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Computationally designed monomers and polymers for molecular imprinting of theophylline and its derivatives. Part I

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Abstract

The main objective of this research was 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 a commonly used functional monomer, such as acrylic acid, methacrylic acid, acrylamide, acrolein, acrylonitrile, styrene, etc. (a total number of 25 monomers were simulated). For each of the simulated monomer, molecular clusters consisting of 10 monomers were built. For each pair of molecular systems, (10 monomers with a ligand and 10 monomers without a ligand) a total energy difference, (ΔE), was calculated in order to estimate the interaction energy between a ligand and the corresponding monomers. The second simulated molecular systems consisted of a ligand and a polymer. For each of the simulated polymers, a polymeric chain with degree of polymerization (DP) 10 was simulated with theophylline or its derivative and the interaction energy (ΔE) was calculated. From simulated polymer systems it was found that just poly(acrylic acid) and poly(itaconic acid) are selective only for theophylline. The functional groups of monomers interacting with ligands are –COOH or CH_2=CH–. The functional groups of polymers are predominantly –COOH. In the case of poly(acrylic acid) and poly(itaconic acid) the distance of closest approach between a polymer and theophylline was between 2.0 and 4.0 Å.

Keywords: Molecularlly imprinting polymers; Bio-ligand; Molecular dynamics 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. It is hoped that thus imprinted material can then be used to selectively detect theophylline. This is a test case study to access the usefulness of computational aids 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

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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 in the material that preferentially bind with a particular molecule (template). In recent years the molecular imprinting technique has focused on using synthetic polymers as imprinting materials 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 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 monomers, there were (beside the ligand) 10 monomers in each cluster. The initial conformations of each of the molecular systems were optimized and energy minimized. NVT MD simulations for 40 ns at room temperature were carried out to obtain equilibrated conformations. For each pair of molecular systems, (10 monomers with a ligand and 10 monomers without a ligand) the total energy difference, (ΔE), was calculated in order to estimate the interaction energy between a ligand and the corresponding monomers in the following manner,

$$\Delta E = E_{\text{cluster}} - (E_{\text{monomers}} + E_{\text{ligand}})$$

where E_{cluster}, is the total energy of the simulated cluster (monomers and ligand), E_{monomers} is the total energy of the ten monomers (without the ligand) and E_{ligand} is the total energy of the ligand.

In the second part of this study, simulated molecular systems consisted of a ligand and a polymer. The polymers were obtained from the above mentioned monomers and had a degree of polymerization of 10 in order to be consistent with previously simulated molecular clusters consisting of 10 monomers. For each of the simulated polymer clusters, NVT MD simulations at room temperature for 40 ns were carried out to obtain equilibrated conformations of a polymer chain without a ligand and of a polymer chain with a ligand. And similar to monomer study, for each pair

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-Vinylbezylimino dicetic acid
25	Poly-	4-Vinylimidazole

of molecular systems, a total energy difference, (ΔE), was calculated in order to estimate the interaction energy between ligand and the corresponding polymer as follows,

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

where E_{cluster}, is the total energy of the simulated cluster (polymer and ligand), E_{polymer} is the total energy of the polymer (without the ligand) and E_{ligand} is the total energy of the ligand.

Also, the closest distance between the active site (group) of a polymer 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 Fig. 1. The abbreviations (as indicated in brackets) will be used on the graphical representations throughout this manuscript.

4. Computational details

4.1. 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 minimiser, 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 parametrized 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 systems [23] and can be used to calculate and minimise the energy of 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 (Coulombic) (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 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 Coulombic (electrostatic) interactions in the

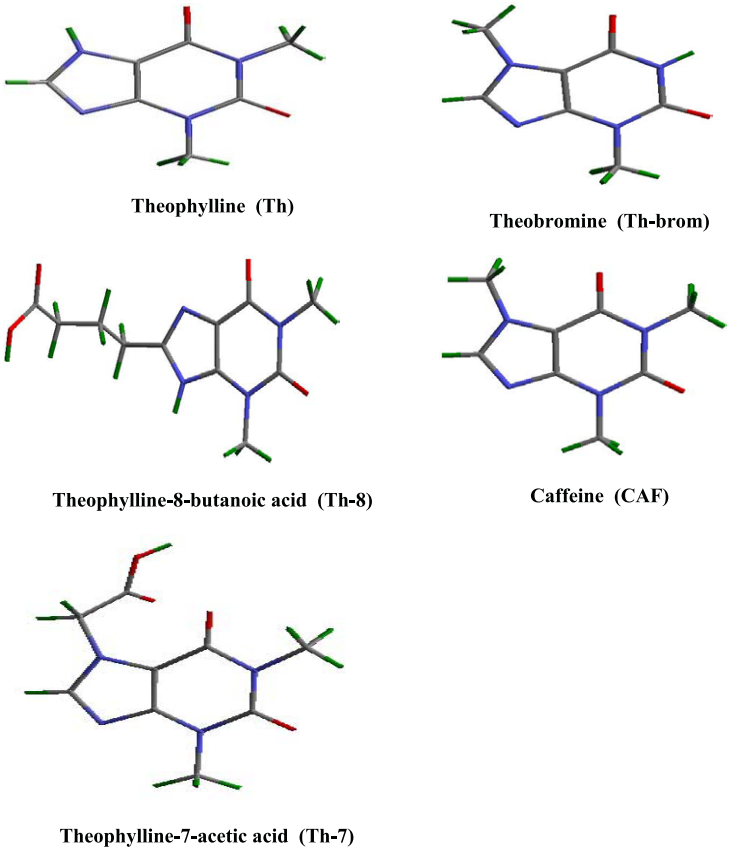


Fig. 1. Structures of the target molecules studied.

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 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 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. The computational procedure used in this research includes the following main steps shown in Fig. 2. As an example, an

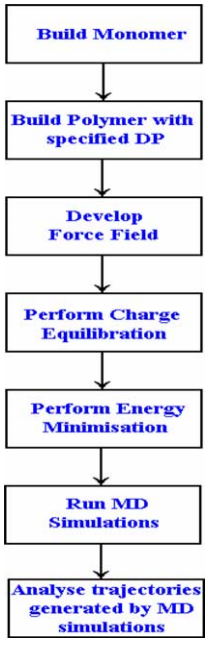


Fig. 2. The main steps in the computational procedure used in this research.

input file of the NVT MD simulation used throughout this research is also presented in Appendix B.

4.2. Systematic and statistical errors

As with laboratory experiments, computer simulation experiments can have both systematic and statistical errors, which, however, can be controlled and minimised. Applying MD simulation, the thermophysical, structural and dynamic properties of polymeric materials can be calculated with an accuracy that strongly depends on the reliability of the potential function, in other words, on the errors arising from the truncation of the intermolecular forces, and statistical errors, arising from insufficiently long sampling period. In practice, MD simulation studies are presently still limited by the speed and storage capabilities of current computers to limited molecular cluster size and computing time scales. In addition, the results of the molecular simulations for any given cluster might converge to different local minima depending on the starting conformation of the system. One of the solutions to this problem was to start from many, widely different initial conformations, and to make sure that the results obtained from them did not differ widely.

5. Results and discussion

5.1. Simulation of monomeric molecular clusters

The simulated monomers were presented in Table 1 and their minimized chemical structures are presented in Appendix A. Each of the simulated molecular clusters was equilibrated. An example of NVT MD plot of energy versus simulation time is presented in Fig. 3. The interaction energies as defined above are plotted in Fig. 4. The simulations for the functional monomers indicate that itaconic acid (21) and ethylene glycol dimethacrylate (10) form the most stable complexes with all of the four ligands in the equilibrated states. 1-Vinylimidazole (1), acrylamide (6), acrylic acid (7) and acrylonitrile (8) are also fairly good candidates for the imprinting monomers. Styrene (19), 4-vinylbenzylimino diacetic acid (24) and 2-acrylamido-2-methyl-1-propanesulfonic acid (3) form the least stable structures and should not be used in the making of the imprint for theophylline. Initial experiments seem to agree that styrene is not a good monomer for creating an imprint with theophylline [27]. In fact, trifluoro methacrylic acid (22), imidazole-4-acrylic acid ethyl ester (11), imidazole-4-acrylic acid (16), 2-hydroxyethyl methacrylate (4) and 2-(diethylamino)ethyl methacrylate (20) all give positive ΔE_s indicating that these monomers would not be good candidates for forming attractive interactions between them and theophylline. 4-Vinylbenzoic acid (23) is an interesting case since it is the only monomer which forms stable complex with theophylline but not with its derivatives, see Fig. 4. Hence, the analysis predicts that in equilibrated state, 4-vinylbenzoic acid (23) will preferentially bind theophylline more strongly than the theophylline derivatives.

The monomer simulations were further analyzed in order to find out which part of the monomer comes closest to the given ligand and determined the magnitude of these distances. The results of this analysis are presented in Fig. 5. In most cases, it was found that the functional group of monomers interacting with ligands tends to be either –COOH or CH_2=CH–. It was found that for the three most stable complexes for theophylline: itaconic acid (21), ethylene glycol dimethacrylate (10) and 4-vinylbenzoic acid (23), the closest distance of approach was

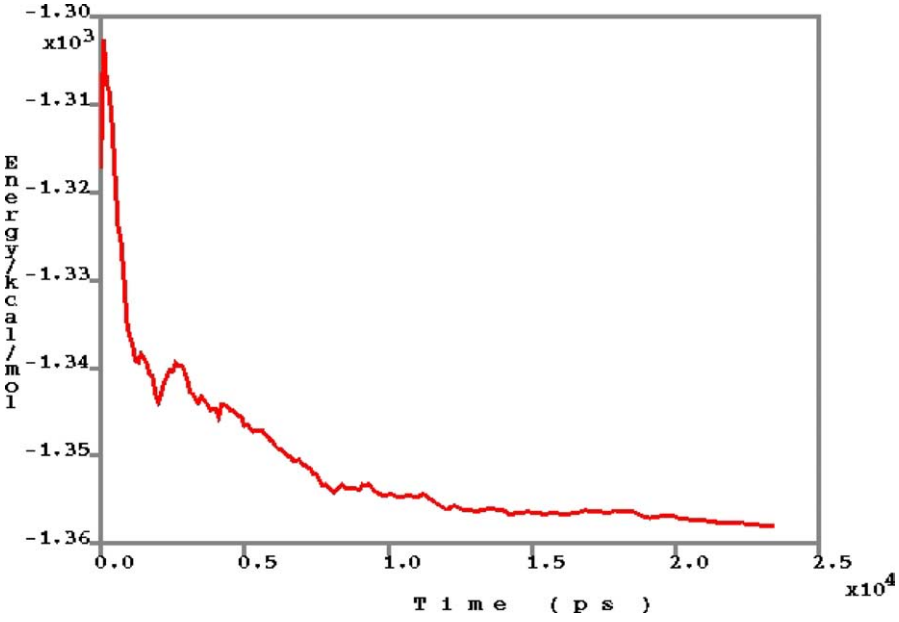


Fig. 3. Plot of NVT MD energy versus simulation time.

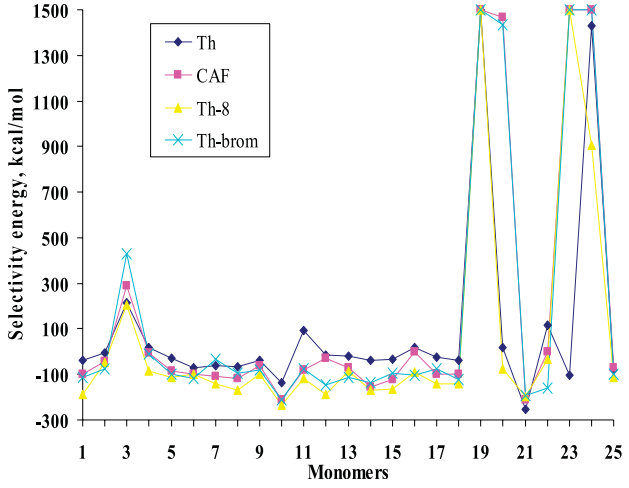


Fig. 4. Graph of the interaction energy between monomers and ligands (in kcal/mol) versus monomers.

approximately 3.5 Å and the binding was predominantly with –COOH (in the case of 4-vinylbenzoic acid (23), –OH was also involved). This clearly indicates H-bonding is involved in these interactions. There does not appear to be a clear correlation between interaction energies and distances. The binding distances fall between 1.0 and 5.0 Å. However, a loose correlation can be noted, namely distances between 2.0 and 4.0 Å tend correspond to negative interaction energies, indicating that this is roughly the distance of closest approach required for the formation of stable complexes. These distances are consistent with the three-dimensional structures of ligands and monomers as determined from their total electronic charge distributions (densities). As an example, the simulated electronic charge distribution of theophylline-8-butanoic acid is presented in Fig. 6 where the electronic charge distribution extends 1–2 Å outside the O or H nucleus. The same statement applies to the monomers, hence the minimal contact distance must fall between 2.0 and 4.0 Å for an attractive interaction to occur. Typical equilibrated conformations of NVT-MD snapshots at 300 K of the simulated monomeric clusters are

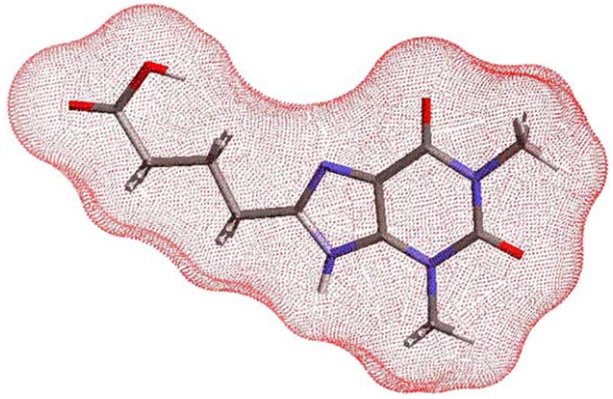


Fig. 6. The total electronic charge density of theophylline-8-butanoic acid.

presented in Fig. 7. In Fig. 7(a) a cavity formation can be seen whereas in Fig. 7(b) theophylline does not interact strongly with styrene monomers.

5.2. Simulation of polymeric molecular clusters

The second simulated molecular systems consisted of a ligand and a polymer. The polymers were obtained from monomers that were simulated and presented above. For each of the simulated polymer, a polymeric chain with DP 10 was simulated with theophylline or its derivative and the interaction energies (ΔE) were calculated and displayed on Fig. 8. Also, the closest contact distances between the active site (group) of a polymer and a ligand was determined. These data are presented in Fig. 9. In the polymer study an additional ligand is investigated, theophylline-7-acidic acid. The motivation for the inclusion of this ligand came from the experiments since theophylline-7-acidic acid was used in the initial formation of the imprinting cavity. The tail of theophylline-7-acidic acid was used to attach theophylline to substrate. From the above simulated polymer systems it was found that most of the polymers form stable complexes with the studied ligands. However, if we focus on the selectivity, just poly(acrylic acid) (7) is selective only for

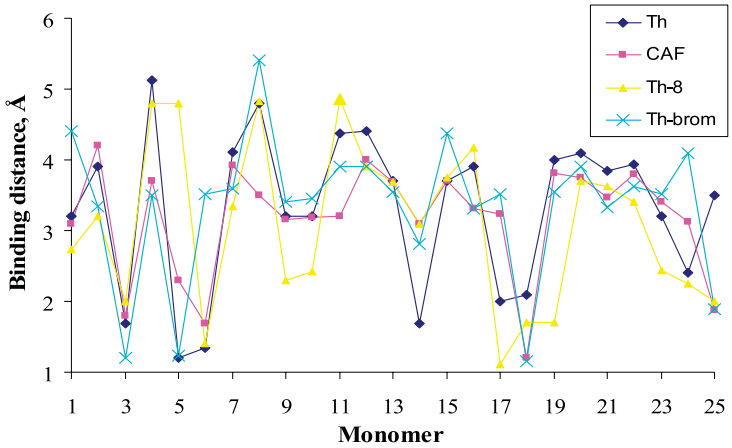


Fig. 5. The closest approach distance of the simulated monomers to ligands (in Å).

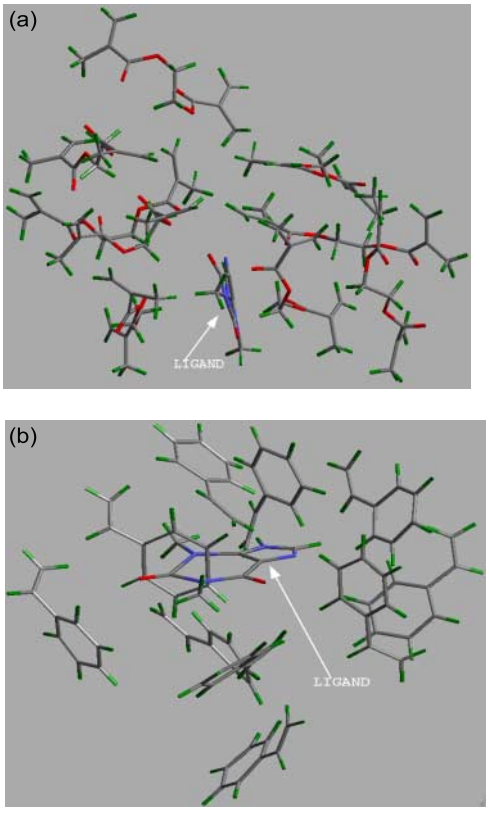


Fig. 7. (a) Ten molecules of ethylene glycol dimethacrylate and one molecule of theophylline. (b) Ten molecules of styrene and one molecule of theophylline.

theophylline. Poly(methacrylic acid) (15) is selective for theophylline and theophylline-7-acetic acid. These data are in good agreement with previously reported experimental data (Sellergren and Anderson, 2000) [28]. Poly(itaconic acid) (21) also forms preferentially stronger complexes with theophylline than with its derivatives. For the theophylline derivatives we note that poly(*N*,*N*-methylene-bis-acrylamide) (14) is selective for theophylline-7-acetic-acid. Poly(imidazole-4-acrylic acid ethyl ester) (11) is selective

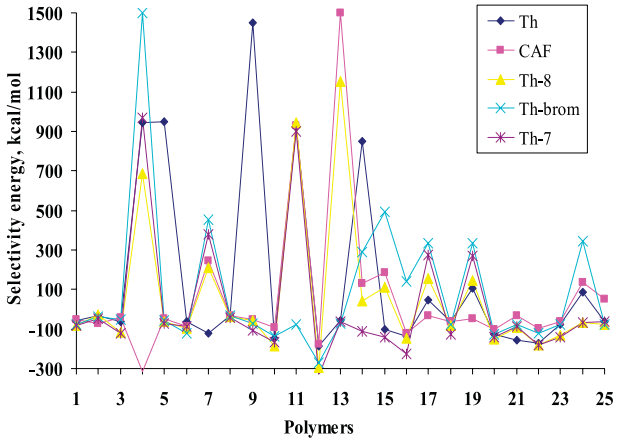


Fig. 8. Graph of the interaction energy between polymers and ligands (in kcal/mol) versus polymers.

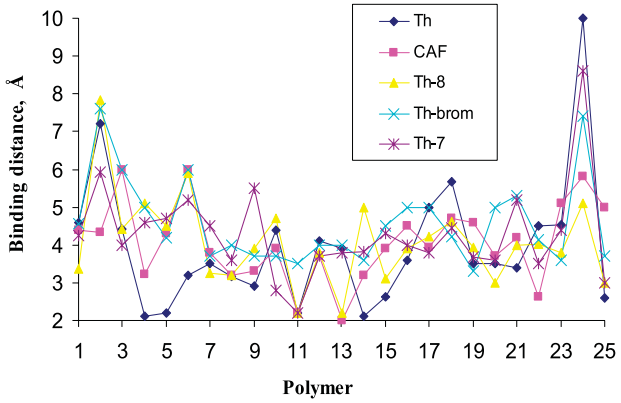


Fig. 9. The closest approach distance of the simulated polymers to ligands (in Å).

only for theobromine. Poly(2-hydroxyethyl methacrylate) (4) is selective for caffeine. The functional groups of polymers interacting with ligands are predominantly –COOH, for example, in the case of poly(acrylic acid) (7) and poly(methacrylic acid) (15) respectively for theophylline and the distance of closest approach is between 2.5 and 3.5 Å. As an example, a typical conformation of simulated ligand–polymer molecular systems at room temperature is presented in Fig. 10. Fig. 10 displays the closest approach distance between the ligand (theophylline-7-acetic acid) and the simulated polymer poly(4-vinylbenzoic acid).

In summary, it is evident from our data that there seems to be a structural/chemical correlation when monomers/polymers and theophylline or its derivatives are bound in respective molecular clusters. For example, our monomer data indicate that –COOH groups and double bonds (i.e. electron rich groups) tend to come closest to the ligands. Our polymer studies indicate that poly(acrylic acid), poly(methacrylic acid) and poly(itaconic acid) interact strongest and preferentially with theophylline. These three systems have many –COOH groups. Again pointing out that –COOH groups are important for binding with theophylline. In Section 5.3, we analyze the total energies of the clusters in order to find out which part contributes most to the intermolecular interactions.

5.3. Analysis of energy components

The aim of this section was to gain a greater understanding of interactions between the simulated molecular clusters and ligands. In particular we were interested in analyzing the intermolecular contributions. For this reason we extracted the various intermolecular energy contributions from the total energies. We investigated the total van der Waals, (vdW), (that included the attractive and repulsive van der Waals contributions), electrostatic, (*Q*), and hydrogen bonding, (H-b), contributions to the total energies. Since energy differences are the quantities of interest to us, we have calculated the respective contributions to the total energy (TE) differences. A

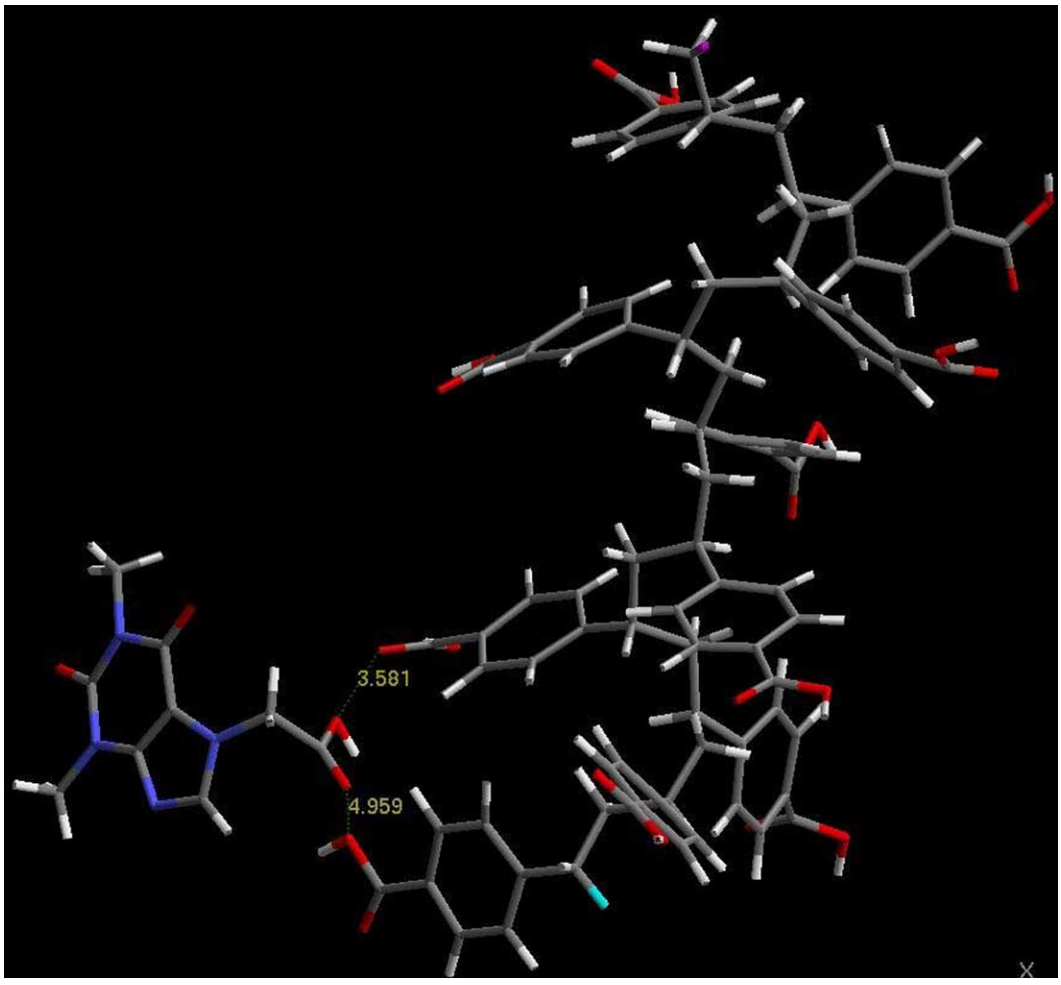


Fig. 10. A display of a typical simulated equilibrated conformation of theophylline-7-acetic acid and one polymeric chain of poly(4-vinylbenzoic acid) (NVT MD at 300 K).

representative plot of these results is shown in Fig. 11. The following observations can be made: the main contribution to the TE difference comes from the total potential energy (PE) difference as in most cases the TE difference curve is

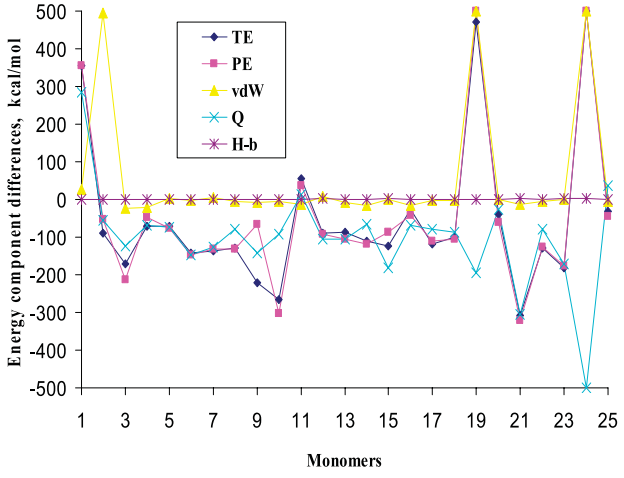


Fig. 11. The energy component differences for the simulated monomers and theophylline.

followed very closely by the PE curve (it appears that kinetic energy (KE) difference does not contribute to the total energy difference significantly). The total PE differences contain contributions from both the bonded and non-bonded interactions. In turn, the main contribution (with the exception of styrene (19) and 4-vinylbenzylimino diacetic acid (24)) to the total PE difference comes from the electrostatic contribution. In the two exceptions the bonded interactions (such as bond, torsional energies etc.) appear to be important contributions to PE difference. The total van der Waals energy difference does not contribute significantly to the TE difference in most cases (the exceptions are: 2-vinylpyridine (2), styrene (19) and 4-vinylbenzylimino diacetic acid (24)). The H-bonding contributions appear to be very small in all cases.

Fig. 12 exhibits the electrostatic contributions for the four ligands. Fig. 12 shows that theobromine and theophylline-8-butanoic acid have, in most cases, stronger electrostatic interactions with monomers than with either caffeine and theophylline. Finally, it should be noted that the lower the energy difference the stronger the interaction between the monomer and ligands. The steric interactions probably

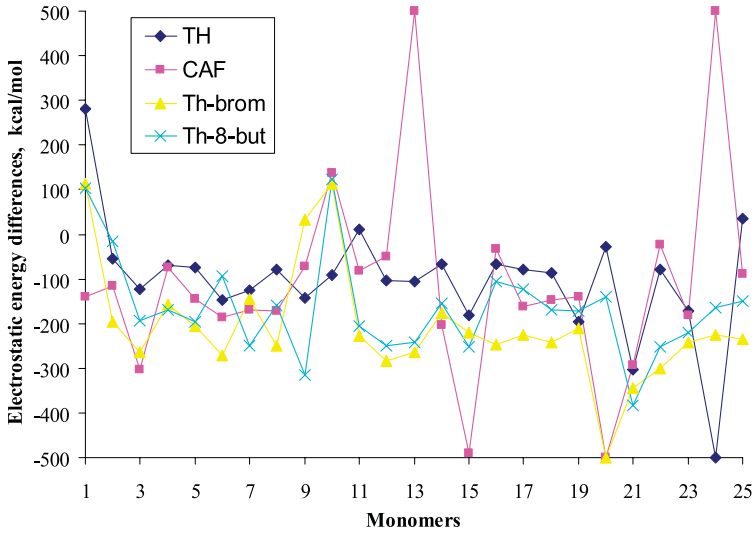


Fig. 12. The electrostatic energy differences for the simulated monomers computed for different ligands ($\Delta E_q = E_{q\text{-cluster}} - (E_{q\text{-monomer}} + E_{q\text{-ligand}})$).

also come into play. Monomers that are more bulky (have more and larger side groups) will tend to interfere with each other when it comes to surrounding the ligands. Hence a combination of electrostatic and steric interactions will determine how close and how tightly the ligand will interact with monomers. Similar tendency was observed for the simulated polymer clusters as well.

It should be pointed out that the TE differences of the simulated molecular clusters in Fig. 11 were computed by necessity from the total energies that were the last energy values as written in the output file of the MD trajectory. This was necessary for the component analysis. The TE energy differences plotted in Figs. 3 and 8 were calculated from the average total energies (averaged over the equilibrated simulation). Since even in the equilibrated system the total energy oscillates about some mean value, the two figures for TE differences are not exactly the same. It is our conclusion that average equilibrated energies of the trajectory file are probably a better choice for most purposes. The main observations as discussed above were the same irrespective of the choice of TE to calculate differences.

5.4. Analysis of hydrogen bond

It appears from our MD study above that the H-bonding contribution to the total energy difference is very small and not important. This is somewhat counterintuitive. One possible explanation of this could be that the major part of H-bonding in the MD simulations is implicitly taken into account in the electrostatic van der Waals interactions rather than in the parameterization of H-bonding, which is probably not very sophisticated in the MD calculations. We have done some quantum mechanical (QM) calculations at RHF/6-31G* level of theory [29] to further investigate the H-bond interactions. All configurations obtained in Figs. 13–15 have been fully geometry optimized. The distances indicated on Figs. 13–15 are in units of Å. In particular we have performed calculations for theophylline in the presence of methacrylic acid. We have obtained four possible configurations for a system consisting of one theophylline and one methacrylic acid. Configuration 1 has the lowest energy and there are two H-bonds present: one between H on methacrylic acid and O on theophylline and the other H on theophylline and O on methacrylic acid as shown in Fig. 13(a). In the second configuration (Fig. 13(b)) which has a slightly higher energy (0.19 eV) there are also two H-bonds at the same location of the theophylline but now methacrylic acid turns around and presents the other O and H is on the methyl group. The next configuration (Fig. 13(c)) has energy 0.23 eV higher than the lowest state and has the H-bond formation between the O on theophylline that is located between its two methyl groups and the H of the –COOH group on methacrylic acid. The last configuration has the energy 0.40 eV higher and has methacrylic acid forming the H-bond at the end of the theophylline that contains the N atom without H attached to it. Next we consider clusters that contain more than one methacrylic acid. First we perform computations for clusters containing one theophylline and three methacrylic acids. A search to find a true ground state with the lowest energy would probably require extensive computations given that it appears that there are many possible configurations with energies very close together. In Fig. 14 two such configurations are displayed. They are 0.12 eV apart. From these two configurations, it is clear that the locations of methacrylic acids around the theophylline correspond roughly to the four lowest configurations that we obtained for one methacrylic acid and theophylline clusters. In the first configuration (Fig. 14(a)) we also see that the H-bond is being formed between two methacrylic acids. When one more methacrylic acid is added, this trend of forming

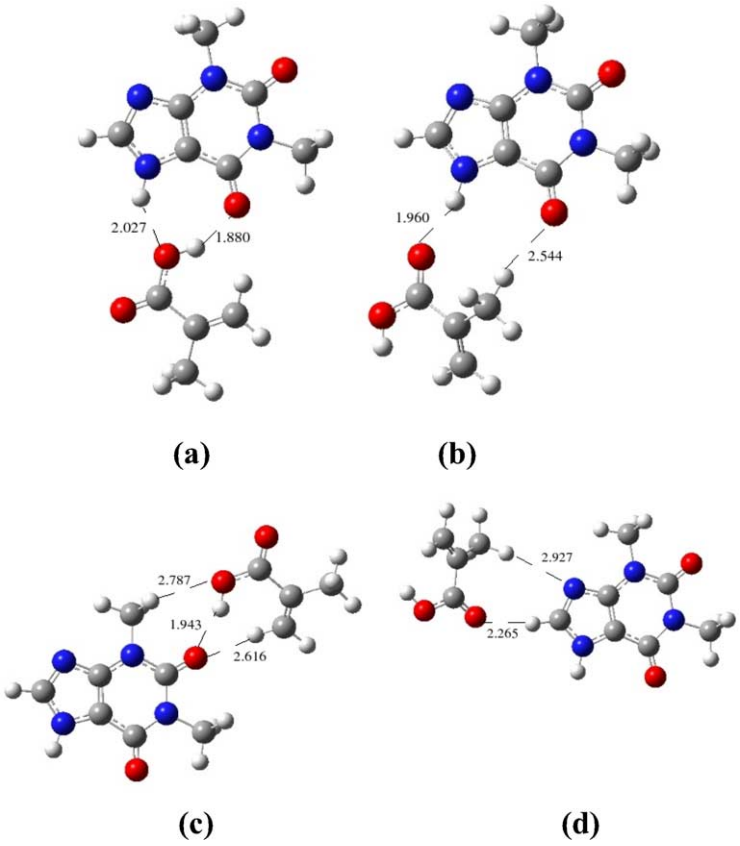


Fig. 13. Illustration of H-bondings between the theophylline and methacrylic acid molecules. Four configurations (a)–(d), (a) being having the lowest energy, (b) the second lowest etc. are displayed.

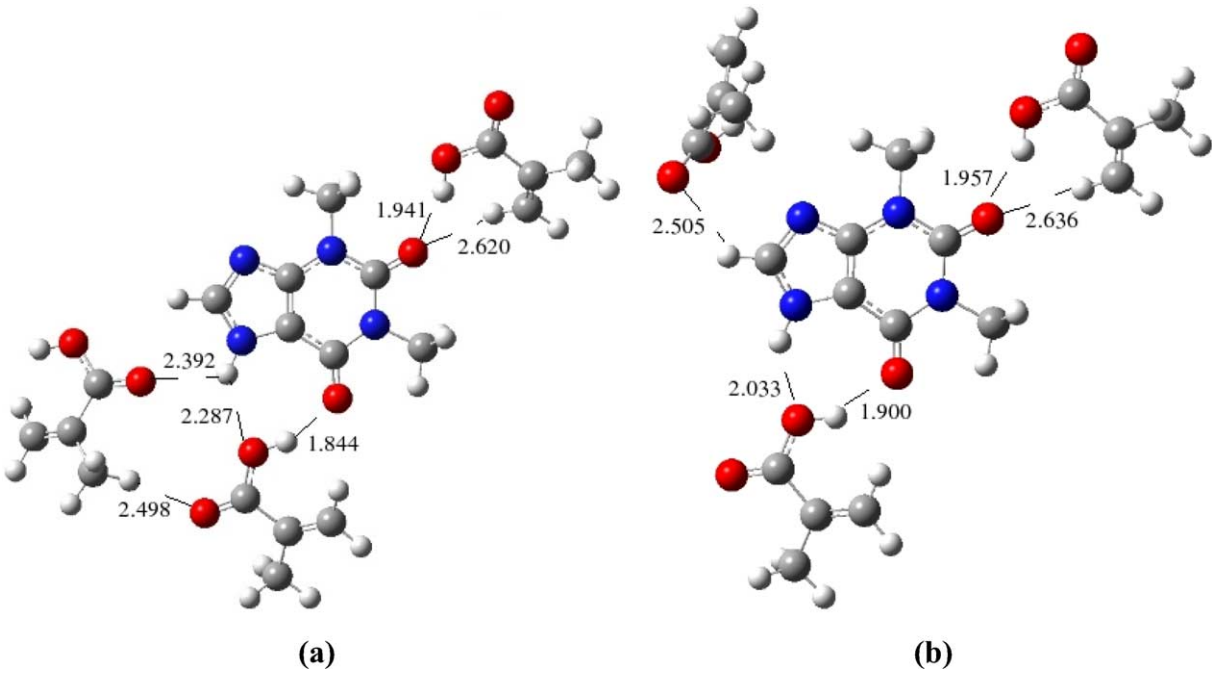


Fig. 14. Examples of two possible optimized configurations (a) and (b) for three molecules of methacrylic acid and one molecule of theophylline.

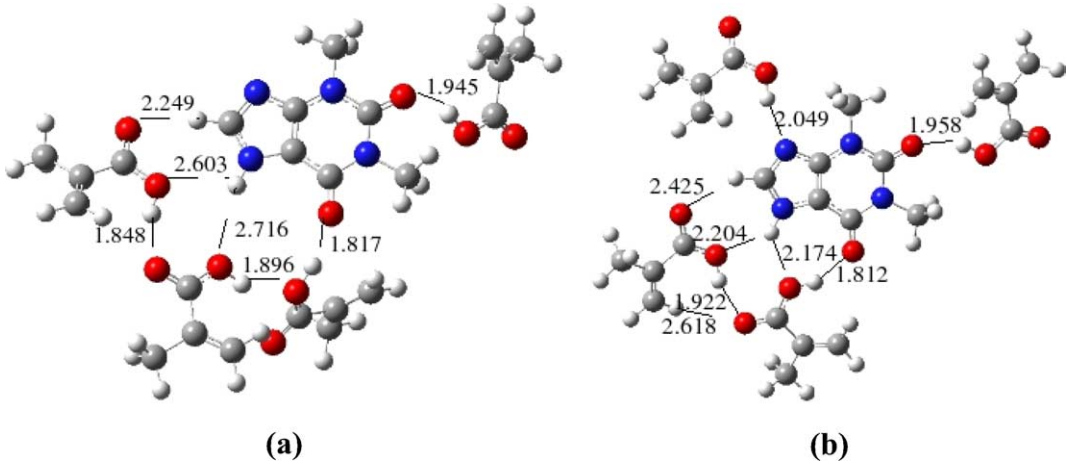


Fig. 15. Examples of two optimized configurations (a) and (b) for four molecules of methacrylic acid and one molecule of theophylline.

H-bonds between methacrylic acids themselves as well between methacrylic acids and theophylline continues as is shown in Fig. 15 where again we obtained two representative configurations of the clusters containing one theophylline and four methacrylic acids. These configurations differ by 0.002 eV. As can be clearly seen from Fig. 15, methacrylic acid preferentially accumulates on the side of theophylline that does not have the methyl groups.

From Figs. 13–15, it can be seen that there are H-bond interactions between theophylline and the molecules of methacrylic acid and as well as H-bonds between the molecules of methacrylic acid. These quantum mechanical calculations clearly show the formation of H-bonding in the interaction between methacrylic acids and theophylline. These results indicate that in most cases the imprinting cavity does depend on H-bonding formation and could lead to different cavities for different ligands based on their structural differences and the ability to form H-bonds.

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. 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. A large number of different polymers and monomers systems have been simulated and analysed. A library of 25 monomers and their corresponding polymers has been established and the interaction energies and closest approach distances computed. Analysis was also performed to see which functional group of the simulated monomer/polymer clusters interacts with which functional group of the ligand. Extensive equilibration procedures were necessary to obtain reasonable results for the simulated molecular clusters and the following conclusions were drawn.

From monomer simulations it was found that itaconic acid and ethylene glycol dimethacrylate form the most stable complexes with all ligands. 4-Vinylbenzoic acid is the only monomer which forms stable complex with theophylline but not with its derivatives. It would appear that 4-vinylimidazole, acrylamide, acrylic acid and acrylonitrile are also fairly good candidates for imprinting materials for theophylline. From polymer simulations it was found that many of the polymers form stable complexes with the studied ligands. However, only poly(acrylic acid) and poly(itaconic acid) are selective only for theophylline. Poly(methacrylic acid) is selective for theophylline and theophylline-7-acetic acid. Poly(*N*,*N*-methylene-bis-acrylamide) is selective for theophylline-7-acetic-acid and poly(4-vinylpyridine) and poly(2-hydroxyethyl methacrylate) are selective for caffeine.

In general, our results suggest that polymers are better material for imprinting technology then corresponding monomers, as more of the studied polymers are selective for the studied ligands than the monomers. 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– and the binding distances between the ligand and monomer or polymer in the most stable cases are between 2.0 and 4.0 Å. For the simulated molecular clusters, monomers and polymers, it was noticed that the electrostatic energy gives the largest energy contribution to the total PE in most cases and in turn PE contribution gives the largest contribution to the TE. H-bonding is formed as a result of a competition between attractive (electrostatic) and repulsive intermolecular interactions. Quantum mechanical calculations present clear evidence for the H-bonding formation in the cluster of theophylline and monomers or polymers.

Acknowledgements

This work is part of a CRTI project. CRTI is an initiative of the Canadian federal government aimed at providing new knowledge, technology, and research necessary for CBRN (Chemical, Biological, Radiological and Nuclear) response and preparedness. See: http://www.crti.drdc-rddc.gc.ca/.

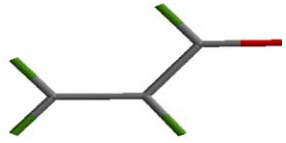
Appendix A

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.

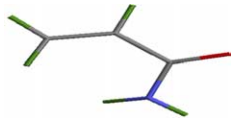
Notes

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

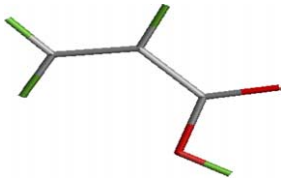
Carbon	Grey
Hydrogen	Green
Oxygen	Red
Nitrogen	Blue
Sulfur	Yellow
Fluorine	Light blue



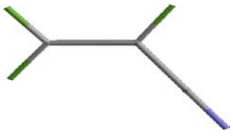
Acrolein



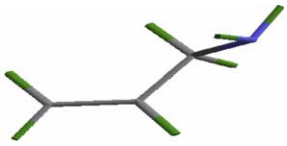
Acrylamide



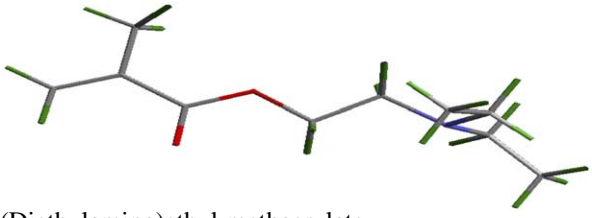
Acrylic acid



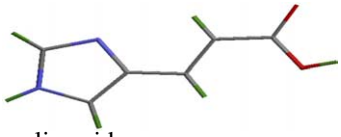
Acrylonitrile



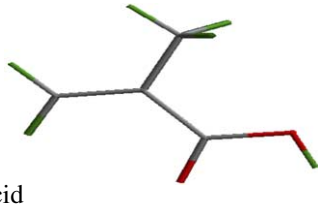
Allylamine



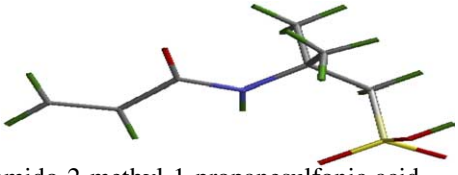
2-(Diethylamino)ethyl methacrylate



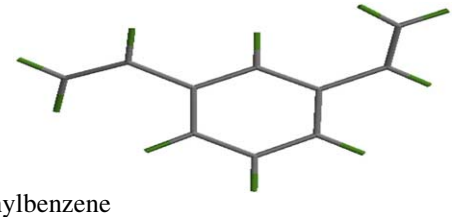
Imidazole-4-acrylic acid



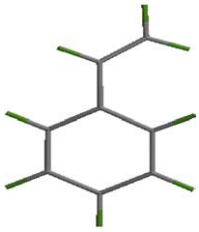
Methacrylic acid



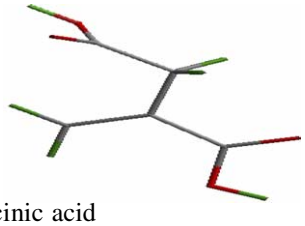
2-Acrylamido-2-methyl-1-propanesulfonic acid



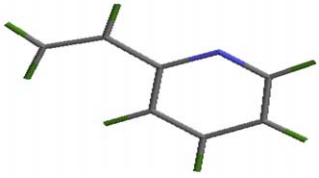
m-Divinylbenzene



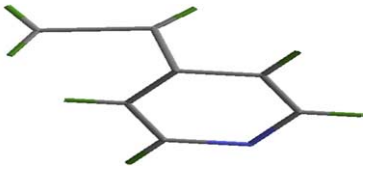
Styrene



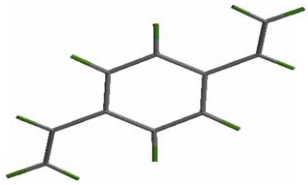
Methylene-succinic acid



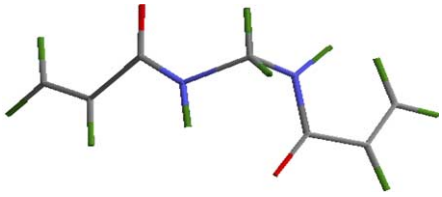
2-Vinylpyridine



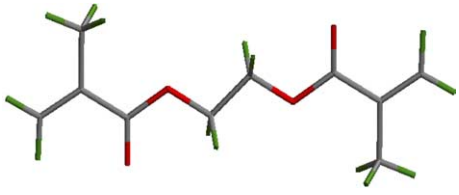
4-Vinylpyridine



para-Divinylbenzene

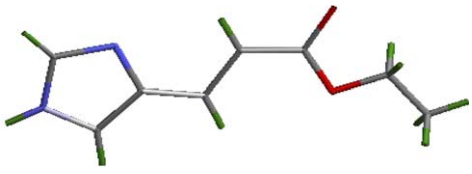


N,*N*-methylene-bis-acrylamide

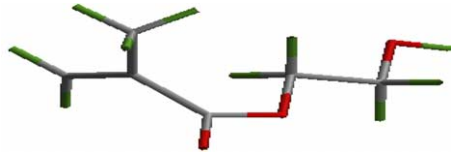


Ethylene glycol dimethacrylate

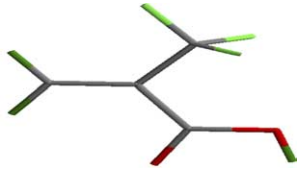
4-Vinylimidazole



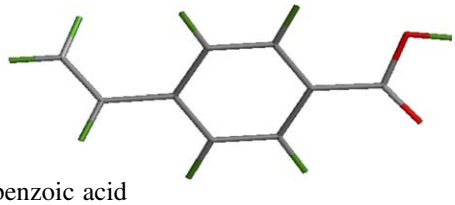
Imidazole-4-acrylic acid ethyl ester



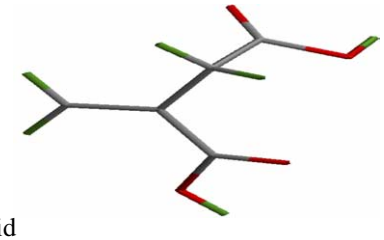
2-Hydroxyethyl methacrylate



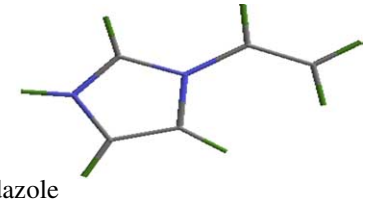
Trifluoro methacrylic acid



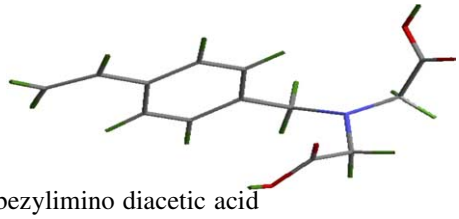
4-Vinylbenzoic acid



Itaconic acid



1-Vinylimidazole



4-Vinylbezylimino diacetic acid

Appendix B

An example of the computer simulation input file used for most of the NVT MD simulations that were running for this research is presented below.

```
# Input File For Discover Generated By Cerius2
# Date: Fri Dec 26, 21:03:40, 2004
# System Name: imprinting polymer
# Begin section:
 begin forcefield=pcff
# Parameter section:
 forcefield parameter\
   +bond_automatic\
   +angle_automatic\
   +torsion_automatic\
   +oop_automatic\
   -bond_stop\
   -angle_stop\
   -torsion_stop\
   -oop_stop\
   -cross_stop
# Nonbond section:
 forcefield nonbond\
   -separate_coulomb\
 vdw\
```

```
  summation_method = atom_based\
   cutoff = 100.00\
   spline_width = 1.00\
   buffer_width = 0.50\
  coulomb\
  - distance_dependent_dielectric\
  dielectric_value = 1.00
# Scaling section:
  forcefield scale\
   bond = 1.00\
   angle = 1.00\
   torsion = 1.00\
   oop = 1.00\
   vdw = 1.00\
   coulomb = 1.00\
   cross = 1.00
# Rattle section:
  rattle bonds
# Dynamics section (Equilibration):
  dynamics\
   time = 5000000.\
   timestep = 1.00000\
   initial_temperature = 298.00\
   + boltzmann\
   ensemble = NVT\
   temperature_control_method = velocity_scaling\
   temperature_window = 10.0000\
   temperature = 298.00\
   deviation = 50.00
# Dynamics section:
  dynamics\
   time = 0.250000E + 18\
   timestep = 1.00000\
   initial_temperature = 298.00\
   ensemble = NVT\
   temperature_control_method = nose\
   q_ratio = 1.00000\
   temperature = 298.00\
   deviation = 50.00\
   execute frequency = 99999\
   command = {print history}\
   execute + before + after frequency = 10000\
    command = {print output\
     + average\
     + batch_average\
     batch_size = 10000\
     + instantaneous\
     + total_energy\
     + kinetic_energy\
     + potential_energy\
     + bond_energy\
     + angle_energy\
     + torsion_energy\
     + oop_energy\
     + cross_term_energy\
     + total_nonbond_energy\
     + coulomb_energy\
     + vdw_energy\
     + repulsive_vdw_energy\
     + dispersive_vdw_energy\
     + hbond_energy\
     + temperature}\
    execute + before + after frequency = 10000\
     command = {print table\
     + average\
     + batch_average\
     batch_size = 10000\
     + instantaneous\
     + total_energy\
     + kinetic_energy\
     + potential_energy\
     + bond_energy\
     + angle_energy\
     + torsion_energy\
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     + vdw_energy\
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     + dispersive_vdw_energy\
     + hbond_energy\
     + temperature}
  # Write coordinate file:
   writeFile coordinate filename = .cor
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