allows easy and low-cost screening of this environmental pollutant by effective recognition cavities in MIP compared with conventional analysis methods such as chromatography or using a sensing phase in the preparation of a biosensor.[27]

2. Computational Method

The quantum calculations were performed using DFT due to the lower computational cost than other calculations besides the electronic interaction.[28-29] Thus, the Gaussian 09W computational chemistry software package was used in the calculations of structure optimization and molecular interaction[30] and the B3LYP method with the base function 6-31 + g (d, p),[31-33] allowing all atomic and molecular coordinates in a minimum state of energy.[13-14] The input matrix for the DFT calculations was obtained by Materials Studio[34] at the ultra-fine level, and the adsorption locator module implemented in the software was used. This method allows for numerous interactions between analyte and monomers,[35-36] so it was possible to interact with each other to find the least energy spatial coordinate for each quantum method in this case of DFT.

The interactions between the analyte and the monomers were given in a ratio of 1:1, 1:2, 1:3, and 1:4 in vacuum and with the implied solvents described below by the Integral Equation Formalism for Polarizable Continuum Method IEFPCM[37-38] implemented in the Gaussian software 09W.[30] The visualization of the molecule's molecular chemical systems and obtaining the chemical structures' figures was used the program Gauss View.[39] Equation 1 shows the interaction energy in which the result allows to evaluate the best complex that can interact as the analyte energy of the whole system and the total energy of the complex is calculated and subtracted the individual energies and energies of the monomers.[40-41]

$$Eint = E_{total} - E_{analyte} - E_{m} \quad (1)$$

First, the calculations were carried out in a vacuum; then, in the complexation process, solvents like water, acetonitrile, toluene, methanol, and ethanol were used. Thus, it is possible to evaluate the effect of each of these media by equation 2, which corresponds to the energy difference between the analyte-monomer complex in a solvent and the energy of the complex in the vacuum.[42-43]

$$\Delta E_{solv} = E_{S} - E_{V} \quad (2)$$

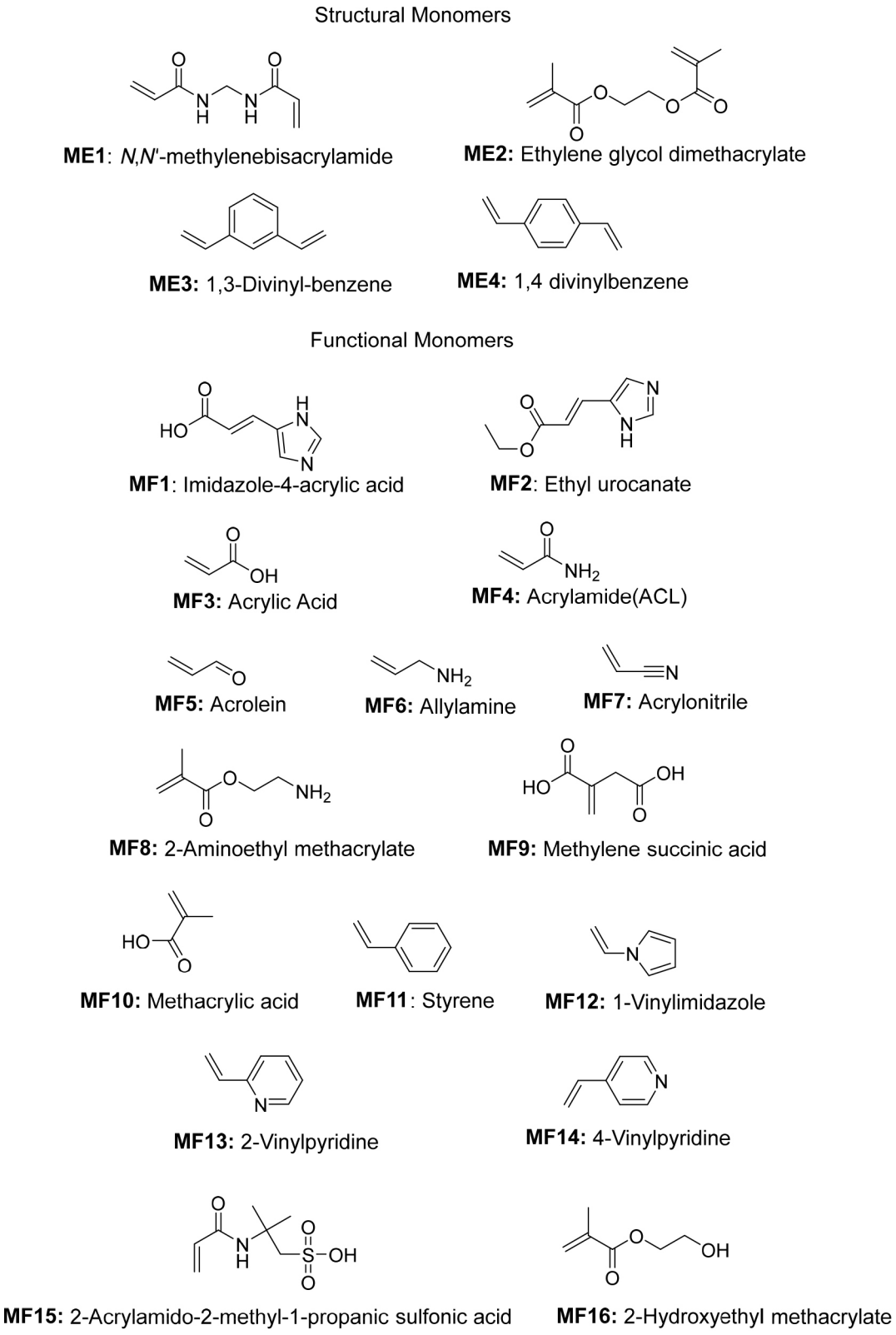

Figure 1. A wide range of functional and structural monomers, along with their chemical structures

3. Methodology

In this work, the calculations were applied using DFT in the B3LYP method with base functions 6-31 + g (d, p) in 6 different media like a vacuum, water, acetonitrile, toluene, methanol, and ethanol. In these media, glyphosate acts as an analyte (Figure 2) and interacts with each of the

20 monomers (Figure 1), in proportions of 1:1, 1:2, 1:3, and 1:4 totaling 480 calculations.

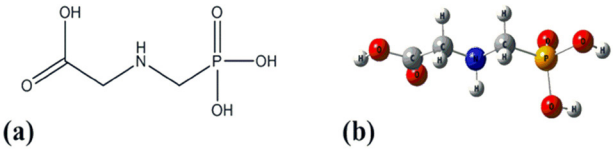

Figure 2. Structural formula of glyphosate: (a) bidimensional structural formula; (b) three-dimensional structural formula

The interaction energies were grouped in each case to verify the differences of energies and the intensity of the energy decreases and the differences between these decreases. This also allows the comparative analysis between the other functional monomers by the absolute value of each interaction energy and the energy difference between the studied proportions. It is understood from equation 3 as the interaction energy difference of the obtained complexes with functional monomers in the proportion 1:4 minus the energy difference of the complexes with functional monomers in the proportion of 1:1. The goal of equation 3 is simply to observe the energy variation of the largest proportion of individual monomer molecules about the lowest proportion. If there is linearity, the proportion of 1:2 and 1:3 can be observed for the addition of monomers, with energy values or not

$$|\Delta E| = 4M_n - 1M_n \quad (3)$$

In this way, the 20 monomers (16 functional monomers and 4 structural monomers) are analyzed from the point of view of interaction energy, from the most negative value to the most positive value of energy. The results are discussed and presented in three groups: 1) 3 higher interaction monomers (lower energy values); 2) 8 monomers of intermediate interaction; 3) 5 monomers of lower interaction (higher energy values). To best describe the results, each medium is presented and discussed separately.

3.1. Interaction of analyte and monomer

3.1.1. Vacuum

Figure 3 shows the results obtained for the vacuum in which the analyte-monomer interaction energy in ratios of 1:1, 1:2, 1:3, and 1:4 except for some monomers and the interaction energy becomes more significant in larger proportions. However, in some cases, there is no energy increase with monomers indicating the non-formation of active sites obtaining the MIP.[44] The more negative the interaction energy the greater the interaction between the analyte and the monomer, so it is possible to observe that for the ratio 1:4 the following order of interaction energy is obtained: ME2 <MF2 <MF1 <MF4 <MF15 <MF9 <MF1 <MF12 <MF10 <MF5 <MF16 <MF3 <MF7 <MF6 <MF14 <MF13 <MF8 <ME3 <ME4 <MF11. In this study functional monomers called group 1 in which the interaction of analyte-monomer takes place in the presence of imidazole-4-acrylic ethyl ester (MF2), imidazole-4- acrylic acid (MF1), and acrylamide (MF4) and for group 2 MF15, MF9, MF12, MF10, MF5, MF16, MF3 and, M18; finally for group 3: MF6, MF14, MF13, MF8, and MF11.

The monomer ME2, called ethylene glycol dimethacrylate (EGDMA), has a density of 1.051 g / cm^3 at 25 °C and water solubility of 5 g L^{-1} at 20 °C. In molecular imprinting techniques mostly, EGDMA is used as a crosslinking agent (ALC) because of its ability to form thermally and mechanically stable polymers and enable rapid mass transfer during synthesis.[45] This compound had the most negative interaction energy between the studied systems indicating that it is the most stable system[46] for obtaining MIP for glyphosate. It is observed from Figure 3 whose medium is a vacuum in which the interaction energy for ME2 gradually decreases from 1:1 ratio to 1:4 ratio reaching -61.78 kcal mol^{-1}.

The spatial arrangements for ME2 (EGDMA) are shown in Figure 4, which allows for the evaluation of the region of the analyte containing sulfur as the most reactive, as it includes hydrogen atoms that enable interactions with the monomer. EGDMA exhibits greater electronic density due to the oxygen atoms in the two ester groups, so interactions occur preferentially in this region. In the 1:2, 1:3, and especially the 1:4 ratios shown in Figure 4a-4d, it is observed that the EGDMA is spatially arranged in a way that increases hydrogen interactions, which explains the more negative interaction energy. This characterizes the values obtained from the physical nature of the interactions.[47]

This way, you can prove the effectiveness of EGMA as the best structural monomer for polymer synthesis. In group 2, some monomers have intermediary interaction energies for the fraction 1:4; these complexes presented mean energy of interaction in the order of -30 kcal mol^{-1}. It is observed that the obtained energies vary, and consequent variation may indicate that the interaction with the analyte is not effective. In the system, MF3 (Figure 3), the addition of monomer oscillated the interaction energy without satisfactory results with increasing proportions. Group 3 groups the highest energy systems between them, indicating that these monomers do not interact effectively with the analyte. In MF13, the increase in the ratio did not cause the energy to decrease as expected. It was observed that in the presence of monomers like MF6, MF8, MF11, and MF14 there were no increase in the interaction due to preferential interaction between the monomers and analyte, thus contradicting the objective of this work. Figure 3 also shows the difference between the interaction energy in the ratio of 1:1 to the 1:4 ratio that may demonstrate when the molar fraction increases occurred greater or less stability of the whole system. So, we have the following order of interaction energy: MF2> MF4> ME2> MF1> MF10> MF5> MF12> MF15> MF9> ME1> MF3> MF14> MF16> MF13> MF7> ME3> ME4> MF8> MF11> MF6.

It is observed that some monomers have larger energy

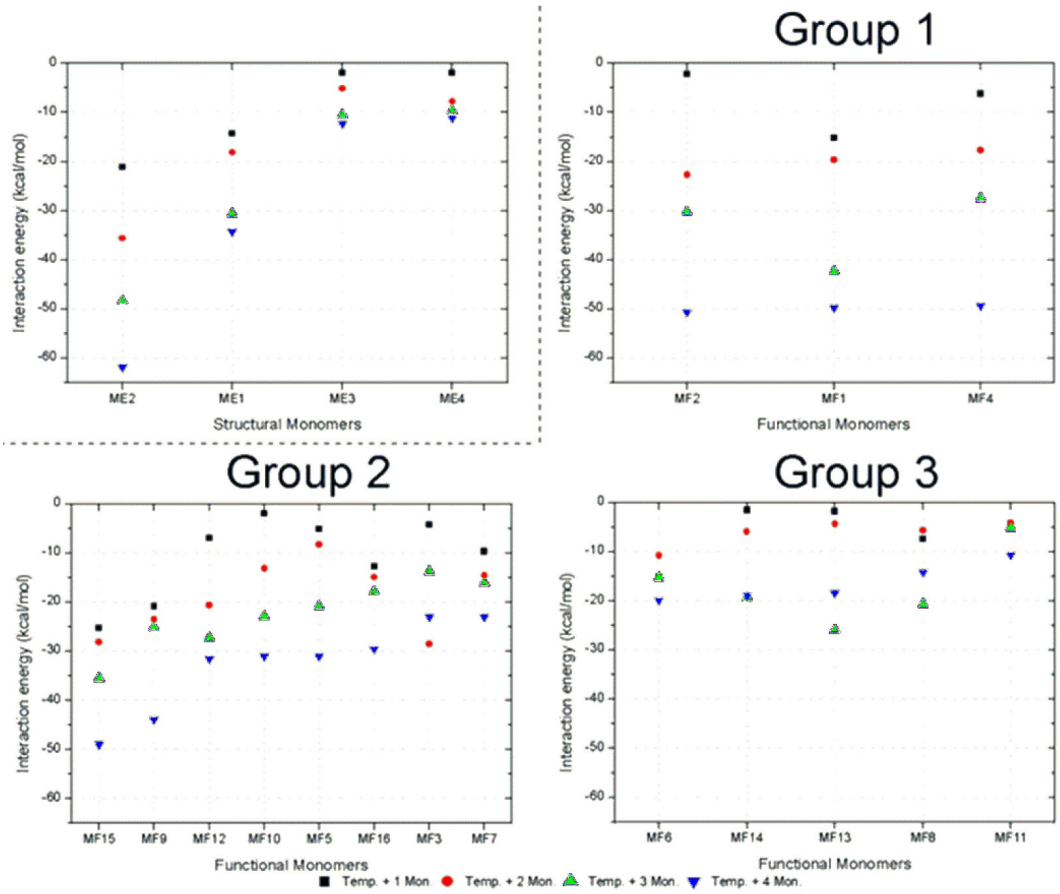

Figure 3. Interaction between monomers and analytes in a vacuum, categorized into three groups (Group 1, Group 2, Group 3)

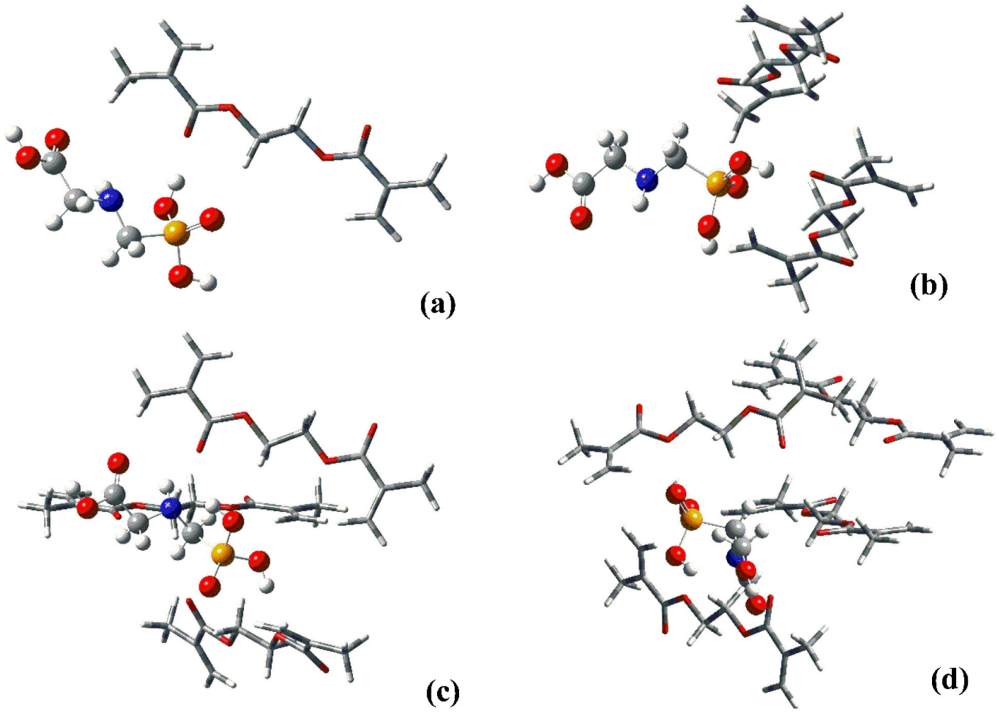

Figure 4. Vacuum interactions for the functional analyte-monomer system (ME2) at proportions: (a) 1:1; (b) 1:2; (c) 1:3; and, (d) 1:4

ranges, such as imidazole-4-acrylic ethyl ester (MF2), acrylamide (MF4), EGDMA (ME2), imidazole-4-acrylic acid (MF1) and methacrylic (MF10). The MF2 monomer, for example, has -2.16 kcal mol^{-1} when only one molecule interacts with the analyte molecule. Increasing the number of monomers in the presence of the analyte ratio 1:2 yields -22.70 kcal mol^{-1} is -30.11 kcal mol^{-1} in the ratio of 1:3 and -50.70 kcal mol^{-1} in 1:4 thus energy of 48.54 kcal mol^{-1}. This may indicate that MF2 may have a desirable selectivity for molecular recognition while functional monomer determines the type of binding at the printed sites on the polymer.[47] The l analyte-monomer interaction depends on an equilibrium process in which these bonds have sufficient energy to form the binding sites. We can easily remove the template by simply washing it which removes recognition cavities.[20]

3.1.2. Evaluation of porogenic solvents

The synthesis and efficiency of the MIP are evaluated for the number and the energetic intensity of the interaction between the binding sites that can be obtained between the analyte and the functional monomer. Thus, the solvent has an important role in the solubilization of synthesis agents, analytes, functional monomers, crosslinking agents (CLA), and radical initiators (IR).[48] In addition, the solvent is responsible for the formation of pores. The morphology and volume of these pores are controlled by the nature and amount of the solvent used; therefore, thermodynamically favorable solvents can produce polymers with well-developed porous structures.[48] Thus, the volume and nature of the solvent are interesting parameters, and these cannot interfere in the synthesis process between the analyte and the functional monomer. The solvation is inserted in the simulation using Gaussian software 09W, and the solvents water, acetonitrile, toluene, methanol, and ethanol were studied individually in the interaction of the monomers with the glyphosate.

3.1.3. Water

Water is a protic solvent (allows the formation of hydrogen bonds) so this solvent is not often used because it can interfere with the electrostatic interactions and hydrogen bonds between the analyte and the functional monomer.[49] However, in this work, water was one of the solvents evaluated in the interaction with the analyte for the understanding of synthetic processes such as suspension polymerization, where the polymers are easily obtained in aqueous solution[49-50] by emulsion polymerization that allows the synthesis of hydrophilic MIP particles.[51] The energy of analyte-monomer interactions, having the water as an implied solvent in the 1:4 ratio, comprises the monomers in order: ME2 <MF15 <MF16 <MF12 <MF3 <MF10 <MF11 <ME3 <MF14 <MF13 <MF6 <MF2 <MF5 <MF8. Observing the methodology of analysis adopted in this work belongs to group 1: MF15, MF16, MF12; group 2: MF3 MF1, MF10, MF9, MF4, MF7, MF11, MF14; and group 3: MF13, MF6, MF2, MF5 and MF8 as shown in Figure 5.

Again, the ME2 is the monomer in the aqueous medium that presented greater interaction having more negative energy. It is observed that in the ratio of 1:4 this functional monomer has interaction energy equal to -37.02 kcal mol^{-1}, a variation of 24.76 kcal mol^{-1}, compared to the results presented in the vacuum. The functional monomers 2-acrylamido-2-methyl-1-propane sulfonic acid (MF15), 2-hydroxyethyl methacrylate (MF16), and 1-vinylamidazole (MF12) are classified within the analytical group 1 of -20 kcal mol^{-1} (Figure 5). The MF15, presented a value in the ratio of 1:4 of -29.23 kcal mol^{-1}, drawing attention to the energy of 14.11 kcal mol^{-1} between the ratio of 1:1 and 1:4. It is suggested that the interaction may be more energetically favorable with the addition of functional monomers due to the interaction of hydrogen bonds, as shown in Figure 6d.

The size of the molecule and the presence of the sulfonic group in the MF15 may be the determining factor for an interaction comparable to the ME2, although the formation of hydrogen bonding in the region of the analyte sulfur atom is observed that has significant importance for analyte-functional monomer interactions. In group 2, the functional monomers present energies of intermediary interactions for the systems in an aqueous medium. It is observed that the energies obtained are quite varied in some cases are small while in some cases are larger suggesting that the interaction with the glyphosate analyte is not effective, for example, in MF4, MF7, MF11, and MF14 had increased energies. Therefore, the use of water as a solvent may not be adequate for some polymerization processes involving this group of polymers since it may interfere with the functional analyte-monomer interaction, especially when hydrogen bonds occur, so the solubility of the functional monomers and the analyte results in polymers of low molecular recognition.[6] Group 3 is the highest energy functional analyte-monomer systems among the systems studied, so these functional monomers do not interact effectively with the analyte. In the system (Figure 5), the addition of these monomers increased the interaction energy or even did not have significant changes. A significant increase in energy was not observed for group 3, suggesting that the functional-analyte-monomer interaction is weak or non-existent. In addition, it is possible to evaluate that the non-increment of energy favorable to the interaction can indicate a preferential interaction between the functional monomers and not with the analyte. Therefore, attempts are made to create polymers whose solvent for these monomers is water. The analyte-monomer interaction energies are shown in the Figure 5, it is possible to evaluate the interaction energy between fractions 1:1 and 1:4, allowing to verify if there is greater or less stability of the whole system with the increase of the fraction in the following order: ME2> MF15> MF3> MF1> MF10> MF10> ME1> MF7> MF7> ME4> MF11> MF6> MF14> ME3> MF2> MF13> MF5> MF8.

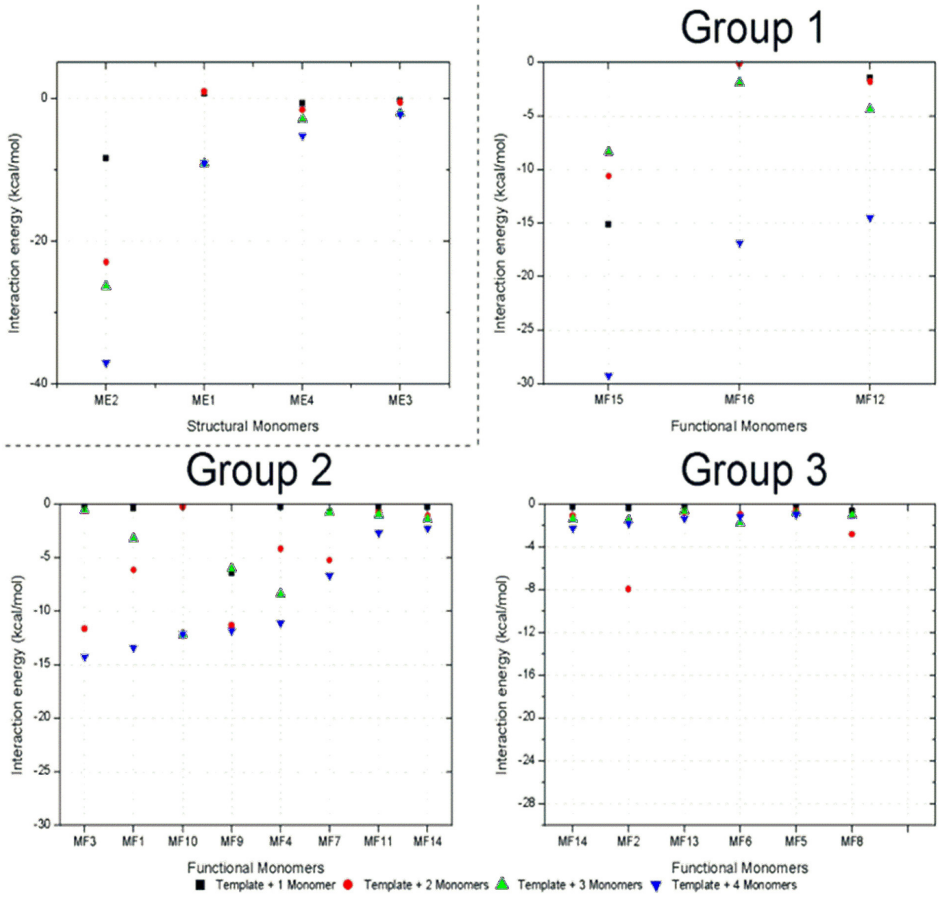

Figure 5. Interaction between analytes and monomers in water, categorized into three groups (Group 1, Group 2, and Group 3)

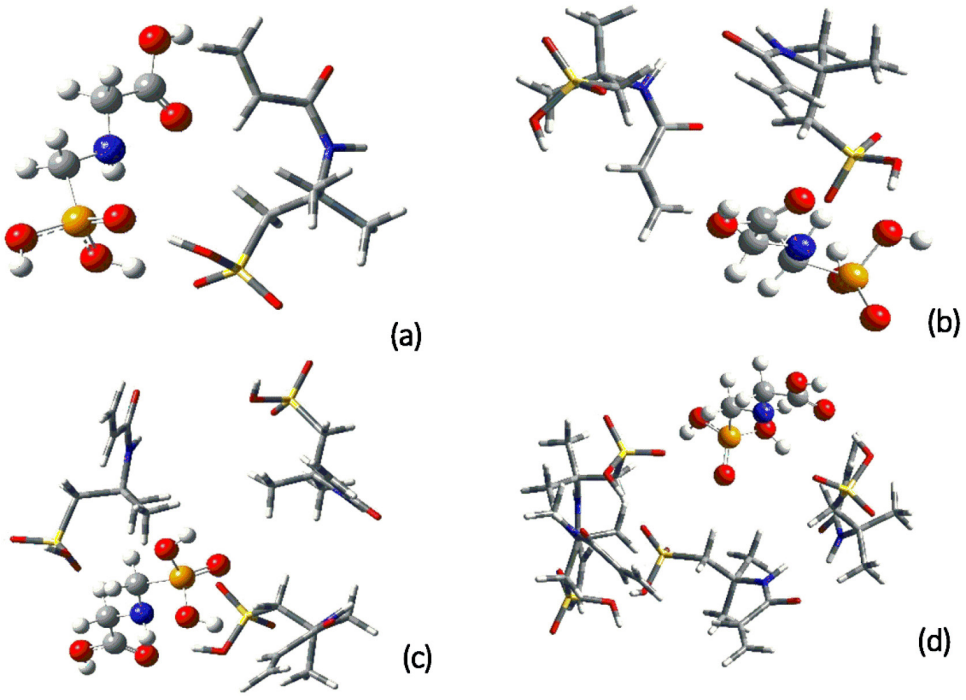

Figure 6. Interaction in water medium for the analytical-functional monomer system (MF10), in proportions: (a) 1:1; (b) 1:2; (c) 1:3; and, (d) 1:4

3.1.4. Acetonitrile

Acetonitrile or methyl cyanide (ACN) is a medium solvent with aprotic polarity. In this work, this solvent was used to evaluate the interaction between the analyte and the functional monomers. In Figure 7, the interaction energies for the systems formed between analyte-monomers are shown. The more negative the energy, the greater the interaction between the analyte and the monomer, so that the following order of this interaction energy can be observed for the ratio 1:4: ME2 <MF1 <MF9 <MF10 <MF15 <MF4 <MF2 <MF7 <MF3 <MF16 <MF12 <MF14 <ME3 <ME4 <MF13 <MF11 <MF5 <ME1 <MF6 <MF8.

According to the analytical methodology adopted in this work, the best analyte-monomer interaction systems with the presence of imidazole-4-acrylic acid (MF1), methylene succinic acid (MF9), and methacrylic acid (MF10); group 2, MF15, MF4, MF2, MF7, MF3, MF16, MF12 and MF14; and group 3 MF13, MF11, MF5, MF6, MF8.The energy between the fractions 1:1 and 1:4 for each system studied shows the order of decreasing sequence: MF1> ME2> MF10> MF9> MF2> MF14> MF12> ME3> ME4> MF6> MF7> MF13> MF11> MF5> MF15> MF8> M16> ME1. In group 1, it is observed that the MF1 presents the lowest energy value when in interaction with the analyte glyphosate in the analyte-functional monomer fraction in the ratio 1:4 of -28.45 kcal mol^{-1}.

The MF9 presented between fractions 1:1 and 1:4 of -15.17 kcal mol^{-1}, which may indicate that Methylene succinic acid promotes good sites of interaction. Similar to the MF10 in which the interaction energy reached -19.85 kcal mol^{-1} and the still higher between the fractions 1:1 and 1:4 of 19.71 kcal mol^{-1}, which shows that methacrylic acid is an excellent functional monomer in polymer synthesis. In group 2, it is observed that the MF16 presents of 3.58 Kcal mol-1 obtained between fractions 1:1 and 1:4.

This monomer is also used as a crosslinking agent in synthesizing MIP in herbicide studies.[52] However, the monomers MF15, MF4, MF2, MF7, MF3, MF12, and MF14 had low energy changes with the fraction increase, such as MF12 and MF14, which presented Δ around 3,00 kcal mol^{-1}. However, it was observed that acrylic acid (MF3) did not show significant results although it shows a relatively low result in the fraction of 1:3 as shown in Figure 8.

This may indicate that the increase in the number of functional monomers does not energetically favor polymer synthesis, and the cavity formed is not sufficient for good selectivity. It is observed that there are hydrogen bonds with the participation of the oxygen and nitrogen atoms which can increase the selective cavity but a distance in the

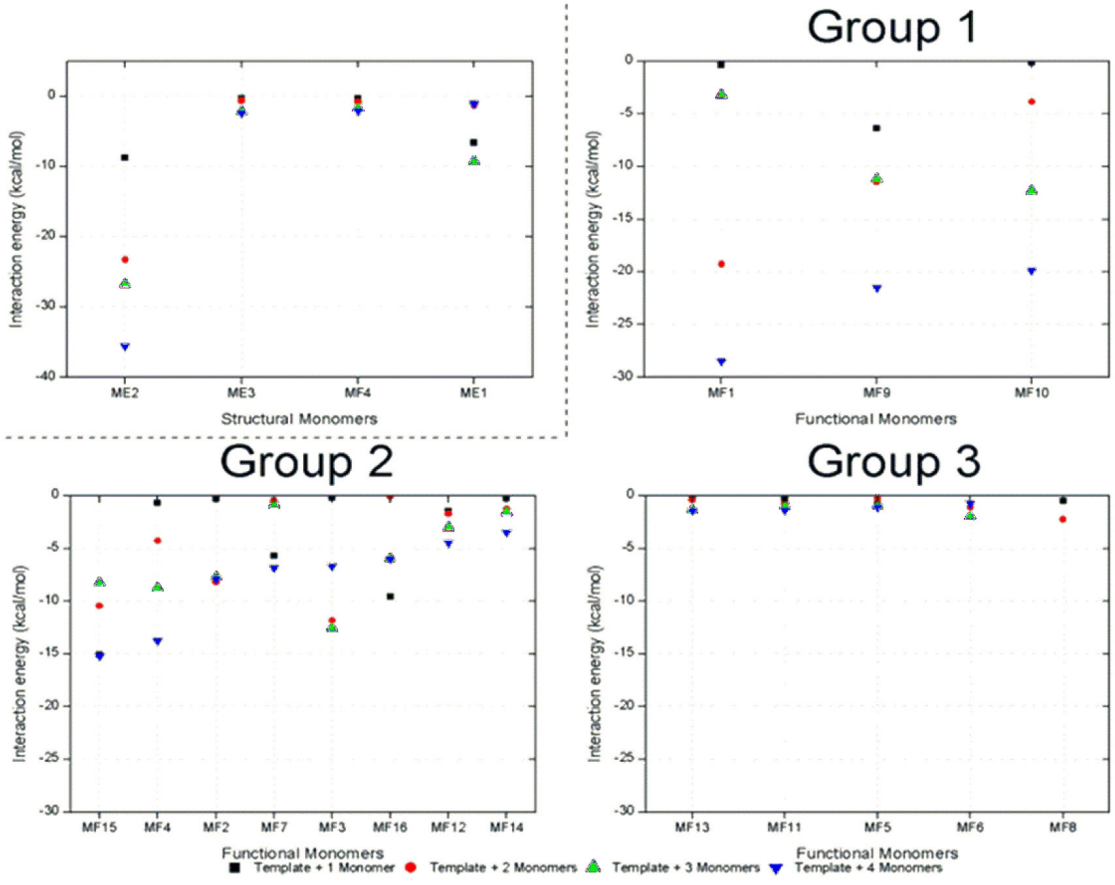

Figure 7. Interaction between analytes and monomers in acetonitrile, divided into three distinct groups (Group 1, Group 2, and Group 3)

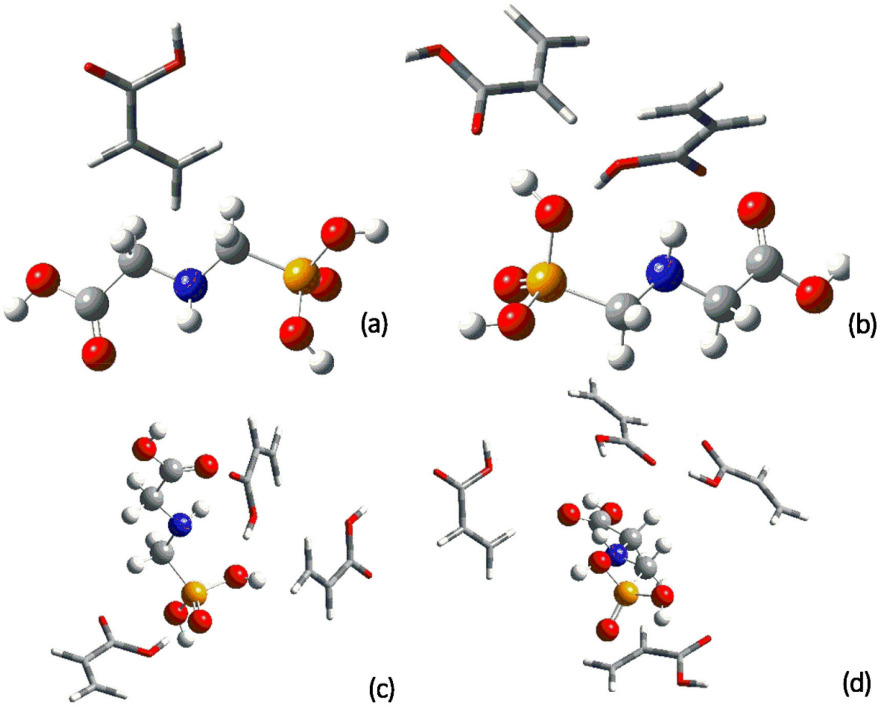

Figure 8. Interaction in acetonitrile medium for the analyte-acrylic acid (MF3) system, in proportions: (a) 1:1; (b) 1:2; (c) 1:3; and, (d) 1:4

spatial arrangement of the monomers in the proportion 1:4 as shown in the Figure 8d. Group 3 is the highest energy analyte-monomer system among the studied systems; with the addition of functional monomers, the interaction energy remained practically unchanged and with higher values. Therefore, they are functional monomers with low efficiency regarding the production of polymers with molecular recognition sites. In the system, MF8 (Figure 7), the addition of monomer increased the interaction energy, unlike that observed in groups 1 and 2. The systems with the presence of MF5, MF6, MF11, and MF13 (Figure 7) are perceived which be around 1.00 kcal, which may indicate a preferential interaction between the monomers and not to the analyte.

3.1.5. Toluene

The solvent toluene is commonly used as the polymerization solvent in the preparation of MIP.[53] In this work, the analyte-monomer systems obtained in this solvent presented more negative interaction energy when compared to the other media investigated in this research, as shown in Figure 9.

The increasing order of interaction energy of the systems with the use of toluene as solvent are ME2 <MF1 <MF1 <MF2 <MF8 <MF16 <MF16 <MF10 <MF5 <ME1 <MF14 <MF3 <MF13 <MF6 <MF12 <MF7 <MF8 <MF8 <ME4 <ME3 <MF11. Thus, in group 1 are 2-acrylamido-2-methyl-1-propanic sulfonic acid (MF15), Imidazole-4-acrylic acid (MF1), and Acrylamide (MF4). In group 2: MF2, MF9, MF16, MF10, MF5, MF14, MF3, MF13; in group 3: MF6, MF12, MF7, MF8 and MF11. In group 1, the interaction 1:4 was generally observed to be lower than -34 kcal mol^{-1}, presenting expressive values suggesting that the addition of monomers to the system favors the interaction energetically. The structural monomer EGDMA (ME2) when interacting with the analyte present in the toluene medium is the most negative interaction energy that is more favorable energy interaction between the studied systems, indicating the system of greater stability to the rigidity of the binding sites,[46] for glyphosate MIP. It is observed from Figure 9 that the energy decreases gradually, when in the ratio 1:1, 1:2, 1:3 and 1:4 the values found are, respectively, - 17.63 kcal mol^{-1}, -29.34 kcal mol^{-1}; -39.39 kcal mol^{-1} and -50.97 kcal mol^{-1}. The other structural monomers like ME1, ME3, and ME4 were not more significant.

Figure 10 shows the spatial arrangement for the analyte-ME2 interaction. The arrangement of the chemical structures allows the identification of hydrogen bonds between the compounds and the preferential interaction of the site with the presence of sulfur and the carbonic medium of the EGDMA (Figure 10b). When in the ratio of 1:4 (Figure 10d), EGDMA binds hydrogen at the other end of the analyte, which may justify the greater interaction of this system.

In group 2, the monomers MF3, MF13, and MF14 did not present a significant effect, although the monomers MF10 in the fraction of 1:2 have interaction energy of -20.07 kcal mol^{-1}, however when the fraction becomes 1:3, this energy increases to -18.31 Kcal mol^{-1}. This is also observed in MF3; when the molar fraction goes from 1:2 to 1:3, the system energy increases. It is also observed that the monomers MF5 and MF16, showed considerable Δ when the molar fraction is increased. In group 3, the

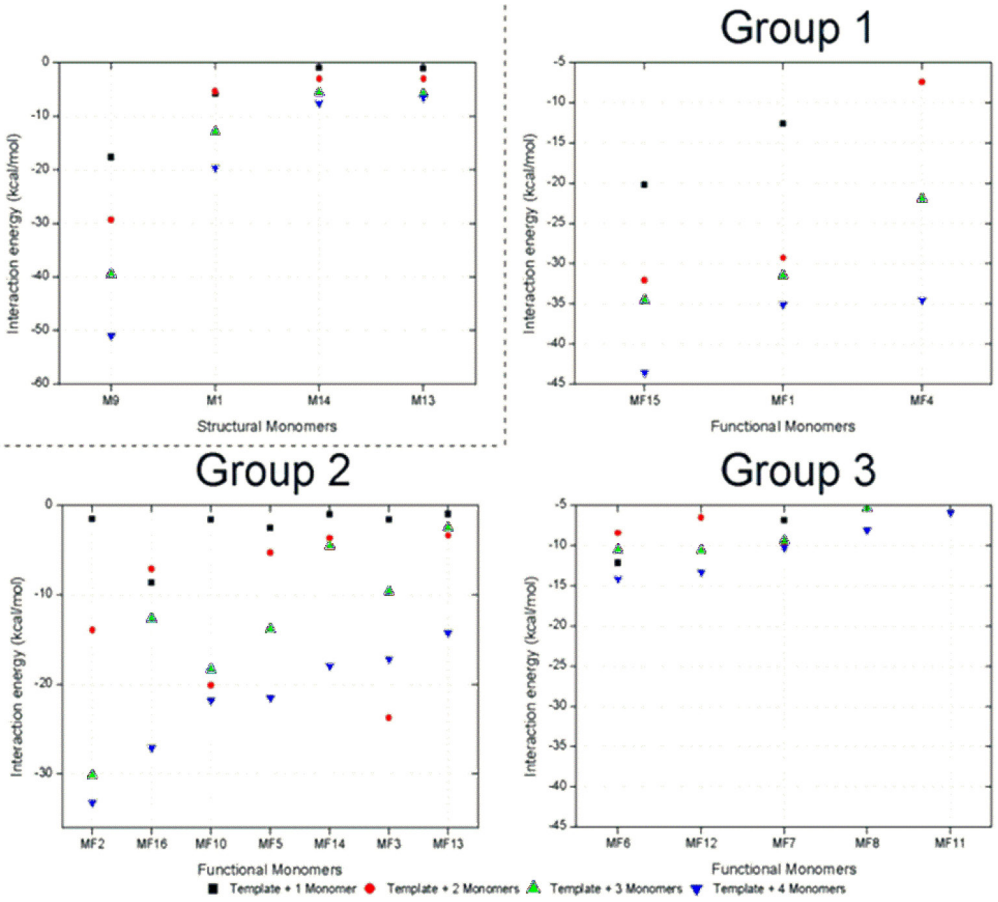

Figure 9. Interaction between analytes and monomers in Toluene, divided into three distinct groups (Group 1, Group 2, and Group 3)

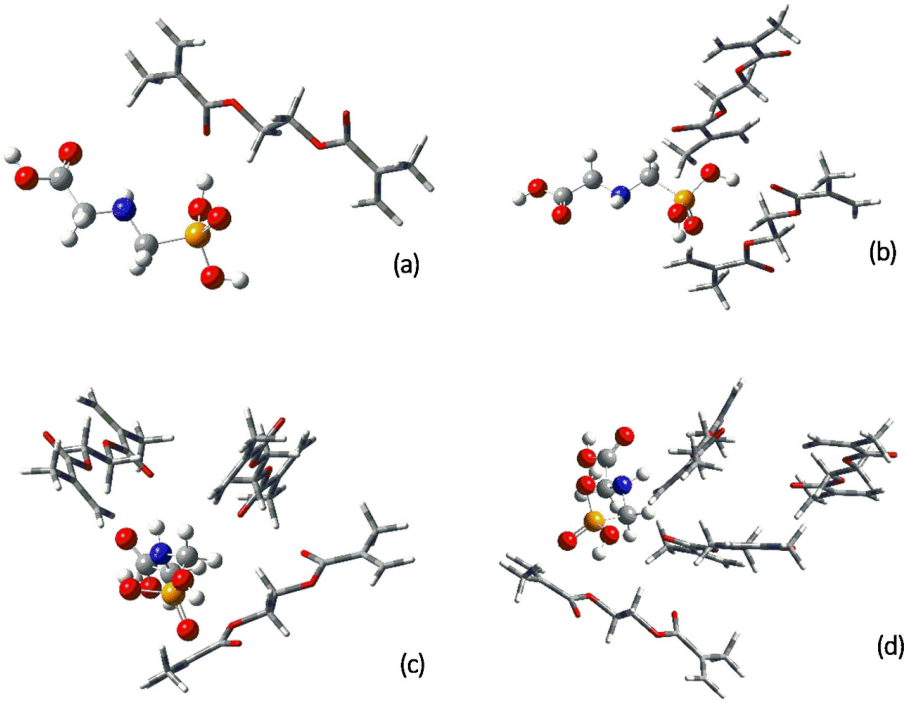

Figure 10. Interaction in toluene medium for the analyte Ethylene Glycol Dimethacrylate-EGDMA (ME2) system, in proportions: (a) 1:1; (b) 1:2; (c) 1:3; and, (d) 1:4

functional analyte-monomer systems MF6, MF12, MF7, MF8, and MF11 had around 4.5 Kcal mol^{-1}. The increase in the proportion of these monomers does not energetically favor the interaction for MIP formation. The ratio between the 1:1 and 1:4 fractions for the studied systems follows the descending order: ME2> MF4> MF2> MF15> MF10> MF10> MF5> MF15> MF14> MF3> MF9> ME1> MF13> MF12> ME4> ME3> MF11> MF8> MF7> MF6. This assumes that the larger the modulus, the greater the energy favoring the system due to monomers.

3.1.6. Methanol

The solvent methanol is widely used in the synthesis of MIP. The results obtained for the analyte-monomer systems in the presence of the methanol solvent (Figure 11) show the following order of interaction energy in 1:4: ME2 <MF15 <MF3 <ME1 <MF2 <MF10 < MF5 <MF16 <MF7 <MF9 <MF12 <ME3 <MF8 <MF6 <MF14 <ME4 <MF11.

It is observed that the EGDMA (ME2) again presents as the structural monomer that better interacts with the analyte glyphosate about ME1, ME3, and ME4. The modulus of these monomers has the sequence: ME2> MF3> MF10> MF2> MF1> MF13> MF16> MF5> ME1> MF15> MF12> MF6> MF7> ME3> MF8> MF14> ME4> MF11> MF9. In group 1, observing the methodology of analysis adopted in this work the monomers with greater interaction in the ratio of 1:4 was 2-acrylamido-2-methyl-1-propanic sulfonic acid (MF15), acrylic acid (MF3), and imidazole -4-acrylic ethyl ester (MF2). Although these monomers belong to the first group presented low interaction energy in a ratio of 1:3 around -10.0 Kcal mol^{-1}. This may indicate that the methanol solvent is not an effective medium for the interactions between the glyphosate analyte and the functional monomers studied.

The system with the presence of MF15 showed a small Δ, and its energy increased between the ratio 1:2 and 1:3, indicating that the addition of this functional monomer in the system can oscillate the interaction energy or even make it more positive. In group 2 are the systems with the presence of monomers MF10, MF4, MF1, MF13, MF5, MF16, MF7, and MF9. These monomers MF1, MF5, MF16, MF7, and MF9 had low increases in the energy of interaction even increasing the proportion, or did not even present significant changes. In the monomers, MF5 and MF16 a slight decrease of the energy occurred when there was an increase of the ratio 1:4 around 7 kcal mol^{-1}.

Methacrylic acid (MF10) showed significant results after the 1:3 fractions, although belonging here to the intermediate

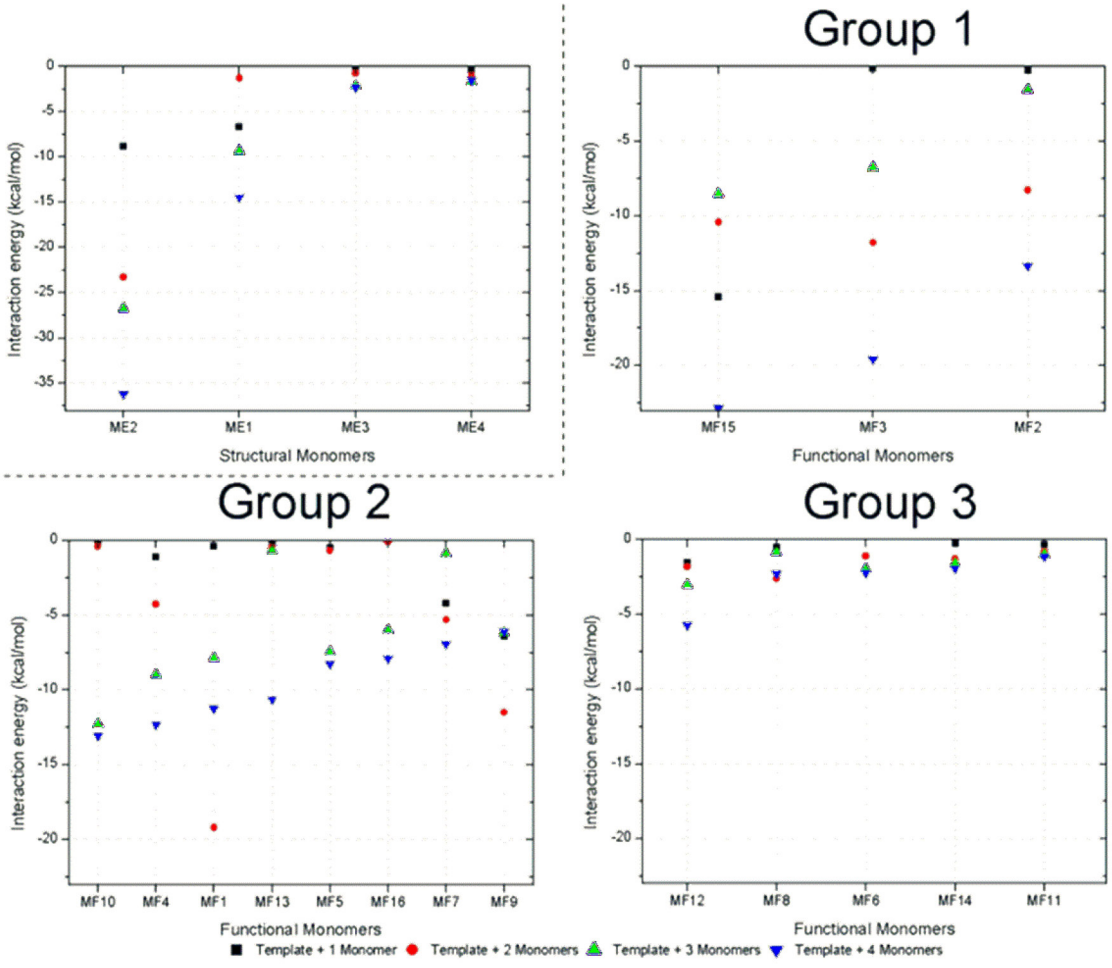

Figure 11. Analyte-monomer interaction in methanol, divided into three distinct groups (Group 1, Group 2, and Group 3)

group is widely used in MIP synthesis. (Figure 12a, b), but in the ratio 1:3, the hydrogen bonding is observed in the ratio of 1:1 to 1:2 (Figure the atoms belonging to the carboxyl group of MF10 and the site with the pres. Despite this, one of the monomers was still separated from other possible sites of the analyte (Figure 12c). In group 3, the monomers MF12, MF8, MF6, MF14, and MF11 did not show any change in the interaction energy even when the proportion was increased, indicating the non-favoring energy for the system, which can show the strong influence of the solvent on the monomer does not allow interaction with the analyte or even favoring the interaction between the monomers.

3.1.7. Ethanol

Ethanol, like methanol, is widely used as a solvent for MIP synthesis, mainly because it is inexpensive since the choice of the monomer is the essential factor for creating porosities in the synthesized polymer. The results obtained for the analyte-monomer systems in the presence of the ethanol solvent (Figure 13) have the following energy interaction order: ME2 <MF2 <MF15 <MF5 <MF10 <MF12 <MF14 <MF4 <MF16 < MF3 <MF7 <ME3 <ME4 <MF13 <MF6 <MF11 <MF8 <MF9. In group 1, the systems with the presence of imidazole-4-acrylic ethyl ester (MF2), 2-acrylamido-2-methyl-1-propanic sulfonic acid (MF15), and acrolein (MF5). For the MF15, the interaction energies between the analyte and functional monomer were more positive in fractions 1:2 and 1:3, and the others that belong to this group did not have as satisfactory results when compared to the previous analysis indicating that the medium ethanol did not show good efficacy for these systems.

The spatial arrangement of the observed interaction between the analyte and MF2 in the proportions studied in the ethanol medium is shown in the Figure 14.

It is observed that in proportions 1:1 and 1:2 (Figure 14a, 14b) MF2 does not interact with the analyte for the formation of hydrogen bonding. In the proportion 1:3 and 1:4, a spatial arrangement occurs that allows the interaction of the pentagon of MF2, which has the presence of nitrogen with the site of the analyte that has the presence of sulfur. This situation allows evaluating that the increase of the proportion is significant for a greater analyte-functional monomer interaction, which is facilitated by the arrangement of the compounds or their accommodation in a minimum state of energy and the hydrogen bonds.

In group 2, the intermediate energy monomers in this set are: MF10, MF12, MF14, MF4, MF16, MF1, MF3, and MF7. Among these, the MF12, MF14 had no increase in energy by up to 1:3, while MF1 had an increase in energy and then a decrease in the ratio of 1:4. The compounds with MF10, MF16, MF1, MF3 and MF7 showed energy oscillation with the increase of the number of monomers. Only MF4 showed a slight decrease in energy with increasing proportion (Figure 13). In group 3, the monomers MF13, MF6, MF11, MF8, MF9 presented weaker interaction energy that has

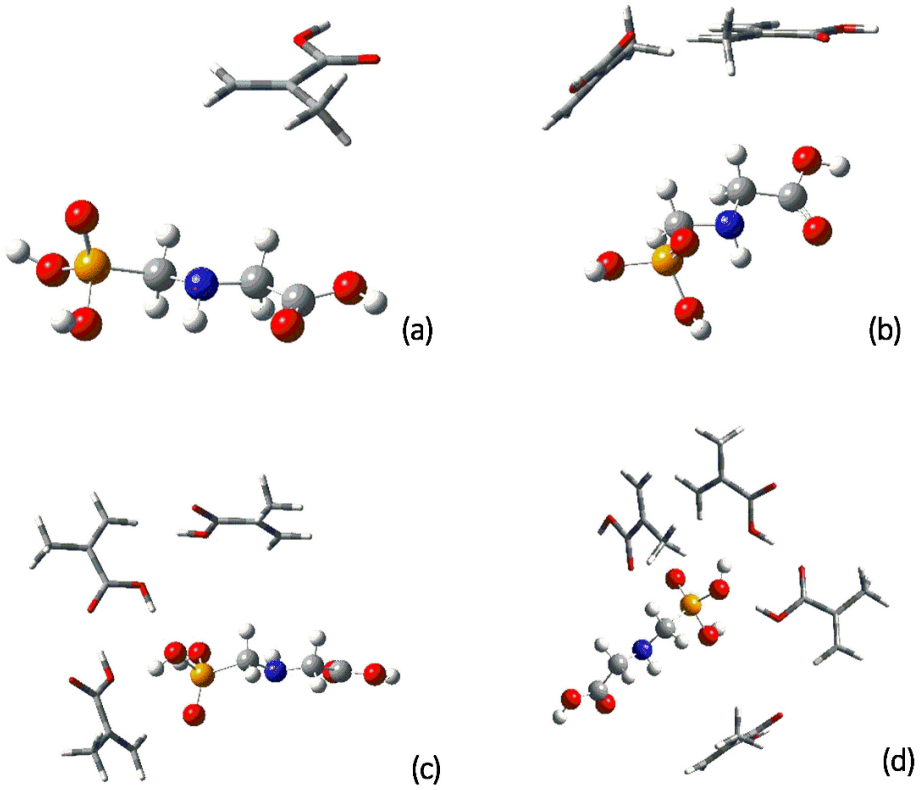

Figure 12. Interaction in methanol medium for the functional analyte-monomer system (MF10), in the proportions: (a) 1:1; (b) 1:2; (c) 1:3; and, (d) 1:4

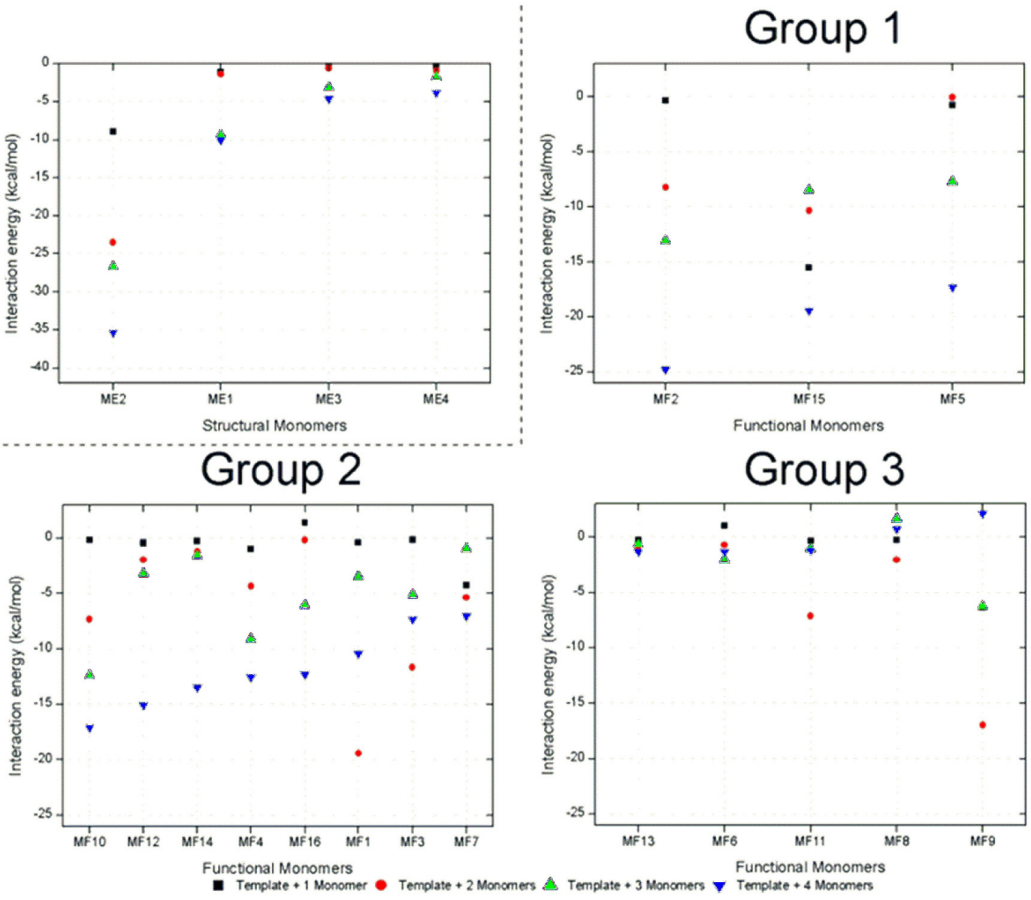

Figure 13. Analyte-monomer interaction in ethanol, divided into three distinct groups (Group 1, Group 2, and Group 3)

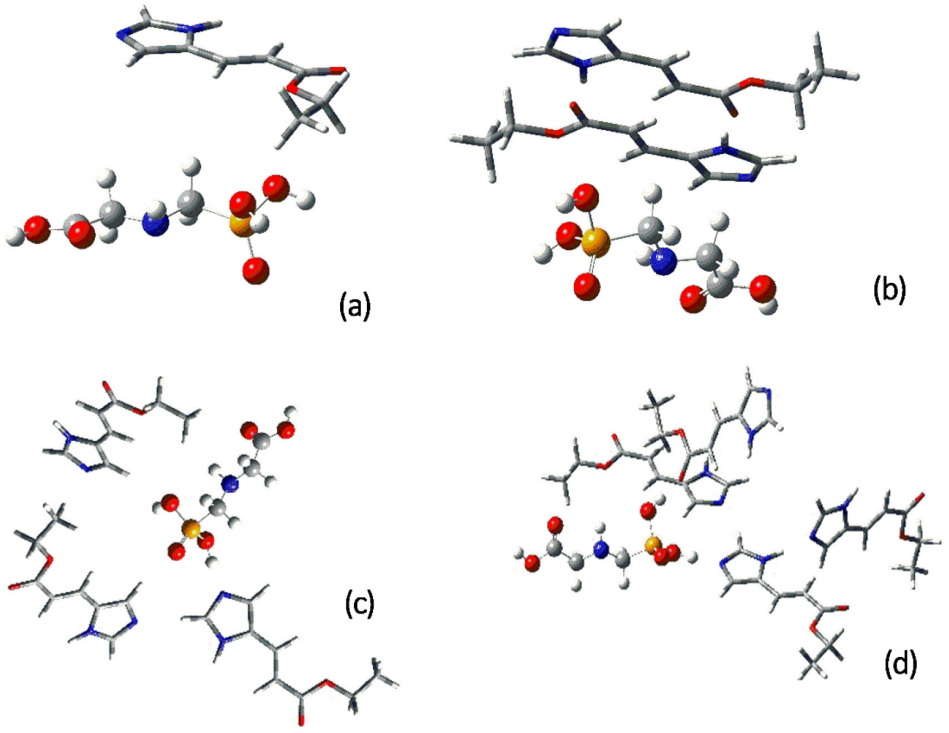

Figure 14. Interaction in ethanol medium for the analyte-imidazole-4-acrylic ethyle-ster (MF2) system, in proportions: (a) 1:1; (b) 1:2; (c) 1:3; and, (d) 1:4

less interaction with the analyte in the presence of ethanol solvent. These compounds had interaction energy ranging in ratios of 1:2 and 1:3. The MF13 and MF9 did not present energy changes with the increase of the proportions. The systems that presented the functional monomers with the highest interaction with the analyte also present higher values resented in decreasing order: ME2> MF2> MF1> MF1> MF1> MF1> MF1> > MF15> ME3> ME4> MF7> MF6> MF13> MF11> MF8> MF9.

4. Results and Discussion

The Density Functional Theory DFT, method B3LYP together with a base set 6-31 + g (d, p), allowed to evaluation of the interaction between the analyte glyphosate and 20 monomers to simulate the production of molecularly printed polymer for the study of glyphosate recognition. Table 1 shows the energy, with the interaction energy values for the systems. In this way, 6 systems highlighted energetically were selected in each medium. In the vacuum, the interaction of the analyte with monomers results in more negative interaction energy values, therefore, a higher interaction, especially in the solvents, was studied in the presence of the monomers ME2 (ethylene glycol dimethacrylate), the EGDMA being a structural monomer often used with crosslinking agent (CLA). Among the functional monomers are imidazole-4-acrylic acid (MF1), acrylamido-2-methyl-1-propane sulfonic acid (M15), methacrylic acid (MF10), imidazole-4-acrylic ethyl ester (MF2) (ACL) (MF4) and acrylic Acid (MF3). Sequentially, MF1 and MF15 also have satisfactory interaction energy for the studied media when interacting with the analyte, as shown in Table 1.

The solvent plays an important role in the complexation and formation of the model molecule, which has the purpose of molecular recognition of glyphosate. Therefore, the solvent should not interfere with this process, and the values should be as small as possible. Thus, Table 2 presents the interaction energy values of the systems with the lower energy functional monomers.

The analysis of these results allows us to verify that toluene is the solvent that favors the complexes' interaction as it presents the average energy of lower interaction between the 6 main systems studied as presented in Table 1. It is noted there are relevant works where MF10 (methacrylic acid), ME2 (ethylene glycol dimethacrylate), and toluene were used in MIP synthesis processes as functional monomer, crosslinking agent and solvent.[52] Thus, this research, which was carried out with 20 monomers and used toluene as one solvent, presented satisfactory results.[53]

Thus, toluene a non-polar, aprotic solvent with a low dielectric constant, is an appropriate medium because it does not interfere in the interactions that occur by electrostatic and hydrogen bonding forces.[54-55] This justifies the use of toluene in papers published in the process of polymerization synthesis.[53] Equation 2 shows the energy difference between the analyte-monomer complex in solution and vacuum, as shown in Figure 10. The EGDMA (ME2) has a lower energy value than the other monomers group of the structural monomers, EGDMA (ME2) in the proportion of 1:4 the variation for toluene, is:

$$\Delta E_{solv} = -50{,}972 - (-61{,}778) \quad (4)$$

$$\Delta E_{solv} = 10{,}0806 \text{ kcal mol}^{-1} \quad (5)$$

In a qualitative/quantitative comparison, the monomers that had little interaction with the analyte from group 3 to toluene while 2-vinyl pyridine (MF13), this one with greater

Table 1. Principal analyte-monomer complexes with interaction energy with the lowest values in the proportion 1:4 in kcal mol^{-1}

Complex	Vacuum	Water	Acetonitrile	Toluene	Methanol	Ethanol
Glyphosate - Imidazole-4acrylic acid (MF1)	-49,73	-13,40	-28,45	-35,09	-11,21	-10,43
Glyphosate - 2-Acrylamido-2-methyl-1-propanesulfonic acid (M15)	-48,99	-29,23	-15,22	-43,58	-22,85	-22,18
Glyphosate -Imidazole-4acrylic ethylester (MF2)	-50,70	-0,98	-7,84	-34,47	-13,07	-24,88
Glyphosate - Acrilamide (ACL) (MF4)	-49,38	-11,09	-13,75	-34,47	-12,28	-12,54
Glyphosate –Methacrylic Acid (MF10)	-31,04	-12,09	-19,85	-21,75	-13,04	-17,10
Glyphosate –Acrylic Acid (MF3)	-23,07	-14,22	-6,67	-17,20	-19,56	-7,33

Table 2. Evaluation of the best complexes with respect to the solvents in a ratio of 1: 4 in kcal mol^{-1}

Complex	Water	Acetonitrile	Toluene	Methanol	Ethanol
Glyphosate - Imidazole-4-acrylic acid	36,33	21,28	14,64	38,52	39,03
Glyphosate - 2-Acrylamido-2-methyl-1-propanesulfonic acid	19,76	33,77	5,41	26,14	26,81
Glyphosate - Imidazole-4-acrylic ethylester	49,72	42,86	16,23	37,63	25,82
Glyphosate - Acrilamide (ACL)	38,29	35,63	14,91	37,1	36,84
Glyphosate – Methacrylic Acid	18,95	11,19	9,29	18	13,94
Glyphosate – Acrylic Acid	8,85	16,4	5,87	3,51	15,74
Média/solvente	24,81	26,85	11,05	26,81	26,36

energy, then for equation 2, we have varied with the dipole moment of the solvent.[53] Therefore, solvents with greater dipole moments can influence the values of , which may imply the solvent's interference in the synthesis process and not be interesting for the formation of the active sites. Among the 5 solvents studied, the toluene presents a lower dipole moment, and, consequently, in average, is the lowest observed. Table 2 presents the interaction energy of the complexes with the presence of each of the 6 monomers analyzed and selected that had lower interaction energy, about the solvent medium. For this calculation, equation 2 was used, which allows evaluating the behavior of the monomer when submitted in different media for observing The performance of the solvents that interfere minimally with the complex, collaborating with the formation of the active sites for molecular recognition is significant for obtaining the MIP.[53]

In this way, the use of equation 2 allows to understand the intensity of the energy of action for each solvent that surrounds the 6 monomers of lower energy interaction. Thus, by this analysis, it is observed that the studied solvents have similar behaviors as the mean of the solvation energy except for toluene. The acrylic acid (MF3), methacrylic acid (MF10), and 2-acrylamido-2-methyl-1-propanesulfonic acid (MF15) are the most suitable means for the synthesis of MIP for glyphosate.

5. Conclusion

The present work presents the analysis by DFT of twenty monomers (16 functional monomers and four structural monomers) in the interaction with the analyte glyphosate in order to be used for selectivity in molecularly printed polymers (MIP). They reveal that ME2 (ethylene glycol dimethacrylate) is structural monomer with the lowest interaction energy in EGDMA is used as a crosslinking agent in the polymer synthesis. Acrylic acid (MF3), methacrylic acid (MF10), and 2-acrylamido-2-methyl-1-propane sulfonic acid (MF15) interacts with glyphosate effectively in some most solvents they had more favorable lower interaction energy. Among the solvents studied, it is observed that toluene presented the best performance in the calculations, but due to environmental hazard reasons, its use is not recommended and suggests the use of the other solvents for polymer synthesis. The results obtained from this research advance to experimental work by optimizing time, lab financial as well as reducing environmental contaminations and preparation of MIP biosensor for molecular recognition of glyphosate.

Authors Contribution

Douglas Gonçalves de Lima: Data curation, Funding acquisition, Formal analysis, Investigation, Original draft writing.

Vanessa Lima dos Santos Teixeira: Data curation, Funding acquisition, Formal analysis, Investigation.

Elpidio Souza de Santana: Data curation Resources, Validation, Visualization, Review and editing.

Deiver Alessandro Teixeira: Conceptualization, Funding acquisition, Formal analysis, Investigation, Project administration, Resources, Software, Validation, Visualization, Original draft writing, Review and editing.

Sabir Khan: Conceptualization, Funding acquisition, Formal analysis, Investigation, Project administration, Resources, Software, Validation, Visualization, Original draft writing, Review and editing.

Maria Del Pilar Taboada Sotomayor: Conceptualization, Funding acquisition, Formal analysis, Investigation, Project administration, Resources, Software, Validation, Visualization, Original draft writing, Review and editing.

Jorge Luiz Brito de Faria: Data curation Resources, Validation, Visualization, Review and editing.

Bibliographic References

1. Tavares, M. I. B.; Bathista, A. L. B. S.; Silva, E. O.; Costa, P. M.; Filho, N. P.; Nogueira, J. S.; ^{13}C-NMR study of *Dipteryx Alata Vogel* starch. *Journal of Applied Polymer Science* **2004**, *92*, 2151. [Crossref]
2. Tavares, M. I. B.; Bathista, A. L. B. S.; Silva, E. O.; Filho, N. P.; Nogueira, J. S.; A molecular dynamic study of the starch obtained from the *Mangifera indica* Cv. *Bourbon* and *Espada* seeds by ^{13}C solid state NMR. *Carbohydrate Polymers* **2003**, *53*, 213. [Crossref]
3. Figueiredo, E. C.; Tarley, C. R. T.; Kubota, L. T.; Rath, S.; Arruda, M. A. Z.; On-line molecularly imprinted solid phase extraction for the selective spectrophotometric determination of catechol. *Microchemical Journal* **2007**, *85*, 290. [Crossref]
4. Hilt, J. Z.; Byrne, M. E.; Configurational biomimesis in drug delivery: molecular imprinting of biologically significant molecules. *Advanced Drug Delivery Reviews* **2004**, *56*, 1599. [Crossref]
5. Teixeira, D. A.; Valente Júnior, M. A. G.; Benedetti, A. V.; Feliciano, G. T.; da Silva, S. C.; Fugivara, C. S.; Experimental and Theoretical Studies of Volatile Corrosion Inhibitors Adsorption on Zinc Electrode. *Journal of the Brazilian Chemical Society* **2015**, *26*, 434. [Crossref]
6. Tarley, C. R. T.; Kubota, L. T.; Molecularly-imprinted solid phase extraction of catechol from aqueous effluents for its selective determination by differential pulse voltammetry. *Analytica Chimica Acta* **2005**, *548*, 11. [Crossref]
7. Cormack, P. A. G.; Elorza, A. Z.; Molecularly imprinted polymers: synthesis and characterization. *Journal of Chromatography B* **2004**, *804*, 173. [Crossref]
8. Khajeh, M.; Yamini, Y.; Ghasemi, E.; Fasihi, J.; Shamsipur, M.; Imprinted polymer particles for selenium uptake: synthesis, characterization and analytical applications. *Analytica Chimica Acta* **2007**, *581*, 208. [Crossref]
9. Courtois, J.; Fisher, G.; Schauff, S.; Albert, K.; Irgum, K.;

Interactions of bupivacaine with a molecularly imprinted polymer in a monolithic format studied by NMR. *Analytical Chemistry* **2006**, *78*, 580. [Crossref]

10. El-Schich, Z.; Zhang, Y.; Feith, M.; Beyer, S.; Sternbæk, L.; Ohlsson, L.; Stollenwerk, M.; Wingren, A. G.; Molecularly imprinted polymers in biological applications. *Biotechniques* **2020**, *69*, 407. [Crossref]
11. Dai, C.-M.; Zhang, J.; Zhang, Y.-L.; Zhou, X.-F.; Duan, Y.-P.; Liu, S.-G.; Selective removal of acidic pharmaceuticals from contaminated lake water using multi-templates molecularly imprinted polymer. *Chemical Engineering Journal* **2012**, *211-212*, 302. [Crossref]
12. Villar-Navarro, M.; Martín-Valero, M. J.; Fernández-Torres, R. M.; Callejón-Mochón, M.; Bello-López, M. A.; Easy, fast and environmental friendly method for the simultaneous extraction of the 16 EPA PAHs using magnetic molecular imprinted polymers (mag-MIPs). *Journal of Chromatography B* **2007**, *1044-1045*, 63. [Crossref]
13. Javanbakht, M.; Fard, S. E.; Abdouss, M.; Mohammadi, A.; Ganjali, M. R.; Norouzi, P.; Safaraliee, L.; A Biomimetic Potentiometric Sensor Using Molecularly Imprinted Polymer for the Cetirizine Assay in Tablets and Biological Fluids. *Electroanalysis* **2008**, *20*, 2023. [Crossref]
14. Javanbakht, M.; Fard, S. E.; Mohammadi, A.; Abdouss, M.; Ganjali, M. R.; Norouzi, P.; Safaraliee, L.; Molecularly imprinted polymer based potentiometric sensor for the determination of hydroxyzine in tablets and biological fluids. *Analytica Chimica Acta* **2008**, *612*, 65. [Crossref]
15. Zhou, X.; Mole, S. J.; Liu, R.; Density functional theory study of vibrational spectra. 4. Comparison of experimental and calculated frequencies of all-trans-1,3,5,7-octatetraene - The end of normal coordinate analysis? *Vibrational Spectroscopy* **1996**, *12*, 73. [Crossref]
16. Hout Jr., R. F.; Levi, B. A.; Hehre, W. J.; Effect of electron correlation on theoretical vibrational frequencies. *Journal of Computational Chemistry* **1982**, *3*, 234. [Crossref]
17. DeFrees, D. J.; McLean, A. D.; Molecular orbital predictions of the vibrational frequencies of some molecular ions. *The Journal of Chemical Physics* **1985**, *82*, 333. [Crossref]
18. Cowen, T.; Karim, K.; Piletsky, S.; Computational approaches in the design of synthetic receptors - A review. *Analytica Chimica Acta* **2016**, *936*, 62. [Crossref]
19. Sanchís, J.; Kantiani, L.; Llorca, M.; Rubio, F.; Ginebreda, A.; Fraile, J.; Garrido, T.; Farré, M.; Determination of glyphosate in groundwater samples using an ultrasensitive immunoassay and confirmation by on-line solid-phase extraction followed by liquid chromatography coupled to tandem mass spectrometry. *Analytical and Bioanalytical Chemistry* **2012**, *402*, 2335. [Crossref]
20. Ramirez, C. E.; Bellmund, S.; Gardinali, P. R.; A simple method for routine monitoring of glyphosate and its main metabolite in surface waters using lyophilization and LC-FLD+MS/MS. Case study: canals with influence on Biscayne National Park. *Science of The Total Environment* **2014**, *496*, 389. [Crossref]
21. Karim, K.; Breton, F.; Rouillon, R.; Piletska, E. V.; Guerreiro, A.; Chianella, I.; Piletsky, S. A.; How to find effective functional monomers for effective molecularly imprinted polymers? *Advanced Drug Delivery Reviews* **2005**, *57*, 1795. [Crossref]
22. Martín-Esteban, A.; Molecularly imprinted polymers: new molecular recognition materials for selective solid-phase extraction of organic compounds. *Fresenius' Journal of Analytical Chemistry* **2001**, *370*, 795. [Crossref]
23. Fang, F.; Wei, R.; Liu, X.; Novel pre-column derivatisation reagent for glyphosate by high-performance liquid chromatography and ultraviolet detection. *International Journal of Environmental Analytical Chemistry* **2014**, *94*, 661. [Crossref]
24. Allender, C. J.; Richardson, C.; Woodhouse, B.; HeardK, C. M.; Brain, K.; Pharmaceutical applications for molecularly imprinted polymers. *International Journal of Pharmaceutics* **2000**, *195*, 39. [Crossref]
25. Vasapollo, G.; Del Sole, R.; Mergola, L.; Lazzoi, M. R.; Scardino, A.; Scorrano, S.; Mele, G.; Molecularly imprinted polymers: present and future prospective. *International Journal of Molecular Sciences* **2011**, *12*, 5908. [Crossref]
26. Marques, J. G. C.; Veríssimo, K. J. S.; Fernandes, B. S.; Ferreira, S. R. M.; Montenegro, S. M. G. L.; Motteran, F.; Glyphosate: A review on the current environmental impacts from a Brazilian perspective. *Bulletin of Environmental Contamination and Toxicology* **2021**, *107*, 385. [Crossref]
27. Sassolas, A.; Blum, L. J.; Leca-Bouvier, B. D.; Immobilization strategies to develop enzymatic biosensors. *Biotechnology Advances* **2012**, *30*, 489. [Crossref]
28. Fonseca, M. C.; Nascimento Jr., C. S.; Borges, K. B.; Theoretical investigation on functional monomer and solvent selection for molecular imprinting of tramadol. *Chemical Physics Letters* **2016**, *645*, 174. [Crossref]
29. Tetko, I. V. The perspectives of computational chemistry modeling. *Journal of Computer-Aided Molecular Design* **2012**, *26*, 135. [Crossref]
30. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, J. E. P. Jr., F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, *Gaussian 09,* 2016. https://gaussian.com /. Accessed on: May 2, 2024
31. Petersson, G. A.; Bennett, A.; Tensfeldt, T. G.; Al-Laham, M. A.; Shirley, W. A.; A complete basis set model chemistry. I. The total energies of closed-shell atoms and hydrides of the first-row elements. *The Journal of Chemical Physics* **1988**, *89*, 2193. [Crossref]

32. Petersson, G. A.; Al-Laham, M. A.; A complete basis set model chemistry. II. Open-shell systems and the total energies of the first-row atoms. *The Journal of Chemical Physics* **1991**, *94*, 6081. [Crossref]
33. Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-Consistent Molecular-Orbital Methods. IX. An Extended Gaussian-Type Basis for Molecular-Orbital Studies of Organic Molecules. *The Journal of Chemical Physics* **1971**, *54*, 724. [Crossref]
34. Biovia, D. S.; *Materials Studio, v. 17.1.0.48,* San Diego, 2017. https://www.3ds.com/products-services/materials-studio/. Accessed on: May 2, 2024
35. Kirkpatrick, S.; Gelatt Jr., C. D.; Vecchi, M. P.; Optimization by simulated annealing. *Science* **1983**, *220*, 671. [Crossref]
36. Metropolis, N.; Rosenbluth, A. W.; Rosenbluth, M. N.; Teller, A. H.; Teller, E. Equation of State Calculations by Fast Computing Machines. *The Journal Of Chemical Physics* **1953**, *21*, 1087. [Crossref]
37. Leite, D. F.; *Tese de Doutorado*. Universidade de São Paulo, São Paulo, 2015. [Link]
38. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V.; Energies, Structures, and Electronic Properties of Molecules in Solution with the C-PCM Solvation Model. *Journal of Computational Chemistry* **2003**, *24*, 669. [Crossref]
39. Dennington, R.; Keith, T. A.; Millam, J. M.; *GaussView, v. 5.0,* Semichem Inc., 2009. https://www.gaussian.com/. Accessed on: May 2, 2024
40. Liu, B.; McLean, A. D.; Accurate calculation of the attractive interaction of two ground state helium atoms. *The Journal of Chemical Physics* **1973**, *59*, 4557. [Crossref]
41. Mukawa, T.; Goto, T.; Nariai, H.; Aoki, Y.; Imamura, A.; Takeuchi, T.; Novel strategy for molecular imprinting of phenolic compounds utilizing disulfide templates. *Journal of Pharmaceutical and Biomedical Analysis* **2003**, *30*, 1943. [Crossref]
42. Dong, W.; Yan, M.; Zhang, M.; Liu, Z.; Li, Y.; A computational and experimental investigation of the interaction between the template molecule and the functional monomer used in the molecularly imprinted polymer. *Analytica Chimica Acta* **2005**, *542*, 186. [Crossref]
43. Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J.; Ab initio study of solvated molecules: a new implementation of the polarizable continuum model. *Chemical Physics Letters* **1996**, *255*, 327. [Crossref]
44. Levi, L.; Raim, V.; Srebnik, S.; A brief review of coarse-grained and other computational studies of molecularly imprinted polymers. *Journal of Molecular Recognition* **2011**, *24*, 883. [Crossref]
45. Philip, J. Y. N.; Buchweishaija, J.; Mkayula, L. L.; Ye, L.; Preparation of Molecularly Imprinted Polymers Using Anacardic Acid Monomers Derived from Cashew Nut Shell Liquid. *Journal of Agricultural and Food Chemistry* **2007**, *55*, 8870. [Crossref]
46. Spivak, D. A.; Optimization, evaluation, and characterization of molecularly imprinted polymers. *Advanced Drug Delivery Reviews* **2005**, *57*, 1779. [Crossref]
47. Kempe, M.; Mosbach, K.; Fischer, L.; Chiral separation using molecularly imprinted heteroaromatic polymers. *Journal of Molecular Recognition* **1993**, *6*, 25. [Crossref]
48. Puoci, F.; Iemma, F.; Cirillo, G.; Picci, N.; Matricardi, P.; Alhaique, F.; Molecularly Imprinted Polymers for 5-Fluorouracil Release in Biological Fluids. *Molecules* **2007**, *12*, 805. [Crossref] [PubMed]
49. Martin, P. D.; Jones, G. R.; Stringer, F.; Wilson, I. D.; Comparison of normal and reversed-phase solid phase extraction methods for extraction of β-blockers from plasma using molecularly imprinted polymers. *Analyst* **2003**, *128*, 345. [Crossref]
50. Okano, T.; Bae, Y. H.; Jacobs, H.; Kim, S. W.; Thermally on-off switching polymers for drug permeation and release. *Journal of Controlled Release* **1990**, *11*, 255. [Crossref]
51. Zhou, T.; Shen, X.; Chaudhary, S.; Ye, L.; Molecularly Imprinted Polymer Beads Prepared by Pickering Emulsion Polymerization for Steroid Recognition. *Journal of Applied Polymer Science* **2014**, *131*, 39606. [Crossref]
52. Piletska, E. V.; Turner, N. W.; Turner, A. P. F.; Piletsky, S. A.; Controlled release of the herbicide simazine from computationally designed molecularly imprinted polymers. *Journal of Controlled Release* **2005**, *108*, 132. [Crossref]
53. Han, Y.; Gu, L.; Zhang, M.; Li, Z.; Yang, W.; Tang, X.; Xie, G.; Computer-aided design of molecularly imprinted polymers for recognition of atrazine. *Computational and Theoretical Chemistry* **2017**, *1121*, 29. [Crossref]
54. Haginaka, J.; Monodispersed, molecularly imprinted polymers as affinity-based chromatography media. *Journal of Chromatography B* **2008**, *866*, 3. [Crossref]
55. Matsui, J.; Okada, M.; Tsuruoka, M.; Takeuchi, T.; Solid-phase Extraction of a Triazine Herbicide Using a Molecularly Imprinted Synthetic Receptor. *Analytical Communications* **1997**, *34*, 85. [Crossref]