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COMPUTATIONAL APPROACH TO INVESTIGATION OF TEMPLATE/MONOMER COMPLEX IN MELAMINE IMPRINTED POLYMERS

In this work a computational approach to investigation of template/monomer complex in imprinted polymers, enable us to select monomers interacting strongly with the melamine, as target analyte. The molecular modeling and performing thermodynamic computations were carried out with the help of a patented protocol developed at Cranfield University, UK. The binding energies shows the acrylamido-2-methyl-1-propanesulfonic acid (AMPSA) is the best binding monomer for melamine followed by itaconic acid and F22 ethylene glycol methacrylate phosphate (EGMP).

Keywords: *molecular imprint polymer, melamine, AMPSA, binding energy, SYBYL 7.3, LEAPFROGTM algorithm.*

Introduction

Molecular imprint polymer (MIP) is a well established approach to develop artificial recognition systems capable of mimicking features of the corresponding biological systems [1]. This imprinting is a relatively inexpensive procedure for preparation of the MIP synthetic receptors with appreciable affinity, selectivity, and toughness. Hence, the development of a chemosensors featuring analyte polymeric recognition elements, prepared by molecular imprinting, could offer an inexpensive yet sensitive and selective method for melamine determination.

In this work such approach was used for the development of chemosensor for melamine detection.

Melamine (fig. 1), a plant metabolite of cyromazine pesticide, can artificially inflate with its 66% nitrogen, the reading for a protein level in, e.g., food products [2]. Melamine was detected recently in baby milk formulas, pet food, animal feed, and protein sources including wheat and corn gluten as well as a rice protein concentrate [3]. Melamine can form lethal kidney stones, especially when combined with cyanuric acid, due to precipitation of insoluble melamine cyanurate. High and prolonged dietary exposure to the melamine results in the formation of bladder stones and increase incidence of urinary bladder tumors in male rats [3]. Therefore, determination of melamine is of biological, clinical, and food industry importance.

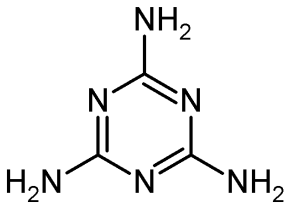

Fig. 1. Structure of Melamine

There have been several attempts on development of generic procedure for MIP preparation; however, the one that has been in prime focus in the recent years is computational design [4].

In order to obtain material with very high affinity, functional monomers able to give very strong complexes with the target analyte need to be chosen.

In this work we have investigated a computational design method (where melamine was used as a model target analyte), which enable us to select from a virtual library those monomers interacting strongly with the target analyte, using molecular modeling and performing thermodynamic computations with help of a patented protocol developed at Cranfield University [5]. The next step is to screen the virtual library against a template to determine the monomers that strongly bind to the template.

Molecular simulation techniques play important role in understanding and imagination of molecular level manners.

These methods are powerful in calculating intra molecular energy and atomic charges in different phases. Molecular simulation softwares are able to depict a three dimensional picture from molecules that help obtained imagine and understand the molecule configurations. Compared with experimental methods, computational approaches have advantages such as: low costs, less time consuming, safe for the human body (many solvents are cancerogen) and safe for the environment – no exposed chemicals. These methods may be successfully applied in rational design and solvent prediction in imprinting polymer.

One of the most established rational approaches in design of imprinted polymers is combinatorial synthesis/screening. However combinatorial approach has its limitations. Considering even a simple two-component system utilizing 100 monomers, it would be

a daunting task of preparing several thousand polymers. It gets further complicated when we look at the possibility of different ratios of the monomer mixtures further inflating the amount of time and resources required. In recent MIP researches, functional monomers and solvents were initially selected and then experimental were performed. In all approaches, the main goal is to find the interaction energy between monomer(s) and template. This energy is the measure of monomer-template stability [6 – 8].

1. The Rational Design Protocol

The rational design of MIPs was carried out on a PC running Linux executing the software packages SYBYL 7.3 (Tripos Inc). The rational design protocol [5] involves 4 steps.

1. Design of functional monomer database.
2. Design of molecular model of template to be screened.
3. Screening using a LEAPFROGTM algorithm.
4. Refining using Molecular Mechanics and Molecular Dynamics simulations.

The first three steps give a very good indication as to the best monomer(s) for polymer preparation in a given solvent. The refining step 4 involves the identification of the optimal monomer-template ratio to be used for the polymer composition.

2. Design of Functional Monomer Database

The first step involves the design of a virtual library of functional monomers. These monomers possess polymerisable residues and residues capable of interacting with a template by electrostatic, hydrophobic van der Waals forces, and dipole-dipole interactions. Preferred monomers are those that are able to interact with the template through non-covalent interactions and that can be polymerised through a radical mechanism.

The library designed for this project contains 25 commonly used functional monomers, these being acidic, basic or neutral molecules. Most of the monomers used for MIP preparation are described extensively in the literature due to their easeness of polymerisation, availability and cost [4]. The charges for each atom of each monomer are calculated and the structures of the monomers refined using molecular mechanicas methods. All the monomers in the database are energy minimised individually to a value of 0.001 kcal/mol. The obtained structures of the monomers in the database are shown in fig. 2.

3. Design of Molecular Model of Template

For the second step, the melamine templates were modeled in a similar manner to that of the monomers. The charges for each atom on the template were calculated and the structures refined using molecular mechanics methods.

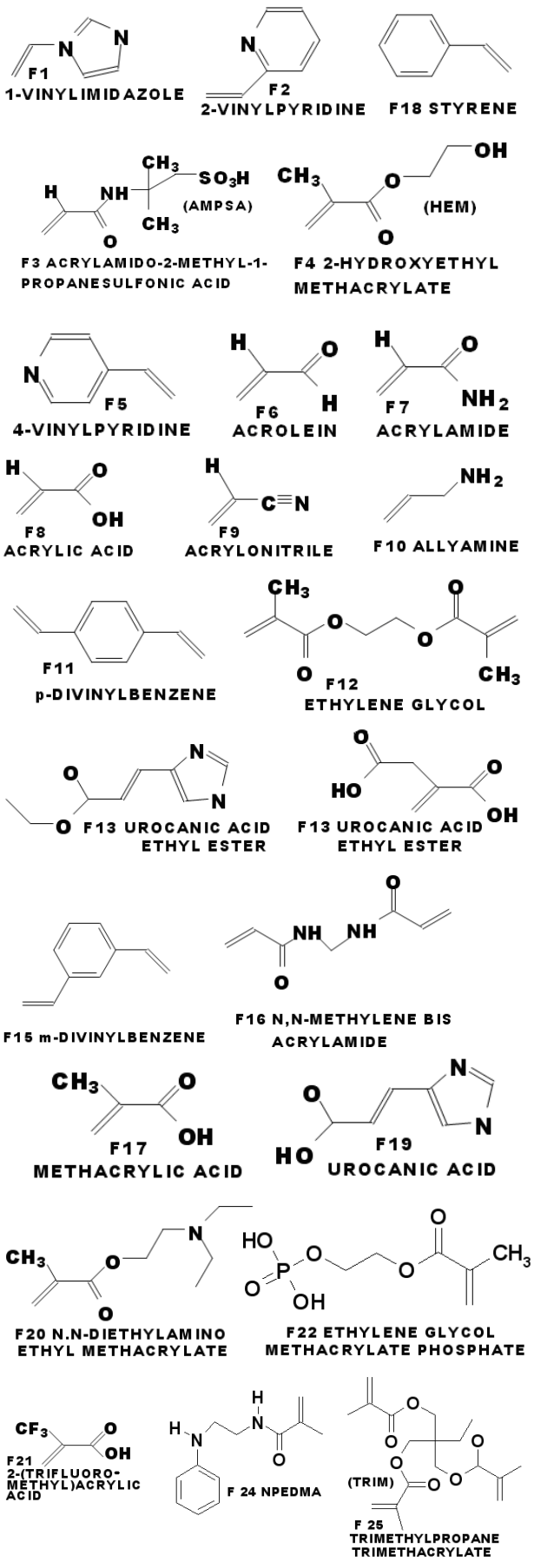

Fig. 2. The structures of the monomers in the database

Energy minimisation was performed to a value of 0.001 kcal/mol and this model was then used for the design of MIPs in the next stage.

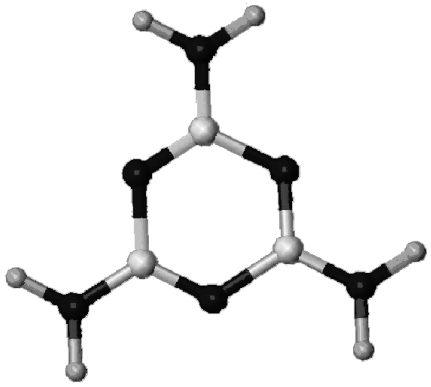

Fig. 3. Minimised structure of melamine

4. Screening using a LEAPFROGTM algorithm

Each of the monomers in the database was then probed for its possible interaction with the templates shown in fig. 3.

The LEAPFROG^{TM} algorithm was used to screen the library of functional monomers for their possible interactions with the template [ ]. The program was applied for 60,000 iterations. The results were examined and the empirical binding scope evaluated. Monomers giving the highest binding scopes represented the best candidates for polymer preparation and for forming the strongest complexes with the template can be found in Table 1.

Table 1

Binding Energy Tables for Melamine with the monomer database

Monomer	Binding, kcal/mol	Scope, kcal/mol
AMPSA	-42.74	-42.74
Itaconis acid	-35.35	-35.35
EGMP	-34.65	-34.65
Acrylamide	-34.63	-34.63
Bisacrylamide	-27.24	-27.24
NPEDMA	-25.65	-25.65
HEM	-24.93	-24.93
DEAEM	-23.33	-23.33
Methacrylic acid	-21.63	-21.63

The binding energies in tabl. 1 shows the AMPSA is the best binding monomer for melamine followed by Itaconic acid and EGMP (fig. 4 – 6).

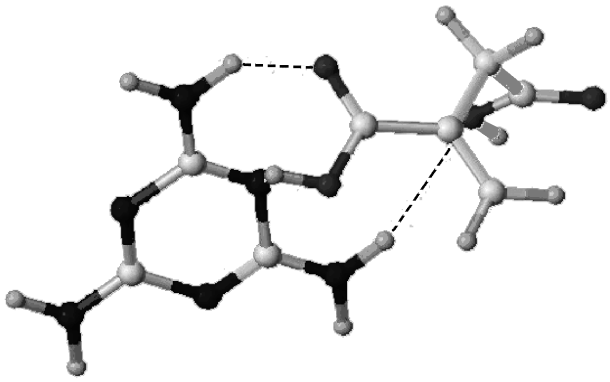

Fig. 4. Melamine-AMPSA complex

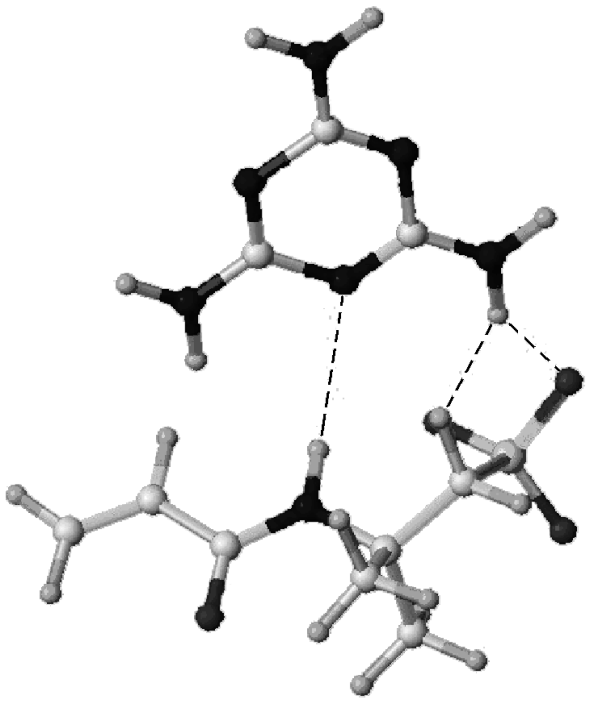

Fig. 5. Melamine-Itaconic acid complex

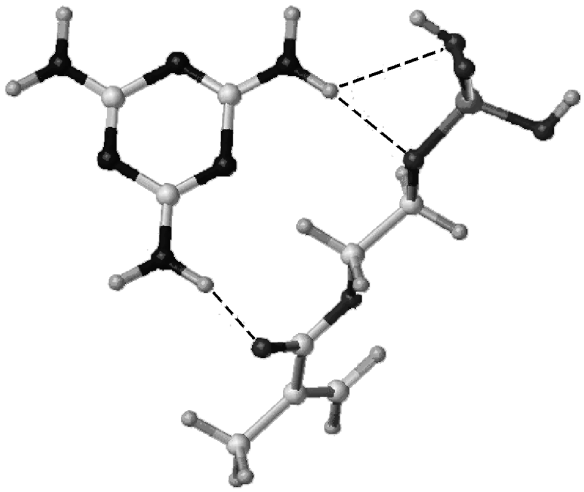

Fig. 6. Melamine-EGMP complex

Conclusion

In this work the computational approach to investigation of template/monomer complex in melamine imprinted polymers was successfully demonstrated.

We can suppose that the monomer forming the most stable complex with a given template would be most suitable for being used to produce MIP with good recognition properties.

From the energies analysis (Table 1), it can be seen that the complex of melamine with AMPSA is the most stable, and AMPSA seems to be the most suitable monomer to produce the melamine imprinted polymer.

The proposed procedure could be very useful for screening the molecularly imprinted systems rapidly in an experiment-free way.

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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ОБЧИСЛЮВАЛЬНИЙ ПІДХІД ДЛЯ ДОСЛІДЖЕННЯ КОМПЛЕКСУ ШАБЛОН/МОНОМЕР У МЕЛАМІН-ІМПРИНТОВАНОМУ ПОЛІМЕРІ

К.М. Музика, М.М. Рожицький

У даній роботі проведено обчислювальний експеримент з дослідження комплексу шаблон / мономер в імпринтованих полімерах, що дає нам можливість вибрати з ті мономери, які найбільш сильно взаємодіють з меламіном, як цільовим аналітом, з використанням молекулярного моделювання і проведення термодинамічних розрахунків за допомогою запатентованого протоколу, розробленого в Кранфілдському університеті (Великобританія). Результати енергії зв'язування демонструють, що найкращими мономерами для меламіну є акриламідо-2-метил-1-пропансульфонова кислота, ітаконова кислота і етиленгліколь метакрилат фосфат.

Ключові слова: *молекулярний полімер відбитку, меламін, AMPSA, обов'язкова енергія, SYBYL 7.3, алгоритм LEAPFROGTM.*

ВЫЧИСЛИТЕЛЬНЫЙ ПОДХОД ДЛЯ ИССЛЕДОВАНИЯ КОМПЛЕКСА ШАБЛОН / МОНОМЕР В МЕЛАМИН-ИМПРИНТИРОВАННОМ ПОЛИМЕРЕ

Е.Н. Музика, Н.Н. Рожицкий

В данной работе проведен вычислительный эксперимент по исследованию комплекса шаблон / мономер молекулярно импринтованных полимеров, что дает нам возможность выбирать из виртуальной библиотеки те мономеры, которые наиболе сильно взаимодействуют с меламином, как целевым аналитом, с использованием молекулярного моделирования и проведения термодинамических расчетов с помощью запатентированного протокола, разработанного в Кранфилдском университете. Результаты энергии связывания приведены в таблице 1. Они демонстрируют, что наилучшими мономерами для меламина являются акриламидо-2-метил-1-пропансульфоновая кислота, итаконовая кислота и этиленгликоль метакрилат фосфат.

Ключевые слова: *молекулярный полимер отпечатка, меламин, AMPSA, обязательная энергия, SYBYL 7.3, алгоритм LEAPFROGTM.*