COMPUTATIONAL STUDY OF THE INTERACTIONS OF COCAINE AND BENZOYLECGONINE WITH METHACRYLIC ACID IN MOLECULARLY IMPRINTED POLYMERS (MIPS).

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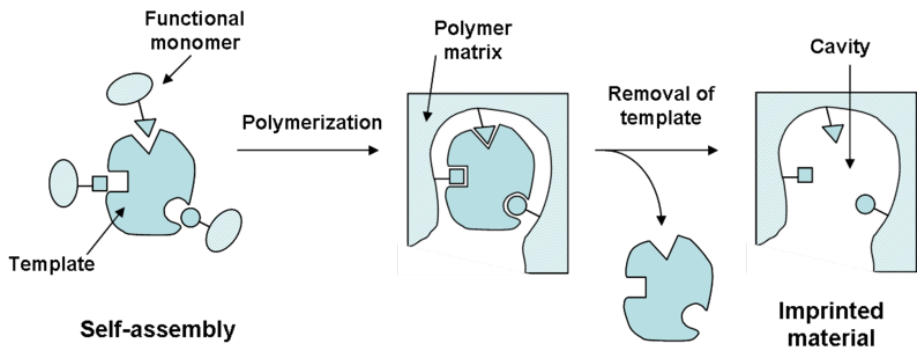
Molecularly imprinted polymers (MIPs) are a class of highly cross-linked polymer that can bind certain target compound with high specificity. The polymers are prepared in the presence of the target molecule itself as the template. The template interacts with functional monomers before being cross-linked in polymerization process. The specific binding site complementary to the target analyte is generated upon the removal of the template from the solid polymers.

The knowledge of the interactions between the target (in this case, cocaine and benzoylecgonine molecules) and the monomer seems to be very important in the design of this MIPs. For this reason, a computational study of the interactions between cocaine and benzoylecgonine molecules, and methacrylic acid is presented. Different position for the interactions and number of molecules of monomer are considered in this DFT study. The effect of solvent is also analyzed.



INTRODUCTION:

Cocaine is one of the most used illicit substances in the world. The benzoylecgonine and the ecgonine are its main metabolites in blood and urine [1]. The detecction of cocaine in blood lasts around 4-6 h while benzoylecgonine may be detected up to 48h, being typical doses around 20-100 mg for cocaine and betwwen 35% and 54% of this initial dose for benzoylecgonine[2].

Gas chromatography coupled to mass spectrometry has widely used for the analysis of cocine and benzoylecgonine in biological matrices[3-5]. The main advantages are its selectivity and sensitivity but, due to the complexity of biological samples, pre-treatment is necessary and laborious.

An analytical tool which could be used to simplify the determinations is solid-phase extraction (SPE) [6]. In traditional SPE materials, the base of separation is the physiochemical retention on functionalized surfaces. An enhancement of the adsorbents molecular selectivity has been achieved with the introduction of molecular imprinted polymers (MIPs).

Molecularly imprinted polymers are a new type of three-dimensional, highly crosslinked material. The technology of molecular imprinting, originally developed in 1931[7], and rediscovered twice in 1949[8] and 1972[9], is in the process of exponential growth[10]. Essentially, this progress is a result of fundamental achievements by Mosbach and Wulff in the areas of non-covalent and reversible covalent imprinting[11,12]. The broad variety of functional monomers currently available makes it possible to design a molecularly imprinted polymer (MIP) specific for potentially any type of chemical compound.

Currently, the selection of the best monomer for polymer preparation is one of the most crucial issues in molecular imprinting.

Two factors are important for the effective recognition of the template by MIP: the strength and quantity of the interactions between the monomers in the polymer network and the template.

Computational Chemistry seems to be a good tool in order to suggest a good monomer to build a molecularly imprinted polymer for a determined template and to indicated the most favorable conditions (ratio template:monomer and the environment).

For this reason, a DFT study was carried out in order to indicate if the methacrylic acid seems to be a good monomer in the recognize of benzoylecgonine and cocaine. The ratio template polymer and the effect of the environment were also analyzed.

COMPUTATIONAL DETAILS:

Different possibilities of interaction between methacrylic acid and benzoylecgonine were studied. In Fig. 1 are collected the complexes between one molecule of methacrylic acid and benzoylecgonine. The structures were fully optimized employing the BP86 functional [13] together with the def-TZVP basis set.

With the same theoretical method, the complexes between two molecules of methacrylic acid and the benzoylecgonine were calculated and the most stable complex is shown in Fig. 2.

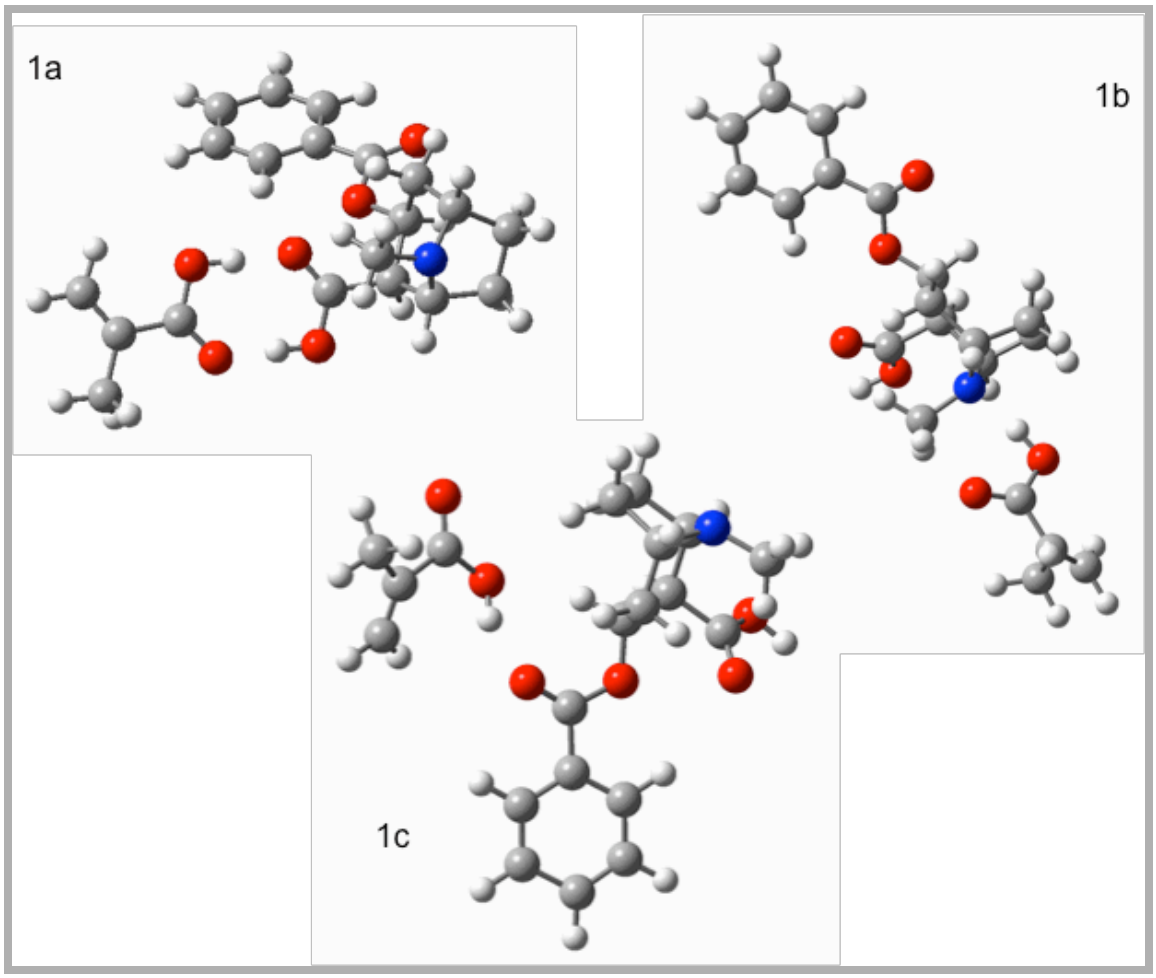


Figure 1. Optimized structures for complexes between methacrylic acid and the benzoylecgonine.

Fig. 3 presents the most stable complex between one molecule of methacrylic acid and cocaine molecule.

The effect of the solvent is taken into account employing the Conductorlike Screening Model (COSMO) method [14].

For all calculations the Turbomole program Program Package for ab initio Electronic Structure Calculations was employed [15].

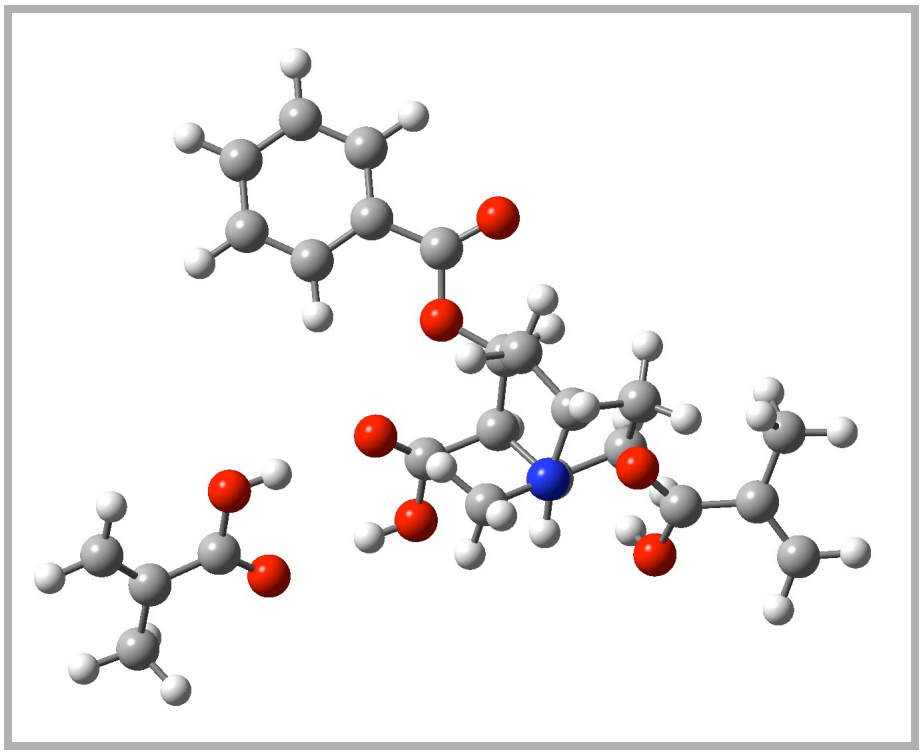


Figure 2. Optimized structure for the most stable complex between two molecules of methacrylic acid and the benzoylecgonine.

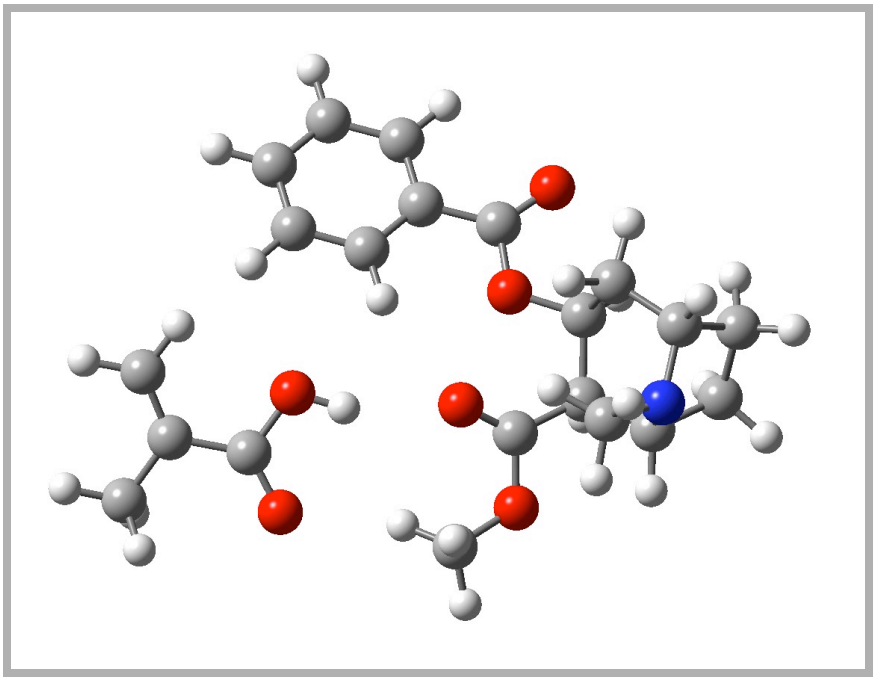


Figure 3. Optimized structure for the most stable complex between methacrylic acid and cocaine.

RESULTS:

Table 1 collected the differences energies between complexes and the separated molecules. As we can observed the stabilization for some of the structures is high (-16,66 kcal/mol). For one molecule of methacrylic acid, the most favorable interaction is observed between the carboxylic groups in benzoylecgonine and methacrylic acid. For two molecules of methacrylic acid, the most favorable complex presents interactions between the carboxylic group of the two molecules of methacrylic acid and the carboxylic group and the N atom in the benzoylecgonine. The energy stabilization for this complex is -27,18 kcal/mol.

In the case of cocaine molecule the complex with interaction between carboxylic group of methacrylic acid and ester group in the cocaine molecule (Fig. 3) presents a high stabilization (-22,5 kcal/mol).

The effect of the solvent has demonstrated to have a big importance. The previous data is in gas phase but when a solvent is taking into account the energy difference between complex and separated molecules is considerable reduced. The COSMO model is a continuum solvation model and we have included different solvents using different dielectric constant. These dielectric constants were 36,64 (for acetonitrile), 28,08 (for a solution 3:1 of acetonitrile and toluene), and 2,40 (for toluene). The values for energy stabilization for the 1a complex were -8,82 kcal/mol, -8,93 kcal/mol, and -13,0 kcal/mol, respectively, for the three solvents.

Structure	ΔE (kcal(mol)
1a	-16,66
1b	-10,56
1c	-6,67

Table 1. Energies for complexes between methacrilyc acid and the benzoylecgonine.

CONCLUSIONS:

The methacrylic acid seems to be a good candidate as monomer in a molecularly imprinted polymer for detection of benzoylecgonine and cocaine. Complexes between these molecules present strong interactions, specially between the carboxylic group of the methacrylic acid and the carboxylic group of the benzoylecgonine or the ester group of the cocaine molecule.

The effect of the solvent is very important in the interactions. On the basis of our calculations, the solvent of smaller dielectric constant should be selected for the reaction of polymerization.

Based on these results, it seems to be interesting the study of more possible monomers in order to suggest to experimental chemist potential MIPS to determinate cocaine in biological media.

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