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Computationally designed monomers and polymers for molecular imprinting of theophylline—part II

Dumitru Pavel*, Jolanta Lagowski

Department of Physics, Memorial University of Newfoundland, St John's, NL, Canada

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Abstract

The main objective of this research is to develop and apply state-of-the-art computational tools to achieve an understanding of intermolecular interactions in molecular imprinting of theophylline into complex polymeric systems. Molecular dynamics (MD) simulations were carried out for different molecular systems in order to predict the interaction energies, the closest approach distances and the active site groups between the simulated molecular systems and different bio-ligands. The minimized structures of five ligands, theophylline and its derivatives (theobromine, theophylline-8-butanoic acid, caffeine and theophylline-7-acetic acid) have been obtained with the use of molecular mechanics approach. NVT MD simulations at room temperature were carried out to obtain equilibrated conformations in all cases.

The first simulated molecular systems consisted of a ligand and commonly used functional monomers, polymers and a substrate. The second simulated molecular systems consisted of a ligand and a monomer or polymer using a solvent (ethanol).

During this study, it was found that electrostatic interactions play the most significant role in the formation of molecular imprinting materials. The simulated functional monomers and polymers with ligands indicate that the functional groups interacting with ligands tends to be either –COOH or CH_2=CH–. It was also found that molecular substrate without functional side groups are recommended for molecular imprinting technology. For both the solvated monomer and polymer systems is that it appears that the presence of the solvent appears to favour the formation of more stable clusters with theophylline than with its derivatives.
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Keywords: Imprinting polymers; Ligand; Molecular simulation

1. Introduction

Molecular simulation techniques are playing an increasingly important role in the designing and the development of materials for various industrial applications. These simulations are likely to benefit the study of materials by increasing our understanding of their chemical and physical properties at a molecular level and by assisting us in the design of new materials and predicting their properties. Simulations are usually considerably cheaper and faster than experiments. Molecular simulations also offer a unique perspective on the molecular level processes controlling structural, physical, optical, chemical, mechanical, and transport properties.

The main objective of this research is to apply state-of-the-art computational tools to achieve an understanding of intermolecular interactions in molecular systems that are employed in the imprinting of theophylline and its derivatives. It is hoped that thus imprinted material can then be used to selectively detect theophylline (or its derivatives). This is a test case study to access the usefulness of computational aid in the development of imprinted monomers/polymers that can then be used for sensing other industrially important compounds. In particular, this research is part of an exploratory investigation whose principal objective is to enhance the capabilities of first responders to determine the presence of hazardous chemical compounds in the environment. Its main goal is the development of portable and direct sensing devices capable of detecting and identifying these hazardous materials [1–5].

Molecular imprinting is a technique of producing cavities

* Corresponding author. Present address: National Research Council of Canada, IMS, Building M50, Room 254, 1200 Montreal Rd., Ottawa, Canada K1A 0R6. Tel.: +1 613 9493045; fax: +1 613 9900202.
E-mail addresses: dumitru.pavel@nrc-cnrc.gc.ca (D. Pavel), dumitru_p@yahoo.co.uk (D. Pavel).

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in the material that preferentially bind with a particular molecule (template). In recent years the molecularly imprinting technique has focused on using synthetic polymers as imprinting material producing the so called artificial recognition elements [6,7]. When compared with biomolecules, the main advantages of molecularly imprinted polymers (MIPs) are their relatively high stability over a wide range of conditions (temperature, pressure, organic solvents, etc.) and low cost. In other words, the artificial recognition elements provide an alternative to the use of the somewhat fragile biological elements (such as enzymes, proteins or antibodies), which lack storage and operational stability in the traditional sensing devices. Applications of imprinting technology are still very few and the field is relatively underdeveloped. Imprinting technology has a great potential for growth, for example, in the pharmaceutical and biotechnology industries [8–13].

Standard molecular imprinting is a process by which functional monomers are allowed to self-assemble around a template molecule and are subsequently cross-linked into place [14–17]. The template is encapsulated in a stable three-dimensional polymer matrix. The template molecule can then be removed, leaving behind a cavity that will bind molecules identical to the template molecule. The imprint is like a lock that is only compatible with the correct key, similar to biological systems, such as enzymes and substrates, antibodies and antigens, and hormones and receptors.

Recognition between a molecular receptor (host) and a substrate (guest) in a matrix containing structurally related molecules requires discrimination and specific binding; this can happen only if the binding sites of the host and guest molecules complement each other in size, shape, and chemical functionality. When these arrays are coupled with sensors employing standard surface analytical or photonic techniques, targeted species will be detectable and identifiable in real time.

In this work, MD simulations were carried out for different molecular systems (clusters) to assess the interaction energies, closest approach distances and the active site groups between the simulated molecular systems and different bio-ligands. In order to test for the selectivity, besides theophylline, four other compounds (theobromine, theophylline-8-butanoic acid, caffeine and theophylline-7-acetic acid) similar in structure to theophylline were employed in this study. The stable structures of the five ligands, theophylline and its derivatives, have been obtained with the use of molecular mechanics approach.

In the first part of this study, simulated molecular systems consisted of a ligand, a substrate, and a commonly used functional monomers, such as acrylic acids, methacrylic acids, acrylamides, acroleins, acrylonitriles, styrenes, etc. (a total number of 25 different monomers were simulated, see Table 1 and Appendix A). For each of the simulated monomer, similar simulations were performed for molecular systems consisted of a ligand, a substrate, and polymers of the above-mentioned monomers. The initial conformations of each of the molecular systems were optimized and energy minimized. Then, NVT MD simulations for 40 ns (nanosecond) at room temperature were carried out to obtain equilibrated conformations in order to analyse the imprinting properties.

Table 1
List of simulated monomers and polymers

No	Polymer	Functional monomer
1	Poly-	1-Vinylimidazole
2	Poly-	2-Vinylpyridine
3	Poly-	2-Acrylamido-2-methy-l-propane sulfonic acid
4	Poly-	2-Hydroxyethyl methacrylate
5	Poly-	Acrolein
6	Poly-	Acrylamide
7	Poly-	Acrylic acid
8	Poly-	Acrylonitrile
9	Poly-	Allylamine
10	Poly-	Ethylene glycol dimethacrylate
11	Poly-	Imidazole-4-acrylic acid ethyl ester
12	Poly-	Methylene-succinic acid
13	Poly-	*m*-Divinylbenzene
14	Poly-	*N*,*N*-Methylene-bis-acrylamide
15	Poly-	Methacrylic acid
16	Poly-	Imidazole-4-acrylic acid
17	Poly-	4-Vinylpyridine
18	Poly-	*p*-Divinylbenzene
19	Poly-	Styrene
20	Poly-	2-(Diethylamino)-ethyl methacrylate
21	Poly-	Itaconic acid
22	Poly-	Trifluoro-methacrylic acid
23	Poly-	4-Vinylbenzoic acid
24	Poly-	4-Vinylbezyl-imino-di-acetic acid
25	Poly-	4-Vinylimidazole

In the second part of this study, simulated molecular systems consisted of a ligand and a solvent (ethanol) for each of the monomer and polymer investigated (Table 1). For each of the simulated molecular clusters, NVT MD simulations at room temperature for 40 ns were carried out to obtain equilibrated conformations of a molecular cluster without ligand and of a molecular cluster with ligand. For each pair of molecular systems, a total energy difference, (ΔE), was calculated in order to estimate the interaction energy between ligand and the corresponding molecular cluster. Also, the closest distance between the active site (group) of the simulated molecular clusters and a ligand was estimated.

To our knowledge, there is very little theoretical/computational effort being carried out for the imprinting materials. Therefore, the present work is also exploratory in nature. We hope that the general methodology presented here can be applied to any molecularly imprinting material and become a reliable, economic and useful tool to aid the design and synthesis process of these materials which can then be used in sensing applications.

2. Monomers and polymers studied

The list of the simulated functional monomers and polymers is presented in Table 1. The numbers from the first column will represent the monomers and polymers on the graphical data presented throughout this manuscript. The minimized chemical structures of the simulated monomers (and at the same time of the monomers used to build up the simulated polymers) are presented in Appendix A.

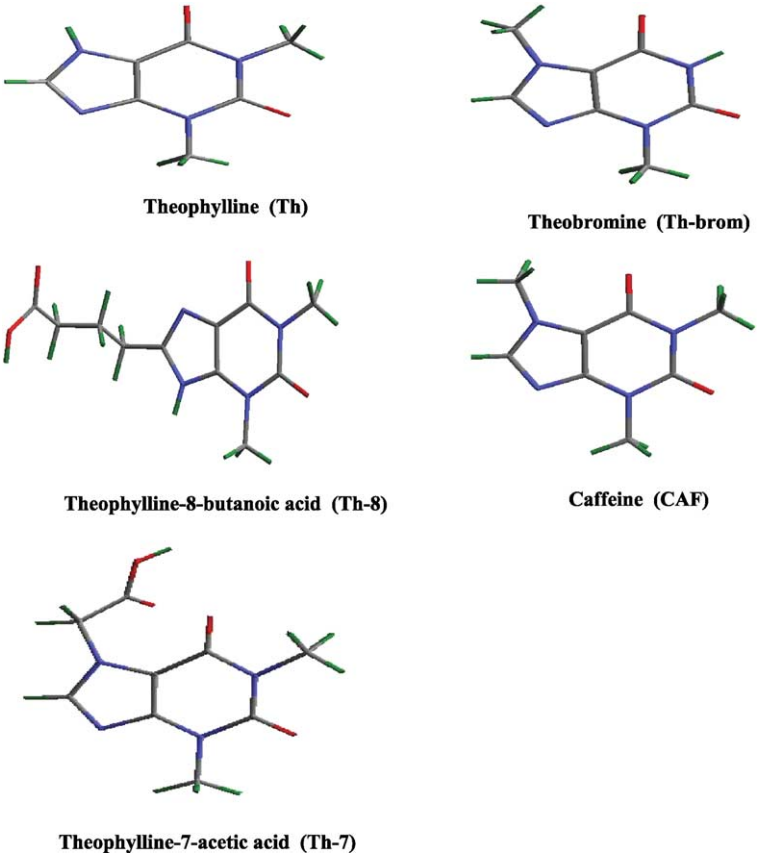
3. Bio-ligands studied

The studied ligands are theophylline (Th), theobromine (Th-brom), theophylline-8-butanoic acid (Th-8), caffeine (CAF) and theophylline-7-acetic acid (Th-7), and their chemical structures are presented in Scheme 1. The abbreviations (as indicated in brackets) will be used on the graphical representations throughout this manuscript.

4. Computational methodology

This section provides the detailed description of the potential interaction function of the molecular mechanics, and the detailed methodology that was employed in our simulations of the investigated molecular clusters. Computer modelling of chemical structures of the monomers and polymers, MD simulations, and conformational and MD analyses were carried out using molecular simulation software for material science [18], Cerius^2 version 4.10, designed by Accelrys Inc., San Diego, CA, USA. The Cerius^2 molecular simulation software was run on a Silicon graphics onyx workstation. The 3D-sketcher, open force-field, charge equilibration, monomer editor, polymer builder, energy minimizer, NVT MD (discover) and dynamic analysis moduli of Cerius^2 software were used in order to perform the computations and to calculate the total energies (E), energy differences (ΔE) and distances (d) of closest approach between the monomers or a polymer and different bio-ligands in a given cluster.

The open force-field (OFF) module allowed us to specify the force field to be used for the simulations. The polymer consistent force field (PCFF) developed by Sun et al., and implemented in Discover module was employed since, in accordance with previous studies [19–23], it was found to be very suitable and reliable for the molecular simulation of organic molecular clusters of monomers and polymers. This force field is parameterized for a large class of organic molecules including H, C, O, S, P, F, Cl and Br, allowing it to be applied to bio- and synthetic polymers. PCFF force field gives accurate geometries for various polymeric



Scheme 1. The energy minimised structures of the studied bio-ligands.

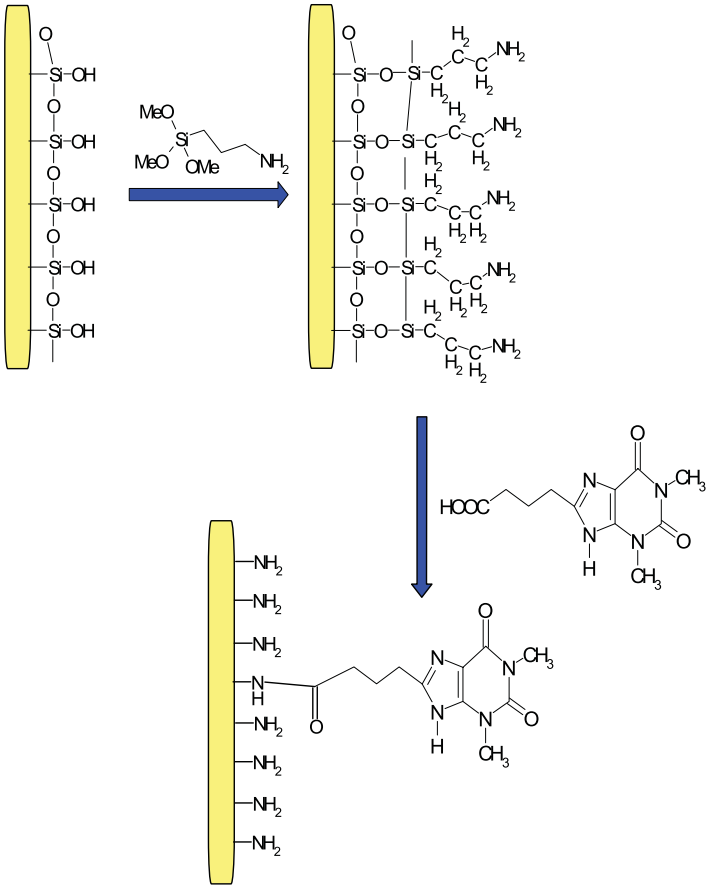


Fig. 1. Chemical structure of the first substrate used for simulation.

systems [23] and can be used to calculate and minimise the energy of a simulated monomeric and polymeric systems. Next, the forces acting on each atom of a model polymer were calculated, which were then utilised to solve Newton's equations of motion for MD simulations.

For the first set of simulations, molecular clusters consisting of 10 molecules of monomer (without ligand) and 10 molecules of monomer with ligand were designed. For the second set of simulations, molecular systems consisting of single polymer chain (without ligand) and a single polymer chain with ligand with DP of 10 were built. The polymer molecule was constructed by using first the Builder module for the monomer and then the polymerizer module for the polymer chain. The initial molecular clusters of the simulated monomers and polymers were optimised and the values of the total potential energy and its components were obtained. The PCFF provides a potential energy interaction function (E_{total}) that accounts for both bonded (E_{b}) and non-bonded (E_{nb}) interactions. The bonded terms typically include harmonic bond stretching (E_{s}), harmonic angle bending (E_{a}), torsional (E_{t}), and inversion (E_{i}) energies. Non-bonded terms typically contain van der Waals (E_{vdW}), electrostatic (Coloumbic) (E_{q}) and hydrogen bond (10–12 potential) (E_{hb}) interactions. In practice it is common to choose a suitably large cut-off distance for the long-range non-bonded interactions. For this study a cut-off distance of 100 Å was chosen. The Mie 6–12 potential [24], that is often referred to in the literature as the Lennard–Jones 6–12 potential function ($u = A/r^{12} - B/r^{6}$), was used to calculate the non-bonded van der Waals interactions. A and B are parameters which determine the size of the attraction ($-B/r^{6}$) and the repulsion (A/r^{12}) interactions between the

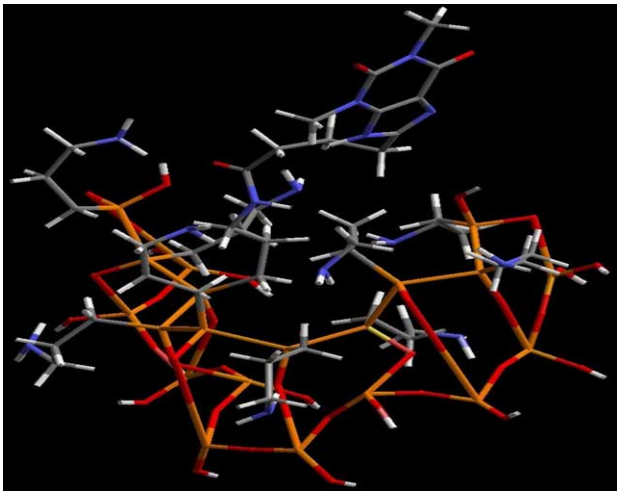


Fig. 2. Snapshot of NVT-MD equilibrated structure of the substrate with an attached molecule of theophylline-8-butanoic acid.

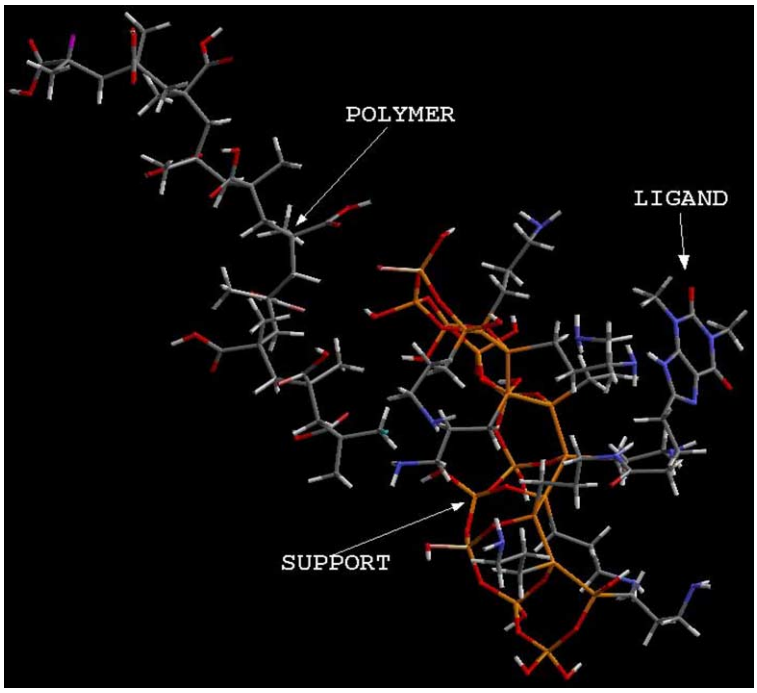


Fig. 3. A typical simulated conformation of the support with theophylline-8-butanoic acid (ligand) and 1 polymeric chains of polymethacrylic acid.

atoms which are separated by a distance r equal to the sum of r_i and r_j, where r_i and r_j are van der Waals radii of the non-bonded atoms i and j. The charge distribution employed to calculate the Coloumbic (electrostatic) interactions in the molecular systems in Cerius^2 was obtained with the charge equilibration method described by Rappe and Goddard [25].

The NVT MD simulations were performed at 300 K, for each constructed and minimised molecular system. For the NVT ensemble, the number of molecules N, volume V and the temperature T of the system are kept constant. MD calculations simulate the natural motions of all atoms in a molecular system over time at non-zero temperature and the

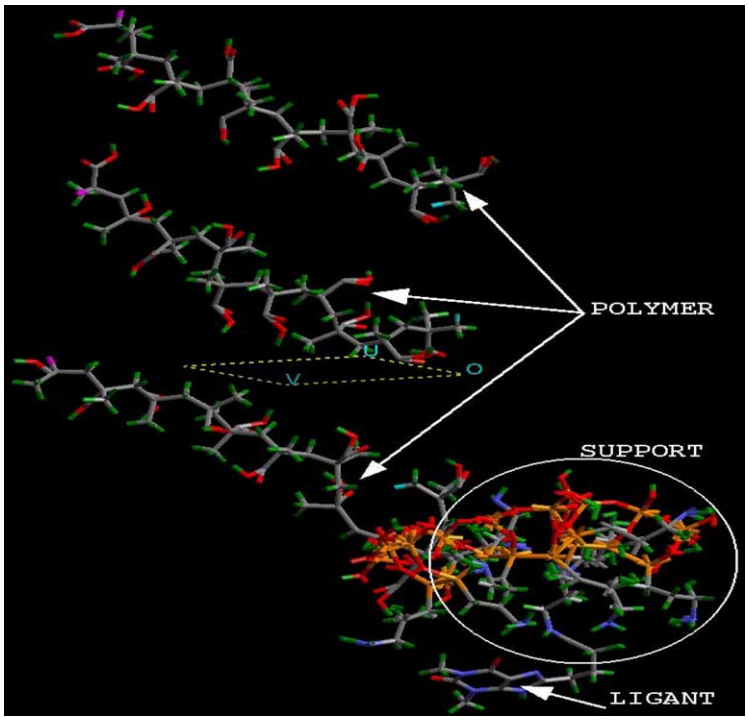


Fig. 4. A typical simulated equilibrated conformation of the support with one molecule of theophylline-8-butanoic acid (ligand) chemically attached and three polymeric chains of polymethacrylic acid.

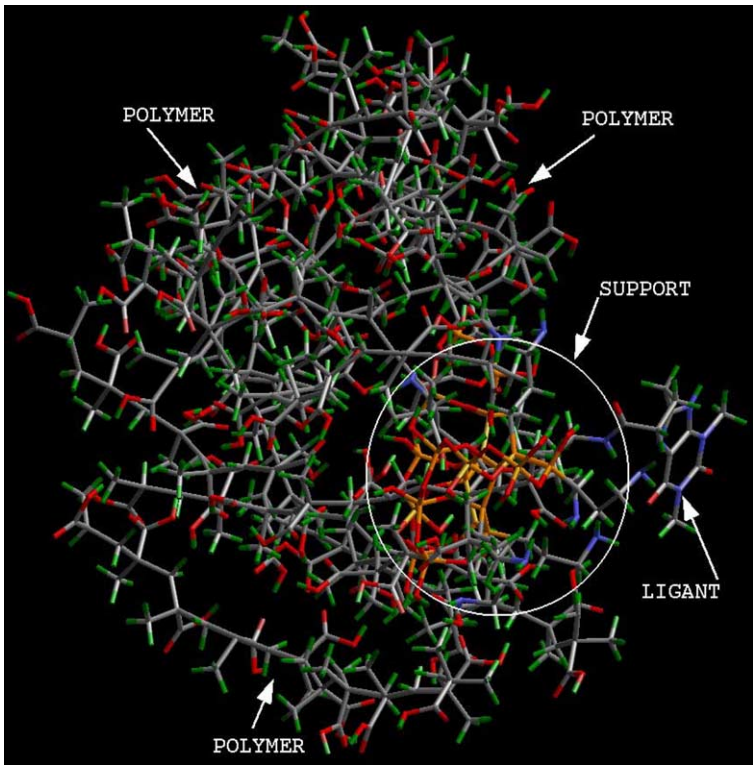


Fig. 5. A typical simulated equilibrated conformation of the support with one molecule of theophylline-8-butanoic acid (ligand) chemically attached and 10 polymeric chains of polymethacrylic acid.

MD algorithm makes use of Newton's equation of motion ($F=ma$), thus giving a complete dynamic description of the polymeric material. In order to ensure that the simulations are carried out for sufficient time, which is one of the most important criteria in equilibrating the system and then to accurately predict its equilibrium properties, the simulation time of NVT MD calculations was between 10 and 40 ns, depending on the size of the simulated molecular system, and the output frequency was every 2000 steps. The time step of 0.001 ps is taken to be constant for all the

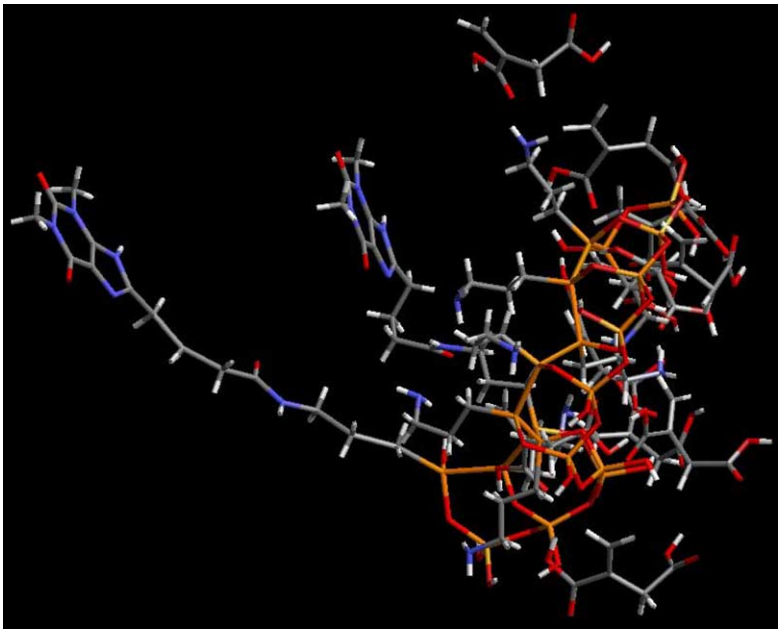


Fig. 6. A typical simulated equilibrated conformation of the support with two molecules of theophylline-8-butanoic acid chemically attached and 10 molecules of itaconic acid.

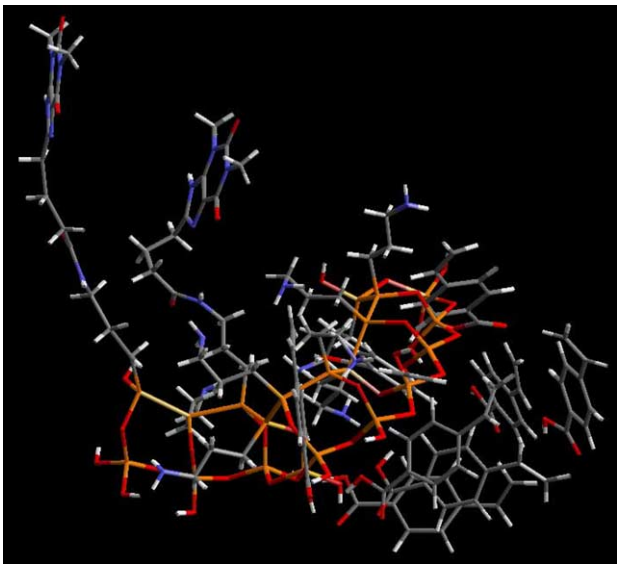


Fig. 7. A typical simulated equilibrated conformation of the support with two molecules of theophylline-8-butanoic acid (ligand) chemically attached and 10 molecules of 4-vinyl-benzoic acid.

simulations. In this MD study the model system exchanges energy with a heat bath in order to maintain a constant temperature. The non-canonical 'T-damping' thermostat described by Berendsen et al. [26] was used for isothermal–isobaric NVT MD simulations. For all the simulations the dielectrical constant was kept constant at value of 1. Trajectory file data generated from NVT MD simulation has been used in all the calculations and analyses (including visual analysis) presented in this research. The trajectory files were analysed by dynamics analysis modules.

5. Results and discussion

5.1. Simulations of molecular clusters containing a support

The first step of imprinting process of theophylline into the monomeric or polymeric materials involves attaching of theophylline derivative such as theophylline-8-butanoic acid or theophylline-7-acetic acid onto the substrate as shown in Fig. 1 and then surrounding the theophylline by either polymers or monomers. It is the goal of these simulations to study the interactions of the theophylline with monomers or polymers while attached to the substrate. A snapshot of NVT-MD equilibrated structure of the substrate (with chemical structure as shown in Fig. 1) with an attached (covalently bonded) molecule of ligand (theophylline-8-butanoic acid) is presented in Fig. 2. Next, polymers or monomers are added to the theophylline-8-butanoic acid attached to the substrate (support). First NVT MD simulation was performed for a system containing one molecule of polymethacrylic acid in addition to theophylline attached to substrate as shown in Fig. 3, where a typical conformation of simulated support-ligand-polymer molecular systems at room temperature is displayed. From Fig. 3, it can be seen that the polymeric chain of polymethacrylic acid is not close to the ligand. We have performed a number of such simulations; for example in Fig. 4 we have increased

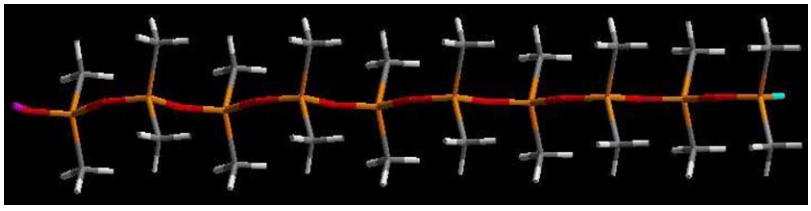


Fig. 8. Second substrate used for simulations: polydimethyl siloxane (PDMS).

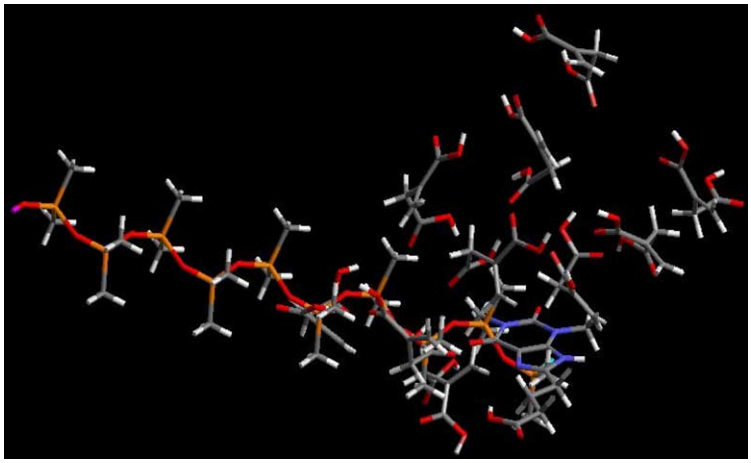


Fig. 9. Simulated molecular system consisting of PDMS, theophylline-8-butanoic acid and itaconic acids.

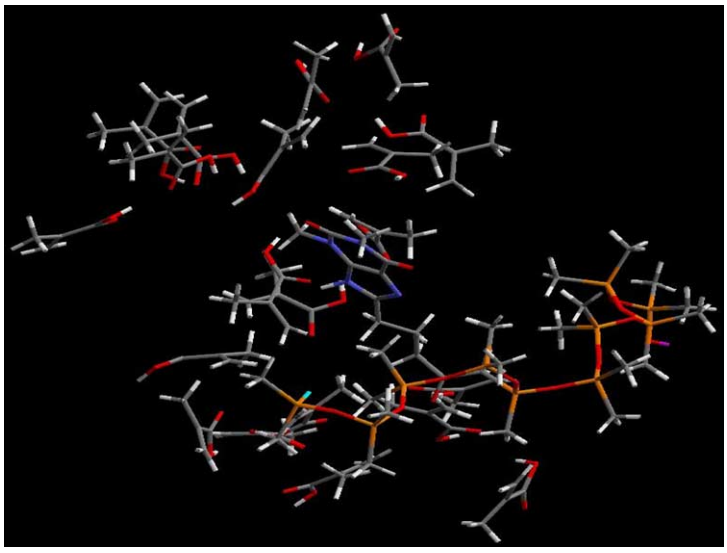


Fig. 10. Simulated molecular system consisting of substrate (PDMS), theophylline-8-butanoic acid and 10 molecules of methacrylic acid.

the number of polymethacrylic chains to three and in Fig. 5, we further increased the number of polymer chains to 10. In all three cases (Figs. 3–5), the polymers preferred to interact with the substrate or themselves rather than surround the ligand. The same trend was observed when we switched from polymers to monomers. Our previous studies indicated that itaconic acid should from stable complexes with theophylline and its derivatives. However, when itaconic acids are used to surround two ligands, once again the acids stay away from the ligands and interact with either the substrate or themselves (Fig. 6). A similar situation is observed when we switch from itaconic acid to 4-vinylbenzoic acid (Fig. 7). In summary, we note that for the representative simulated systems, monomers and polymers, in the presence of the substrate with theophylline-8-butanoic acid covalently attached to it, were closer to substrate or themselves than to a ligand. This is contrary to our expectation. It is clear from Figs. 3–7 that the substrate has a stronger affinity to monomers and polymers than to the ligand. These figures suggest that the electrostatic non-bonded interactions (including the H-bonds) between the functional groups, –COOH, of polymers or monomers and functional groups, $–NH_2$, of substrate, give rise to relatively strong attractive interactions between them, whereas the $–NH_2$ groups tend to repel the ligand away from the substrate. These investigations suggested to us that $–NH_2$ functional groups should be removed from the substrate before the ligand is surrounded by either monomers or polymers. This, in fact, is what needs to be done experimentally, i.e. the $–NH_2$ groups are washed away before the imprinting process can proceed (experimental work is currently undergoing).

In further simulations, we have considered a substrate without $–NH_2$ functional groups. We began our simulations using polydimethyl siloxane, (PDMS), as a substrate as shown in Fig. 8. When this newly formed substrate with the theophylline-8-butanoic acid attached to it is surrounded by say itaconic acids (Fig. 9), the monomers, as required, have a stronger affinity to the ligand than to the substrate. The same trend is observed when methacrylic acids (Fig. 10) or polymethacrylic acid chain (Fig. 11) is introduced to PDMS with the attached ligand. The closest distances of approach between the ligand and monomers or polymer are of the order 3.0–4.5 Å which is a good indicator that non-bonded electrostatic interactions are formed between the ligand and the monomers or polymers. As a conclusion, molecular substrates without functional side groups are recommended for molecular imprinting of theophylline.

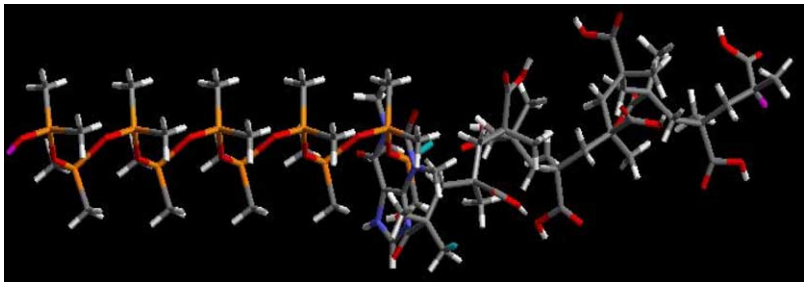


Fig. 11. Simulated molecular system consisting of substrate (PDMS), theophylline and polymethacrylic acid (one polymeric chain).

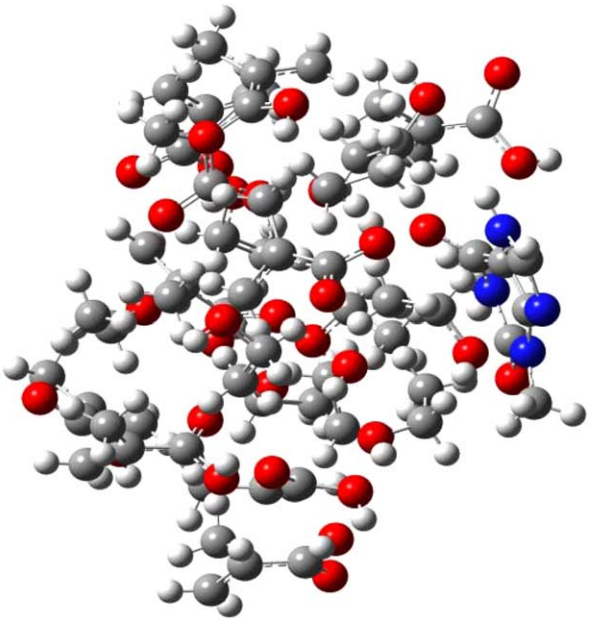


Fig. 12. A typical NVT-MD equilibrated conformation of the solvated molecular cluster (10 molecules of methacrylic acid, 10 molecules of ethanol and one molecule of theophylline).

5.2. Molecular simulation of solvent molecular clusters

As mentioned in the Introduction section, the more realistic modeling of the imprinting molecular systems should not only include the substrate but also the effects of the solvent since, nearly all imprinting processes are performed in the presence of the solvent. In this section, MD atomistic simulations were carried out for monomer and polymer molecular systems containing solvent in order to predict the interaction energies between ligand and monomers or polymers dissolved in a solvent. The solvent used for this study was ethanol. The monomer (or polymer) /solvent ratio was 1:2. That is, the simulated monomer molecular clusters contained 10 molecules of monomers, 20 molecules of ethanol and one molecule of each ligand considered during this study. For comparison purposes and better understanding of monomer–solvent–ligand interactions, some simulations were also performed for monomer/solvent ratio of 1:1. It was noticed that the results displayed similar trends. Hence, this study will focus on the results obtained from simulating systems containing monomer/solvent in 1:2 ratio. The solvated polymer clusters consisted of a single polymer chain with DP of 10, 20 solvent (ethanol) molecules and one molecule of each of the studied ligand. The DP was 10 in order to be consistent with the number of monomer molecules used for the simulated solvated monomer clusters. The initial conformations of each of the studied molecular cluster were optimized and energy minimized (first of all for monomer and solvent, and then, for monomer, solvent and ligand, and then similar simulations for polymers were performed). Then, NVT MD simulations for 40 ns at room temperature were carried out to obtain equilibrated conformations. The interaction energies and the distances of closest approach were calculated. The interaction energy, ΔE, was calculated in the following way

$$\Delta E = E_{\text{cluster}} - (E_{\text{monomer/polymer+solvent}} + E_{\text{ligand}})$$

where E_{cluster}, is the total energy of the simulated cluster (monomer/polymer, solvent and ligand). An example of simulated solvent cluster (10 molecules of methacrylic acid, 10 molecules of ethanol and one molecule of theophylline) is presented in Fig. 12. From this example, it can be seen that the solvent (ethanol) molecules are very well mixed with the monomer molecules (forming a homogenous solution), as a result there are strong physical interactions between the monomer and ethanol, especially between the monomer –COOH groups and solvent –OH groups. From Fig. 12 it can also be notice that both, the monomer with its –COOH functional group and the solvent with its –OH functional group, interact with the ligand (in this case with

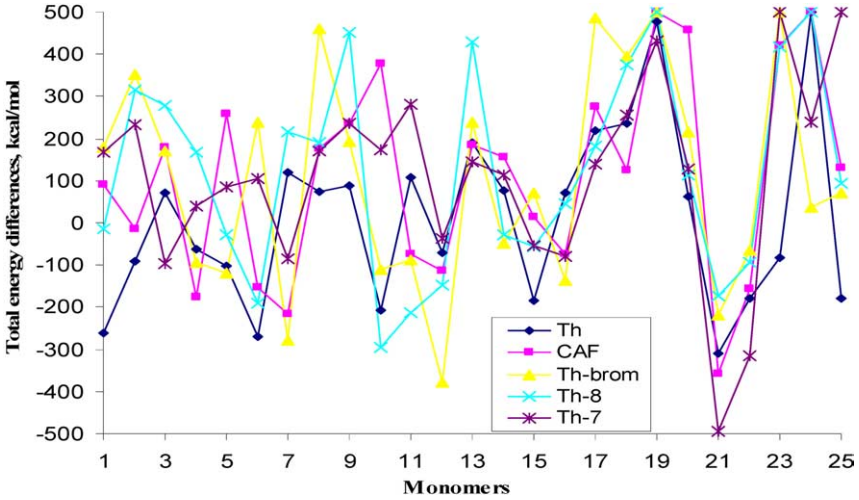


Fig. 13. Difference of total interaction energy (average data) of simulated monomers with solvent to ligands, ($\Delta E = E_{\text{cluster}} - (E_{\text{monomer+solvent}} + E_{\text{ligand}})$).

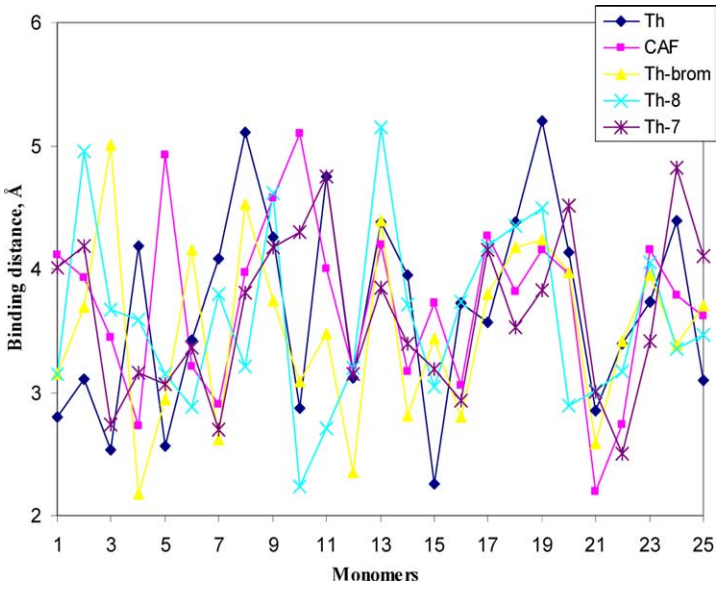


Fig. 14. Binding distance of the simulated monomers and solvent to ligands.

theophylline). The distance of close approach of 2.80 Å is within its excellent value for such kind of molecular systems to form H bonds, however, similarly to previously simulated molecular clusters [27] the predicted H bond interactions are less than 10 kcal/mol. The very low value of the H bond interaction can be explained by the fact that, due to the partial electrostatic character of the hydrogen bond, part of its value is incorporated into the 'main' electrostatic interactions which are calculated by the simulation program, and, at the same time a small amount of the hydrogen interactions may also be incorporated into the physical van der Waals interactions.

The simulated data for monomers are presented in Figs. 13 and 14, and the simulated data for polymers are presented in Figs. 15 and 16. These data are an estimation of the ligand interaction with the simulated solvent clusters for the formation of molecularly imprinting process. From Fig. 13 we note that there are six possible monomers (in the presence of the solvent) that form selectively most stable complexes with theophylline. They are: 1-vinylimidazole, 2-vinylpyridine, acrylamide, methacrylic acid, 4-vinylbenzoic acid and 4-vinylimidazole. It would appear from this data that in the presence of a solvent, theophylline forms more stable complexes than without the solvent (where only itaconic acid and 4-vinylbenzoic acid were selectively more stable with theophylline than its derivatives). The distances of closest approach for these six cases lie between 2 and 4 Å (Fig. 14). Similarly for the solvated polymer simulations, we found seven polymers, which preferentially formed more stable complexes with theophylline than with its

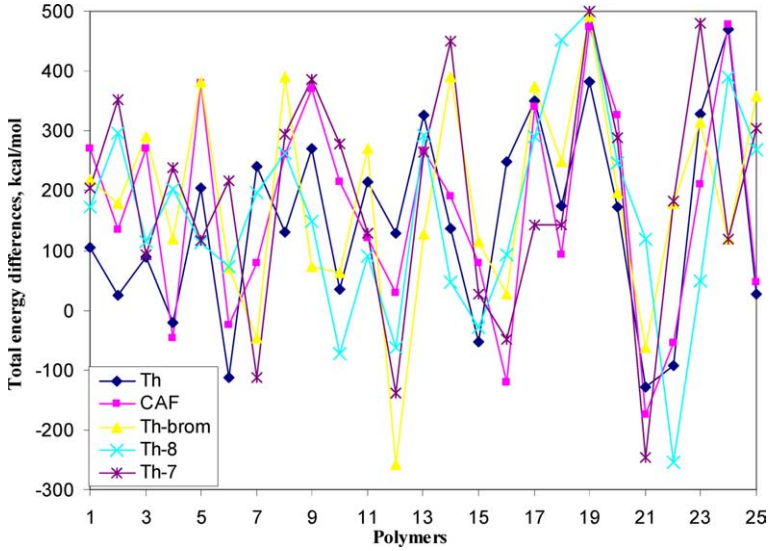


Fig. 15. Difference of total interaction energy (average data) of simulated polymers with solvent to ligands, ($\Delta E = E_{\text{cluster}} - (E_{\text{polymer+solvent}} + E_{\text{ligand}})$).

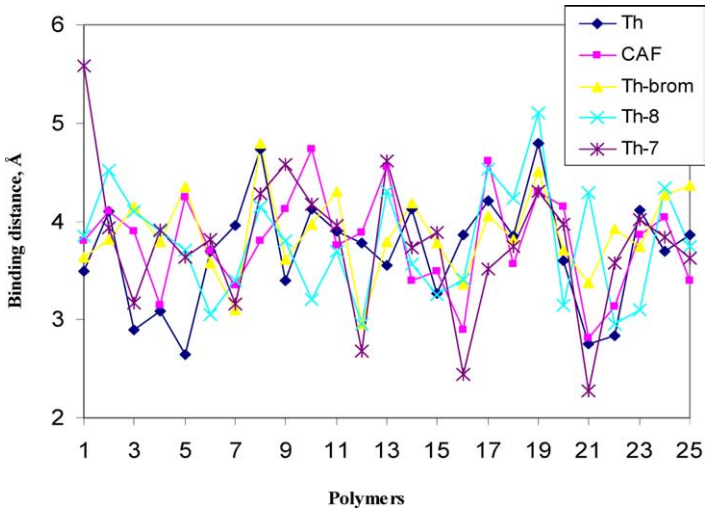


Fig. 16. Binding distance of the simulated polymers and solvent to ligands.

derivatives. They are: poly(1-vinylimidazole), poly(2-vinylpyridine), poly(acrylamide), poly(acrylonitrile), poly(methacrylic acid), poly(2-(diethylamino)ethyl methacrylate) and poly(4-vinylimidazole). This should be compared with the fact that just as for monomers, there were only two polymers: poly(acrylic acid) and poly(itaconic acid) that preferentially formed more stable cluster with theophylline than with its derivatives when no solvent was included in the system. The distances of closest approach for these seven cases lie between 2 and 4 Å (Fig. 15). The general conclusion for both the solvated monomer and polymer systems is that it appears that the presence of the solvent appears to favour the formation of more stable clusters with theophylline than with its derivatives.

6. Conclusions

Atomistic modelling is a useful tool for studying the microscopic structure and understanding the mechanisms of physical processes on atomic and molecular levels. Molecular simulations of material structure have reached the level, where they are now useful in gaining insights into the molecular origins of behaviour of bulk polymers.

A large number of different polymers and monomers systems have been simulated and analyzed. A library of 25 monomers and their corresponding polymers has been established and the binding energies and binding distances computed. In the present work the molecular clusters have been investigated by extensive NVT MD simulations in order to obtain a better insight about the molecularly imprinting formation, mechanism and properties. Extended equilibration procedures were necessary to obtain reasonable imprinting models for the simulated molecular clusters and the following conclusions were drawn.

The simulated functional monomers and polymers with ligands indicate that the functional groups interacting with ligands tends to be either –COOH or CH_2=CH–. Simulated molecular systems of monomers and polymers with binding distance between 2.0 and 4.5 Å are more favourable to form molecular imprinting materials. Molecular systems of monomers and polymers with negative binding energy are predicted to be good candidates for the formation of molecular imprinting materials. For the simulated molecular clusters, monomers and polymers, it was noticed that the electrostatic energy gives the largest energy contribution to the total energies. In most cases, electrostatic energy contributions play the most significant role in the binding of monomers/polymers to ligands. Molecular substrate without functional side groups, such as, polydimethyl siloxane, are recommended for molecular imprinting technology. For both the solvated monomer and polymer systems is that it appears that the presence of the solvent appears to favour the formation of more stable clusters with theophylline than with its derivatives.

Acknowledgements

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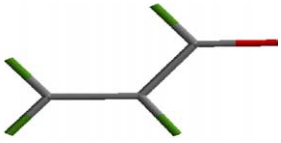
Appendix A

The energy minimised structures of the simulated monomers, and at the same time of the monomers that were used to build up the polymers are presented below.

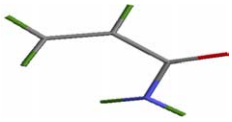
Notes

The atoms color of all of the simulated molecular systems presented throughout this manuscript are as following:

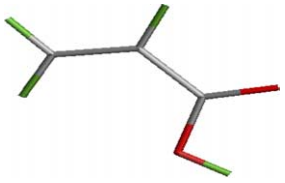
Carbon	Grey
Hydrogen	Green
Oxygen	Red
Nitrogen	Blue
Sulfur	Yellow
Fluor	Light blue



Acrolein



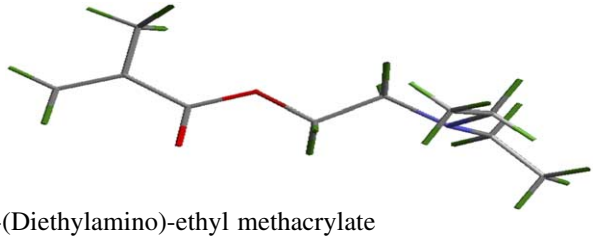
Acrylamide



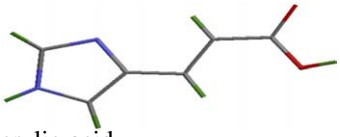
Acrylic acid

Acrylonitrile

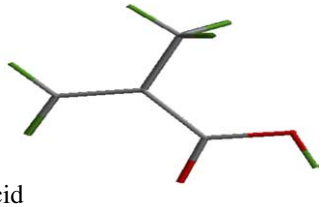
Allylamine



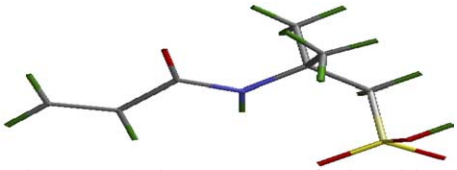
2-(Diethylamino)-ethyl methacrylate



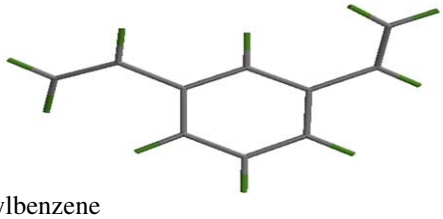
Imidazole-4-acrylic acid



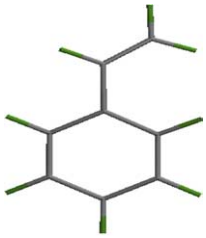
Methacrylic acid



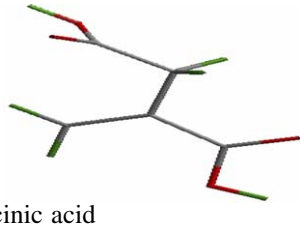
2-Acrylamido-2-methyl-1-propanesulfonic acid



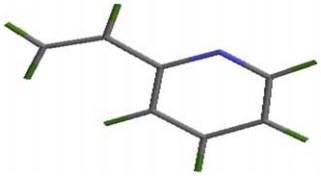
m-Divinylbenzene



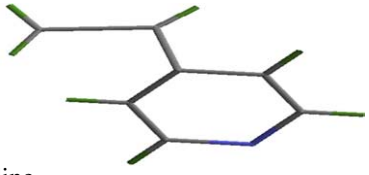
Styrene



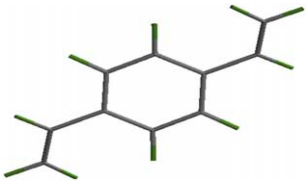
Methylene-succinic acid



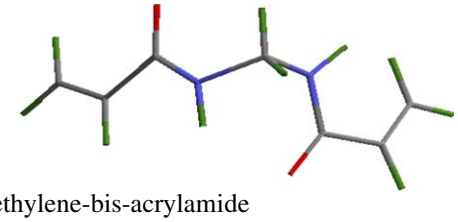
2-Vinylpyridine



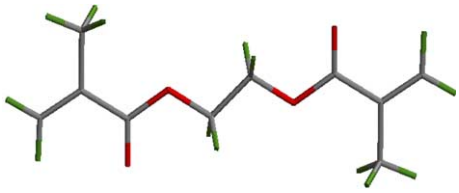
4-Vinylpyridine



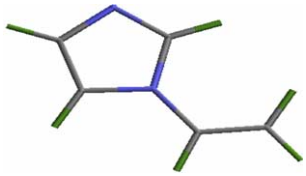
para-Divinylbenzene



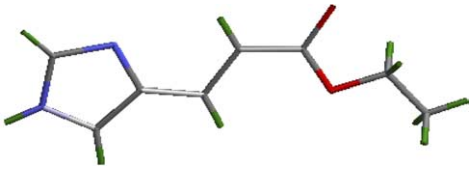
N,*N*-Methylene-bis-acrylamide



Ethylene glycol dimethacrylate

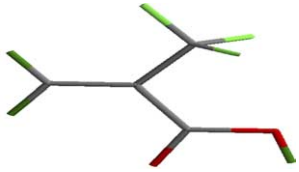


4-vinylimidazole

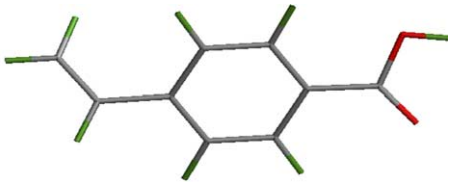


Imidazole-4-acrylic acid ethyl ester

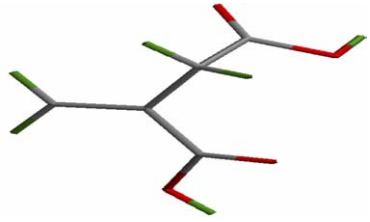
2-Hydroxyethyl methacrylate



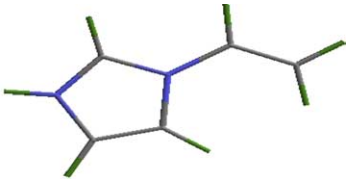
Trifluoro-methacrylic acid



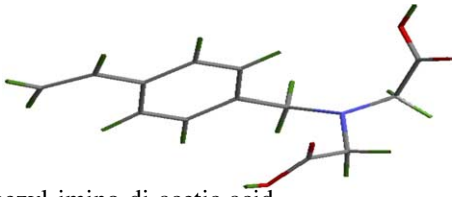
4-vinylbenzoic acid



Itaconic acid



1-Vinylimidazole



4-Vinylbezyl-imino-di-acetic acid

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