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# Computational investigation and synthesis of a sol–gel imprinted material for sensing application of some biologically active molecules

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ABSTRACT

A hybrid sol–gel material was molecularly imprinted with a group of neurotransmitters. Imprinted material is a sol–gel thin film that is spin coated on the surface of a glassy carbon electrode. Imprinted films were characterized electrochemically using cyclic voltammetry (CV) and the encapsulated molecules were extracted from the films and complementary molecular cavities are formed that enable their rebind. The films were tested in their corresponding template solutions for rebinding using square wave voltammetry (SWV). Computational approach for exploring the primary intermolecular forces between templates and hydrolyzed form of the precursor monomer, tetraethylorthosilicate (TEOS), were carried out using Hartree–Fock method (HF). Interaction energy values were computed for each adduct formed between a monomer and a template. Analysis of the optimized conformations of various adducts could explain the mode of interaction between the templates and the monomer units. We found that interaction via the amino group is the common mode among the studied compounds and the results are in good agreement with the electrochemical measurements.



## 1. Introduction

Molecular imprinting is a widely studied and applied technique for the design of smart materials. This technique was invented for the first time by Dickey in 1949 when he succeeded to create molecular cavities for some dye molecules [1]. In general, molecular imprinting is carried out by the incorporation of the template molecule during the polymerization process. After the extraction of the template from the cross-linked polymer matrix, a three-dimensional cavity is left in the polymer. The molecular cavity is complementary in shape, size and functional group orientation/interaction with respect to the template molecule [2–4]. In the last two decades molecular imprinting has been applied in several of fields. For example, this is the case in high performance liquid chromatography, food analysis, capillary chromatography and solid phase extraction [5–7]. Moreover, molecular imprinting has been applied widely in the design of recognition elements in biosensors [8–12].

Computational methods are essential and are acquiring an increasing role in the design and development of imprinted materials. Simulations adopted by various computational methods are crucial for better understanding the intermolecular interactions between the template molecules and functional monomers used in the imprinting process. In the last few years, a considerable computational work has been dedicated for improving the properties of molecularly imprinted material. Thus, Breton et al. [13] applied molecular simulation to select the best functional monomers which are able to interact with some selected herbicides as template molecules. Li and co-workers [14] used Hartree–Fock method (HF) for the selection of the best functional monomer to use in the imprinting of aniline. Pavel et al. [15–17] adopted computational tools to investigate the intermolecular interactions occurring during the imprinting of theophylline, theobromine, and caffeine into a complex polymer matrix. Another work by Chianella et al. [18,19] used a virtual library of functional monomers in various applications.

On the other hand, sol–gel materials have been extensively used for the purposes of molecular imprinting. Imprinting of sol–gel materials has acquired great interest recently [20–22] due to their unique physical properties. In the first part of this work, we have investigated the molecular imprinting of a group of molecules of biological interest, into a hybrid sol–gel matrix [23]. The matrix was synthesized by the acid hydrolysis of a mixture of tetraethylorthosilicate (TEOS) and phenyltriethylorthosilicate (PTEOS). Imprinted sol–gel materials were spin coated as thin films on the surface of a glassy carbon electrode. The resulting modified electrodes were then characterized for the template molecules using cyclic voltammetry (CV). After the extraction of template molecules the imprinted films were subjected to rebinding experiments in presence of different molecules to investigate the selectivity of the imprinted films.

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**Table 1**
Electrochemical characterization results of template molecules encapsulated into sol–gel films using cyclic voltammetry between −0.2 to +1.0 V in PBS (pH 7.2 and 10 mmol $L^{-1}$).

| Template molecules | Oxidation current ($I$) ($10^{-5}$ A) | Template molar concentration in the sol mixture (mol $L^{-1}$) | Normalized[a] oxidation current ($10^{-4}$ A mol$^{-1}$ $L^{-1}$) | Oxidation potential (mV) |
|---|---|---|---|---|
| Dopamine | 1.0360 | 0.0130 | 7.9700 | 375 |
| Norepinephrine | 1.2220 | 0.0156 | 7.8200 | 520 |
| Dopa | 0.3273 | 0.0133 | 2.4610 | 380 |
| Epinephrine | 0.3693 | 0.0156 | 2.3670 | 535 |
| Tyramine | 0.5051 | 0.0231 | 2.1860 | 705 |

[a] Normalization is done by dividing the current response by the molar concentration of the template molecules in the sol mixture after mixing the template with hydrolyzed monomers.

In the present work, the intermolecular interactions between the basic monomer units (TEOS) in the hydrolyzed form were investigated by calculating the interaction energy between the monomer and various template molecules. Each template molecule is expected to form a "pre-polymerization" adduct with the monomer units. The stability of this complex is expected to affect greatly the properties of the imprinted polymer and therefore, the selectivity of the film [24–26].

## 2. Experimental

### 2.1. Reagents

TEOS (>99%) and PTEOS (>99%) were used as functional monomers for the polymerization process. Dopamine, tyramine, dopa, dopac, tyrosine, epinephrine, and norepinephrine are ≥99% pure, while catechol ≥98% pure. The foregoing compounds were used as template molecules in the imprinting process and as test molecules for rebinding experiments. Phosphate buffer solution (PBS) (pH 7.2, 10 mmol $L^{-1}$) was prepared from sodium dihydrogen phosphate and disodium hydrogen phosphate. 2-Ethoxy ethanol and absolute ethyl alcohol were used as solvents for dissolving template molecules and monomers for the polymerization process. Hydrochloric acid and distilled water were used for hydrolysis of functional monomers during the polymerization. All chemicals were supplied by Aldrich (Milwaukee, WI, USA). Chemicals were used as they were received.

### 2.2. Equipments

Glassy carbon electrodes from BAS (USA) with 3 mm diameter were used as working electrodes. A platinum wire from BAS (USA) was used as counter electrode. All cell potentials were measured against Ag/AgCl as a reference electrode from BAS (USA). One compartment, three electrodes cell, made of glass (30 mL) and fitted with gas bubbler was used for all electrochemical measurements. Electrochemical characterization including cyclic voltammetry (CV) and square wave voltammetry (SWV) were carried out by a BAS-100B electrochemical analyzer (Bioanalytical systems, BAS, West Lafayette, USA). A workstation with Gaussian software was used for the computational work.

### 2.3. Procedures

#### 2.3.1. Imprinted film preparation

The glassy carbon electrodes were polished using 0.05 μL alumina slurry on Buehler felt pads, and then rinsed thoroughly with deionized water and ethanol. Electrodes were then electrochemically activated before spin coating. The electrode surface was then activated by polarization at +1.6 V for 60 s and at −1.6 V for the same period. The electrode was finally cycled between +1.0 and −0.2 V until a stable CV was obtained [26,27]. Tetraethylorthosilicate (400 μL, 1.791 mmol) was mixed with phenyltriethylorthosilicate (65 μL, 0.351 mmol) in 3.0 ml of 2-ethoxy ethanol. The solution was stirred until a homogeneous mixture was obtained. A solution of 0.1 M HCl (100 μL) was added drop-wise with continuous stirring, and 90 μL $H_2O$ were added in the same manner. The mixture was stirred gently for 2.5 h. A 1.0 mL aliquot of the prepared sol–gel mixture was mixed with different amounts of template solutions to give a definite molar concentration of the template molecules as indicated in Table 1. The resulting mixtures (sol–gel and template) were stirred for 2.0 h. The imprinted sol–gel mixture was spin coated on the surface of the glassy carbon electrode at a spinning rate of 2500 rpm for 45 s. The electrodes were allowed to dry overnight, and then they were electrochemically characterized by cyclic voltammetry (CV) in the potential window −200 to +1000 mV at a scan rate 100 mV $s^{-1}$. Template molecules were extracted from the imprinted film by repeated CV [28]. The current response was followed until a value near zero is obtained. Electrodes were allowed to dry overnight before rebinding experiments were carried out.

#### 2.3.2. Rebinding experiments

Modified electrodes were dipped for 15 min in rebinding solutions containing different test molecules of concentration 50 μmol $L^{-1}$ each. This step was followed by electrochemical characterization using SWV technique. The "incubation" time for the rebinding of the analyte to be successful was selected in such a way that high sensitivity and stability of the current response was obtained in the test experiment (a period of 10 min was sufficient and was used throughout this study).

#### 2.3.3. Computational work

In this section, the type of interactions between the monomer unit (tetraethylorthosilicate) in the hydrolyzed form and different template molecules are investigated. Each template molecule is supposed to form complexes with the repeat unit (monomer unit) of the sol–gel matrix on the surface. The stability of these pre-polymerization complexes is expected to affect the properties of the imprinted polymer. Structural geometries are optimized by calculating the interaction energy ($\Delta E$) of each of these adducts [20,21]. All computations were performed using Gaussian software in "Windows" interface. Computations were accomplished with Hartree–Fock using a specified basis set 3-21G. Interaction energies for different complexes were calculated using the following equation:

$$\Delta E = E(\text{template} - \text{monomer}) - E(\text{template}) - \sum(E\,\text{monomer})$$

## 3. Results and discussion

### 3.1. Electrochemical characterization of the imprinted sol–gel films

The imprinted sol–gel films were electrochemically characterized using cyclic voltammetry. Each template molecule was imprinted in sol–gel material with a specific molar concentration optimized by trial and error to produce the best-imprinted films. Each template molecule showed a specific current response at a given oxidation potential [23]. Imprinting efficiency of various template molecules can be assessed carefully by normalizing the current response with respect to the molar concentration of the template in the polymerization mixture. As indicated in Table 1, and taking the current response of the analyte oxidation as the indicator, the imprinting efficiency of template molecules could be arranged as follows:

$$I_{\text{dopamine}} > I_{\text{norepinephrine}} > I_{\text{dopa}} > I_{\text{epinephrine}} > I_{\text{tyrmine}}$$

where $I$ represent the current response and express the imprinting efficiency. Although the molar concentration of dopamine template in the polymerization mixture is the lowest, it shows however the highest imprinting efficiency (as indicated from the highest normalized current response). This result indicates that dopamine is the most interacting molecule with the imprinting matrix.

### 3.2. Rebinding-ability of imprinted films towards their template molecules

Rebinding experiments were carried out in two steps. First, the imprinted film modified electrodes were dipped into the test solution of different template molecules from which rebinding takes place. Second step was the electrochemical characterization of the electrodes using SWV. The adsorption of template molecules into the imprinted sites takes place through weak forces like dipole-dipole interaction and/or hydrogen bonds between the template and the oriented functional groups inside the molecular cavities created into the sol–gel material. Accordingly, there are two factors that control the rebinding capacity/selectivity of the imprinted films. The first factor is the size of the molecular templates with respect to the molecular cavities being created which is the principle factor. Thus, the molecule of the right size and shape anchors more preferably than other molecules into the imprinted cavities [29–31]. Therefore, relatively larger molecules or smaller ones cannot fit specifically into the cavities. The second factor is structural or electrostatic in nature (the average charge density) which will affect the selectivity and rebinding capacity of a given molecule. This factor is related directly to the type of the functional groups in the rebinding molecular moieties which in turn affects their electrostatic interaction with the molecular cavities. Unmatched electrostatic characteristics are the basis upon which rebinding step is affected. The extracted molecules leave the cavities with a "memory effect" that retains the type of "pre-formed" bonds after the release of the molecules. Therefore, molecules with similar or smaller size as the cavities in the sol–gel matrix may still not be able to rebind with efficacy. This is because these molecules are unable to interact with the oriented functional groups inside the molecular cavities.

Rebinding experiments were carried out by dipping the electrodes modified with the molecularly imprinted films into a stagnant (No stirring is done during the process) test solution for 15 min. Percentage recognition (%Re) was calculated for each molecule being tested. The percent recognition of different molecules was calculated by normalizing the current response of each with respect to the current response of the molecule being

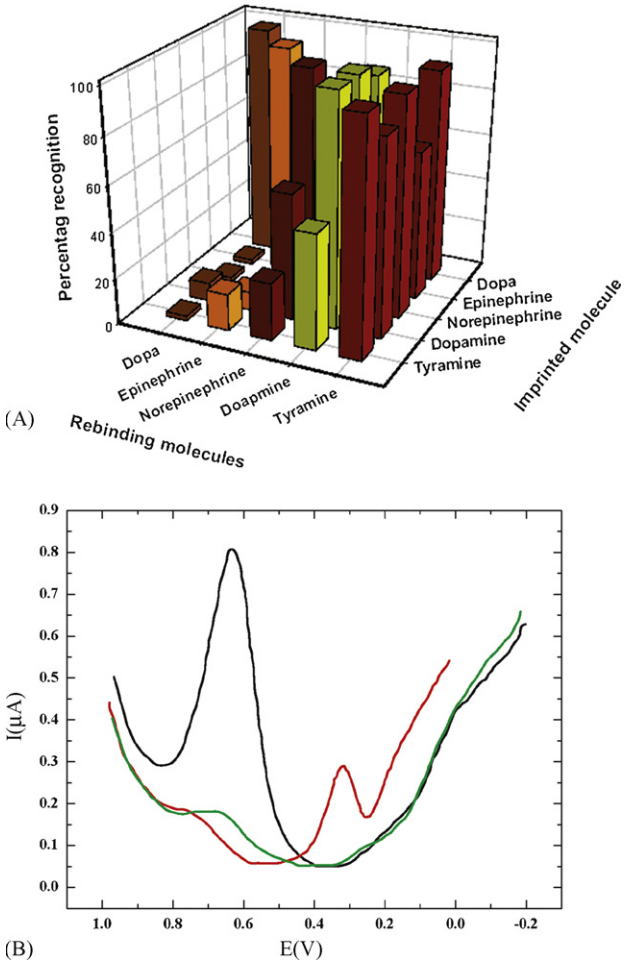


**Fig. 1.** (A) Recognition histogram representing the percentage of rebinding of different molecules with respect to dopamine-, tyramine-, norepinephrine-, epinephrine-, and dopa-imprinted sol–gel films. Rebinding experiments are carried out from rebinding solutions 50 μmol $L^{-1}$ at room temperature. (B) Square wave voltammograms (SWVs) of tyramine-imprinted sol–gel films after dipping the electrodes in solutions of molar concentration 50 μmol $L^{-1}$ of tyramine (—), norepinephrine (▬), dopa (▬).

imprinted into the film as indicated in the following equation.

$$\%Re = \left(\frac{I_m}{I_t}\right) \times 100$$

Current response of each molecule ($I_m$) is proportional to the rebinding capacity of template molecule into the imprinted film ($I_t$). The selectivity of tyramine-, dopamine-, norepinephrine-, epinephrine- and dopa-imprinted films were examined by testing these films in solutions of their templates in presence of other interfering molecules as illustrated in the selectivity histogram shown in Fig. 1A based on the calculated percentage recognition of each molecule being tested towards the imprinted films. Tyramine-imprinted film showed relatively low interference from norepinephrine and epinephrine. Whereas other molecules like dopa did not interfere with the tyramine-imprinted film. Surprisingly dopamine showed some interference with the tyramine-imprinted films. Although tyramine is smaller in molecular size compared to dopamine, the interference should be unrelated to size factor in this case. The interference of dopamine could be explained in terms of the similarity in functional groups of the two molecules except that tyramine carries only one hydroxyl group. Diffusion of dopamine into tyramine-imprinted film is facilitated by the electrostatic interaction between dopamine

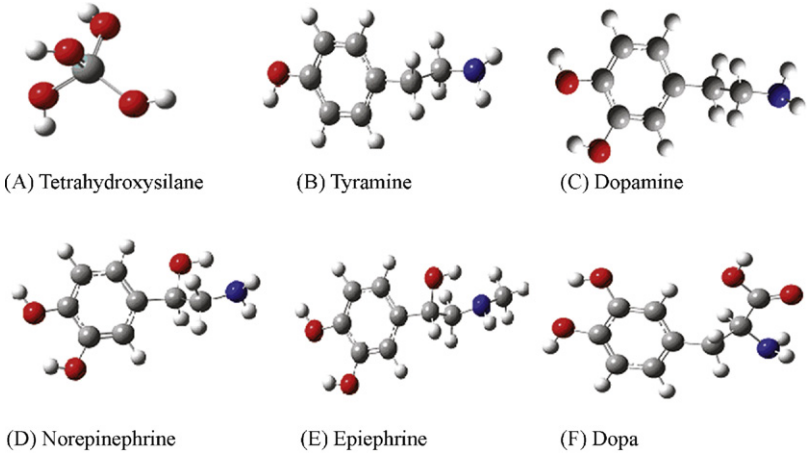


**Fig. 2.** Optimized conformations of the tetrahydroxysilane (THS) monomer and different template molecules.

molecules and the oriented functional groups inside the molecular cavities previously created by tyramine. Fig. 1B represents the SWV of tyramine-imprinted films after being tested in tyramine, norepinephrine, and in dopa, respectively. Similarly, dopamine imprinted film suffers relatively high interference from tyramine and norepinephrine. Norepinephrine, epinephrine, and dopa-imprinted films suffered interference from dopamine and tyramine. These two moieties are smaller in molecular size than norepinephrine, epinephrine, and dopa.

It can be concluded that the imprinted films whose template molecules are smaller in molecular size than the rebinding molecule suffer less interference while those of larger molecular size are more interfered by molecules of smaller molecular size. For instance, the imprinted films were tested in solutions of dopac and catechol. These two molecules showed almost no rebinding to the imprinted films. Dopac does not contain an amino group compared to the other template molecules. This fact justifies the importance of electrostatic interaction of the template and the oriented functional groups inside the molecular cavities. Although catechol is smaller in molecular size than these molecules it showed no rebinding to their imprinted films which confirms that not only the molecular size determines the rebinding capacity and selectivity of the imprinted film but also the electrostatic features of the templates.

### 3.3. Investigation of the electrostatic interactions between the monomer molecules and template during the Pre-Polymerization process

Work done in this part is a computational approach aiming at optimizing and investigating the type of intermolecular electrostatic forces that explain the interaction between the monomer units used during the polymer synthesis and the template molecules being imprinted [15,17]. Computations were achieved using electronic structure and Gaussian software was selected for the calculations with Hartree–Fock method. A simple basis set 21-3G, was specified for calculation which is neither a split valence double zeta nor a minimal basis set [32]. First, optimization of the molecular structures of the template molecules with the calculation of the minimized energies of their respective structures was carried out. Optimized molecular structure conformations of tetrahydroxysilane (THS) hydrolyzed monomer, tyramine, dopamine, norepinephrine, epinephrine, and dopa molecules (monomer units) are shown in Fig. 2(A–F). We carried out three levels of computations; the first level was to calculate interaction energy between a monomer unit and template molecules with a molar ratio 1:1 (monomer:template). The second level focused on the calculation of interaction energy between monomer and template molecules with a molar ratio 2:1 (monomer:template). In the third level, we calculated interaction energy between a disiloxane dimer molecule and various template molecules.

Interaction energy between template molecules and the monomer unit was calculated using the equation described in Section 2.3.3. These relatively low molar ratios were selected so as to keep the computation time reasonable. It is important to mention that as in the case of similar computational data the higher the value of interaction energy between two molecular moieties the more stable the complex formed between these moieties. This results in better binding interactions and therefore enhanced current response that was observed in the corresponding electrochemical measurements.

#### 3.3.1. One monomer–template interaction energy

In this section, we will discuss the results of interaction energy of tyramine, dopamine, norepinephrine, epinephrine, and dopa with one monomer molecule (tetraethylorthosilicate) in its hydrolyzed form, THS. It is important to mention that computations were considered in the gas phase. All the input files were introduced into the program using "Gaussian Viewer" software which enabled us to insert the template with the monomer units more conveniently. Computations were carried out till the minimum interaction energy values were obtained. The calculated interaction energy (stabilization energy) values between the monomer unit (THS) and each molecule of the templates are shown in Table 2. The interaction energies of different template molecules in this case were found to decrease as indicated in the following arrangement:

$$[\Delta E_{\text{dopamine}} > \Delta E_{\text{norepinephrine}} > \Delta E_{\text{dopa}} > \Delta E_{\text{tyramine}} > \Delta E_{\text{epinephrine}}]$$

**Table 2**
The interaction energy between template molecules and tetrahydroxysilane monomer (THS), the molar ratio is (1:1).

| Interaction complex | Interaction energy (au) | Interaction energy (Kcal mol$^{-1}$) |
|---|---|---|
| Dopamine | −0.03554 | −22.30 |
| Norepinephrine | −0.02914 | −18.29 |
| Dopa | −0.02832 | −17.77 |
| Tyramine | −0.02564 | −16.09 |
| Epinephrine | −0.02363 | −14.82 |

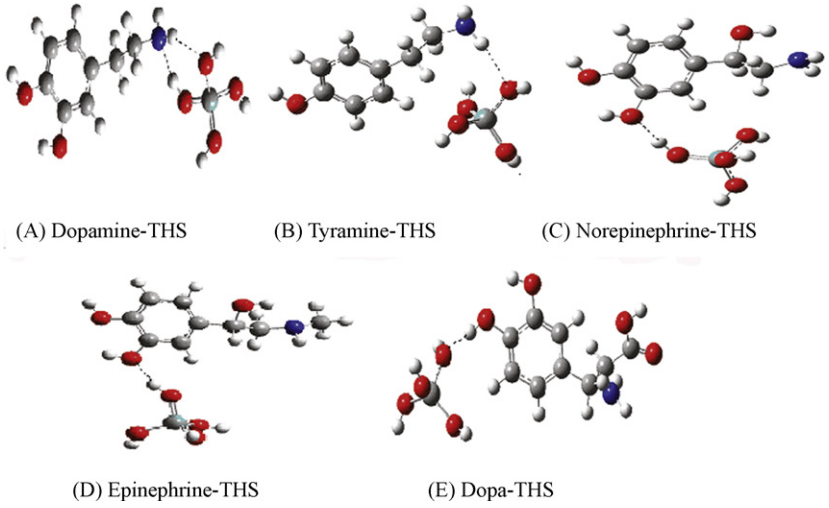


**Fig. 3.** Optimized geometries of the interaction complexes adducts formed between (THS) monomer and different template molecules with molar ratio 1:1 (THS:template).

These results showed that dopamine has the highest interaction energy with the monomer molecule while epinephrine possesses the smallest value. From these results, we conclude that dopamine forms the most stable adduct with the precursor monomer during the polymerization process. Also, dopamine is expected to rebind to the imprinted material better than the other molecules. The stability of complexes expected to be formed between the different template molecules and the monomer unit is viewed to decrease in the same arrangement shown above. The computation data confirms the results obtained in the electrochemical experiments to a large extent [23]. Thus, the normalized current responses of the imprinted molecules are arranged almost in the same manner as the interaction energy is arranged (cf. Table 2):

$$[I_{\text{dopamine}} > I_{\text{norepinephrine}} > I_{\text{dopa}} > I_{\text{epinephrine}} > I_{\text{tyramine}}]$$

The type of interaction between monomer units and template molecules can be better described by the analysis of the optimized geometries of template molecules with monomer. Fig. 3 illustrates the optimized geometries for the most stable complexes formed between the hydrolyzed monomer THS and tyramine, dopamine, norepinephrine, epinephrine, and dopa with the molar ratio 1:1, respectively. These geometries are in good correlation with the calculated interaction energies for each pair. Also, the optimized geometries describe the expected intermolecular forces underlying the formation of the pre-polymerization complex between the monomer and the template molecules.

As indicated in Fig. 3A, dopamine monomer (adduct) is expected to be formed through two H-bonds with THS between the amino group and two hydroxyl groups on the silicon atom. Two points of interaction between amino group and two hydroxyl groups justifies the relatively large interaction energy for dopamine molecule. Tyramine is expected to form only one H-bond between the amino group and one hydroxyl group on the silicon atom which justifies the relatively small interaction energy value between tyramine and the monomer unit as illustrated in Fig. 3B.

Norepinephrine and epinephrine interactions occur between m-hydroxyl group on the benzene ring and hydroxyl groups on silicon atom as illustrated in Fig. 3C and D), respectively. Although the two molecules undergo the same interaction, they did not have the same value of interaction energy as indicated in Table 2. This result can be explained from the fact that the two molecules with different structures have different electron density that allowed their interaction differently with the monomer unit. Difference between electron density distributions around the templates can give more sight on the role of small structural changes and how they can affect the molecular recognition properties of MIP materials. As indicated in Fig. 3E, dopa molecule interacts with the monomer hydroxyl group via p-hydroxyl group on the benzene ring. The change in the interacting center and the magnitude of interaction in the previously mentioned pairs occurs frequently due to the change in the chemical structure of the template which affects the total electron density around the template molecule.

### 3.3.2. Two monomer–template interaction energy

This level of calculation is performed to optimize the interaction energy values between different template molecules and monomer units with the molar ratio 1:2 (template:monomer). On one hand, the interaction energy arrangement was changed but dopamine still shows the highest interaction energy as given in Table 3.

$$[\Delta E_{\text{dopamine}} > \Delta E_{\text{dopa}} > \Delta E_{\text{norepinephrine}} > \Delta E_{\text{epinephrine}} > \Delta E_{\text{tyramine}}].$$

In this case dopa interaction energy with the two monomers is higher than that of norepinephrine and tyramine interaction energy decreases compared to epinephrine. The arrangement is more realistic and is in good agreement to a large extent with the electrochemical data of anodic current responses of the imprinted molecules discussed in section one. Fig. 4 illustrates the optimized geometries of the intermolecular interaction between monomer units and template molecules with the molar ratio 2:1.

Dopamine molecule as illustrated in Fig. 4A interacts strongly with the two-monomer units through the amino group and m-hydroxyl group on benzene ring of the molecule. Only this mode of interaction allows the two-monomer units to undergo mutual interaction with each other which is reflected by the highest interaction energy of the adduct. Interaction of one of the monomer units with the amino group of dopamine indicates that this group

**Table 3**
The interaction energy between template molecules and tetrahydroxysilane monomer (THS), the molar ratio is (1:2).

| Interaction complex | Interaction energy (au) | Interaction energy (Kcal mol$^{-1}$) |
|---|---|---|
| Dopamine | −0.09987 | −62.67 |
| Norepinephrine | −0.08216 | −51.56 |
| Dopa | −0.09270 | −58.17 |
| Tyramine | −0.04977 | −31.23 |
| Epinephrine | −0.07486 | −46.98 |

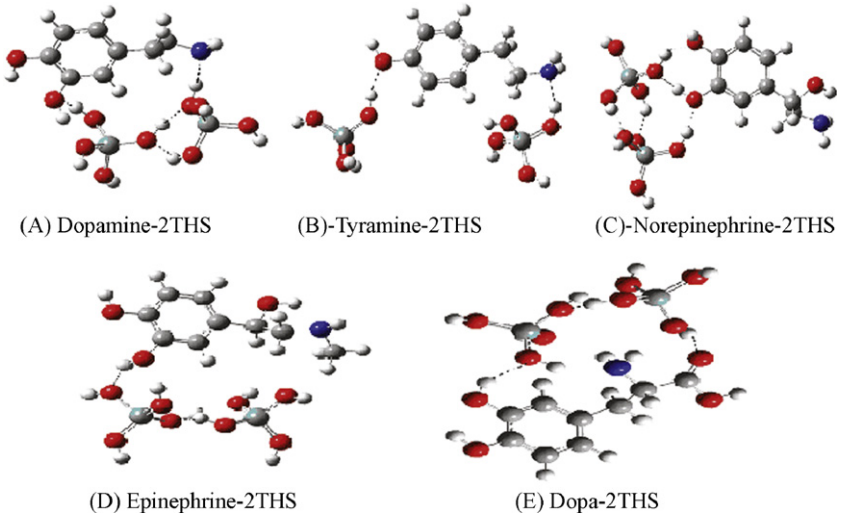


**Fig. 4.** Optimized geometries of the interaction adducts formed between THS monomer and different template molecules with molar ratio 2:1(THS:template).

is the most interacting center in dopamine molecule. As illustrated in Fig. 4B, tyramine tends to form two H-bonds with the two monomers. The amino group undergoes the first interaction while the p-hydroxyl group undergoes the second one. In this case the interaction between the two-monomer units are very limited and great spatial separation between them is observed which justifies the low value of interaction energy obtained. The reason for change in the interaction energy arrangement for dopa and norepinephrine can be attributed to the presence of carboxylic group on the structure of dopa. Carboxylic group as illustrated in Fig. 4E acts as a second interaction center for one of the monomers. Also, it has to be mentioned that the monomer units arrange themselves around the template in such a way to minimize the complex energy.

Norepinephrine tends to interact with the two-monomer units through m- and p-hydroxyl groups in addition to a mutual interaction between the two-monomer units as illustrated in Fig. 4C. In case of norepinephrine, it is clear that the amino group is less interacting than the hydroxyl groups on benzene ring. This may be due to the change in the electron density around the molecule which affects the reactivity of amino group. Epinephrine is less interacting with the monomers compared to norepinephrine. Only m-hydroxyl groups of epinephrine interact with two monomers while the two monomers interact to a great extent with each other as illustrated in Fig. 4D. The molecule of Dopa showed high interaction with the two monomers than in case of interaction with one monomer unit. In this case, dopa molecule interacts through carboxylic acid group, amino group, and m-hydroxyl on the benzene ring. As illustrated in Fig. 4E, this confirms the relatively high value of interaction energy.

From the foregoing results it can be concluded that the large difference between the two levels of interaction energies indicates that the increasing stability of the pre-polymerization adducts formed between monomer units and the template molecules, is not only due to the interaction between templates and monomers but also due to the interaction between the monomer molecules.

### 3.3.3. Dimer–template interaction energy

The main idea of this is to investigate the effect of condensation of the monomer units on the interaction energy with template molecules by comparing the interaction energy values obtained in Section 3.3.2 (Table 3) with the results obtained in Section 3.3.3 (Table 4).

As mentioned earlier, alkyl orthosilicates used in sol–gel synthesis undergoes hydrolysis in presence of acid catalyst. Hydrolyzed alkyl orthosilicates are the monomer units which form the pre-polymerization complexes with the template molecules. Monomer units could also condense before the formation of adducts with template molecules giving rise to dimers which in turn are able to condense with each other forming tetramers or with other monomer units forming trimers. In this section of work the computations is used to explore the interactions expected to arise between different template molecules and disiloxane dimer which is formed by the condensation of two THS molecules.

Dimer total energy was optimized then the total energies of the dimer combined with the template molecules were computed for each template individually. Computations were carried out repeatedly with different orientations of the dimer molecule with respect to the template molecule till the minimum interaction energy value was attained. Interaction energy between template molecules and dimer molecule resulted in the following energy arrangement as given in Table 4.

$$[\Delta E_{\text{dopamine}} > \Delta E_{\text{dopa}} > \Delta E_{\text{epinephrine}} > \Delta E_{\text{norepinephrine}} > \Delta E_{\text{tyramine}}]$$

Computational data indicated in Table 4 revealed two important results; the first is that dopamine is the most interacting molecule even with dimer moieties which depicts how strong is the interaction of dopamine with all moieties in the polymerization mixture. In other words, it can be mentioned that dopamine nuclei are the most interacting moieties in forming the non-covalent adducts with monomers and dimers. The second and more important result is that all the template molecules showed higher interaction energy in case of the interaction with two-monomer molecules than in case they interact with a dimer molecule formed by the condensation of two-monomers units. In other words, template molecules form more stable adducts (pre-polymerization adducts) with monomer units than they do with condensed units like dimers, trimers,

**Table 4**
The interaction energy between template molecules and disiloxane dimer.

| Interaction complex | Interaction energy (au) | Interaction energy (Kcal mol$^{-1}$) |
|---|---|---|
| Dopamine | −0.04847 | −30.41 |
| Dopa | −0.04676 | −29.34 |
| Norepinephrine | −0.03483 | −21.85 |
| Epinephrine | −0.03748 | −23.52 |
| Tyramine | −0.01816 | −11.39 |

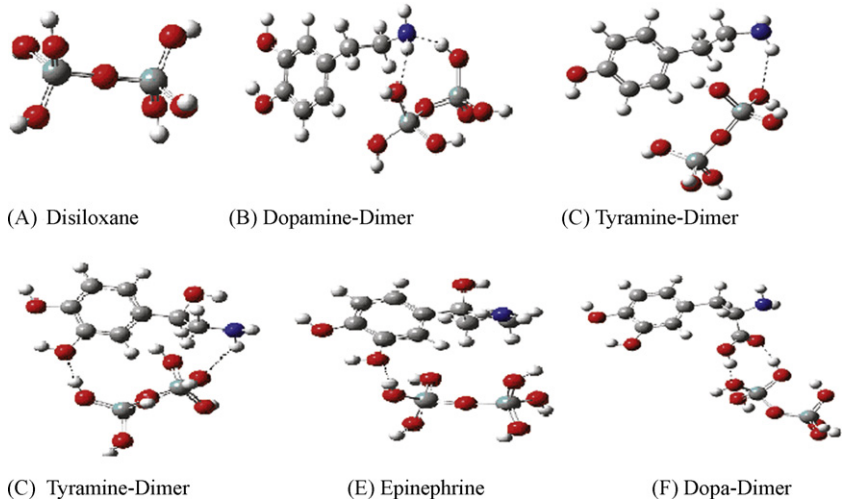


**Fig. 5.** Optimized geometries of the interaction adducts formed between disiloxane dimer and different template molecules with molar ratio 1:1 (dimer:template).

tetramers, etc. Therefore, it is advisable to mix template molecule solution with monomer unit solution before the start of condensation step which would allow for better interaction to obtain large number of imprinted sites of the template molecule into sol–gel material. The optimized conformations of the dimer molecule and the optimized geometries of the pre-polymerization adduct formed between the template and the dimer molecules are illustrated in Fig. 5. The optimized conformation of disiloxane dimer is also indicated in Fig. 5A.

Dopamine interaction with the dimer is restricted to the amino group as illustrated in Fig. 5B. As shown in the figure, the dimer molecule is "twisted" in such a way that two hydroxyl groups from two separate silicon atoms form two H-bonds with the amino group which justifies the stability of its complex. Dopa trails dopamine as the most interacting molecule. Dopa molecule was found to interact via its carboxylic acid group with two hydroxyl groups on the same silicon atom of the dimer; meanwhile the amino group is not interacting to any extent as illustrated in Fig. 5F. Norepinephrine molecule was found to interact with m-hydroxyl group on the benzene ring via one hydroxyl group on the silicon atom besides an interaction with the amino group by another hydroxyl group on the second silicon atom as illustrated in Fig. 5D. While epinephrine molecule interacts only with m-hydroxyl group on the benzene ring as illustrated in Fig. 5E. Substitution of amino group prevents the interaction with the lone pair of electrons of the nitrogen. Tyramine interacts via the amino group but only with one hydroxyl group as illustrated in Fig. 5C. From the three energy arrangements we could arrange the stability of the pre-polymerization adducts in terms of interaction energy calculations as follows.

$$[\text{dopamine} > \text{norepinephrine} \approx \text{dopa} > \text{epinephrine} \approx \text{tyramine}]$$

The use of higher basis set could be better in calculation, and we already tried this but it could be computationally expensive for the purpose of this study. So that a modest basis set (21-3G) was preferred for comparing stability of potential pre-polymerization adducts formed at the beginning of imprinting process. Moreover, the difference in the binding energies for different conformations of the same complex was insignificant so that it was not critical to make basis set superimposition error correction (BSSE).

Non-molecularly imprinted polymer film was already prepared and tested for rebinding process for all molecules in the study. The response for all the moieties was less than 5%.

## 4. Conclusions

Sol–gel imprinted glass materials could be used as smart recognition elements for sensing of a group of molecules of biological interest. Selectivity of the imprinted materials is largely controlled by both the molecular sizes of the imprinted molecules and their chemical structures. Computational investigations of the intermolecular interactions between the template molecules and the monomer units could enhance our understanding of the electrostatic forces underlying the formation of the pre-polymerization complexes in the imprinted mixture.

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## References

[1] F.H. Dickey, Natl. Acad. Sci. U.S.A. 35 (1949) 227–229.
[2] J. Liu, G. Wulff, Angew. Chem. Int. Ed. Engl. 43 (2004) 1287–1290.
[3] G. Wulff, R. Vesper, R. Grobe Einsler, A. Sarhan, Makromol. Chem. 178 (1977) 2799–2816.
[4] G. Wulff, S. Schauhoff, J. Org. Chem. 56 (1991) 395–400.
[5] Q.F.H. Sambe, C. Kagawa, K.K. Kunimoto, J. Haginaka, Anal. Chem. 75 (2003) 191–198.
[6] O. Ramstrom, K. Skuder, J. Haines, P. Patel, O. Bruggeman, J. Agric. Food Chem. 49 (2001) 2105–2109.
[7] Spegel P. Schweitz, S. Nilsson, Anal. Chem. 75 (2003) 6608–6613.
[8] F.L. Dickert, R. Sikorski, Mater. Sci. Eng. 10 (1999) 39–46.
[9] L.I. Anderson, C.F. Mandenius, K. Mosbach, Tetrahedron Lett. 29 (1988) 5437–5440.
[10] M. Jakusch, M. Janotta, B. Mizaikoff, K. Mosbach, K. Haupt, Anal. Chem. 71 (1999) 4786–4791.
[11] D. Kriz, O. Ramström, A. Svensson, K. Mosbach, Anal. Chem. 67 (1995) 2142–2144.
[12] S. Al-kindy, R. Badea, M. Deaz-Garcia, Anal. Lett. 35 (2002) 1763–1774.
[13] F. Breton, R. Rouillon, E.V. Piletska, K. Karim, A. Guerreiro, I. Chianella, S.A. Piletsky, Biosens. Bioelectron. 22 (2007) 1948–1954.
[14] J. Yao, X. Li, W. Qin, Anal Chim. Acta 610 (2008) 282–288.
[15] D. Pavel, J. Lagowski, Polymer 46 (2005) 7528–7542.
[16] D. Pavel, J. Lagowski, Polymer 46 (2005) 7543–7556.
[17] D. Pavel, J. Lagowski, C.J. Lepage, Polymer 47 (2006) 8389–8399.
[18] I. Chianella, M. Lotierzo, S.A. Piletsky, I.E. Tothill, B.N. Chen, Anal. Chem. 74 (2002) 1288–1293.
[19] I. Chianella, K. Karim, E.V. Piletska, C. Preston, S.A. Piletsky, Anal. Chim. Acta 559 (2006) 73–78.
[20] K.J. Shea, D.Y. Sasaki, J. Am. Chem. Soc. 113 (1991) 4109–4120.
[21] J. Damenm, D.C. Neckers, Tetrahedron. Lett. 21 (1980) 1913–1916.
[22] J. Damenm, D.C. Neckers, J. Org. Chem. 45 (1980) 1382–1387.

[23] N.F. Atta, A.M. Abdel-Mageed, Talanta, doi:10.1016/j.talanta.2009.07.014.
[24] Y. Dineiro, M.I. Menendez, M.C. Blanco-Lopez, M.J. Lobo-Castanon, A.J. Miranda-Ordieres, P. Tunon-Blanco, Anal. Chem. 77 (2005) 6741–6746.
[25] Y. Dineiro, M.I. Menendez, M.C. Blanco-Lopez, M.J. Lobo-Castanon, A.J. Miranda-Ordieres, P. Tunon-Blanco, Biosens. Bioelectron. 22 (2006) 364–371.
[26] W.G. Dong, M. Yan, Z. Liu, G.S. Wu, Y.M. Li, Sep. Purif. Technol. 53 (2007) 183–188.
[27] I. Turyan, D. Mandler, Anal. Chem. 69 (1997) 894–897.
[28] G. Shustak, S. Marx, I. Turyan, D. Mandler, Electroanalysis 15 (2003) 398–408.
[29] X. Zhua, J. Cai, J. Yang, Q. Sua, Y. Gaob, J. Chromatogr. A 1131 (2006) 37–44.
[30] H.Y. Wang, J.G. Jiang, L.Y. Ma, Y.l. Pang, React. Funct. Polym. 64 (2005) 119–126.
[31] W.-Y. Chen, C.-S. Chen, F.-Y. Lin, J. Chromatogr. A. 923 (2001) 1–6.
[32] M.A. Zenh, P. Kathirvel, P. Nogueira, A. Fernando-Silva, Biosens. Bioelectron. 23 (2008) 1843–1849.