Journal of Molecular Modeling

Computational Studies on Binding, Solvent, and pH Effects on S-propranolol and Methacrylic Acid Complex.

--Manuscript Draft--

Manuscript Number:	JMMO-D-20-00861R1
Full Title:	Computational Studies on Binding, Solvent, and pH Effects on S-propranolol and Methacrylic Acid Complex.
Article Type:	Original paper
Keywords:	S-propranolol; MAA; Molecularly Imprinted Polymers; pH; IR spectra; solvent study
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Funding Information:	National Science Foundation (EPSCoR (grant # OIA – 1757220)) — Dr. Julia Saloni
Abstract:	Density functional theory methods have been applied to understand binding of s-propranolol, a template, to a methacrylic acid molecule acting as a functional monomer using basic 1:1 model. The model has been expanded to study an effect various pH by adding hydronium and hydroxide ions to the template-monomer system, to mimic acidic and basic environments, respectively. This could be considered as a model study towards a potential use of molecular imprinting method for the design of a transdermal patch for a topical and direct delivery of s-propranolol to hemangiomas. In addition, this study provides detailed binding sites analysis of the template and functional monomer verified by the theoretical IR spectra analysis, as well as solvent and pH effects on template-monomer binding energy.
Response to Reviewers:	February 26, 2021 Manuscript ID: JMMO-D-20-00861 To the Editor of the Journal of Molecular Modeling Dear Professor Clark, Please find attached revision of the manuscript entitled “Computational Studies on Binding, Solvent, and pH Effects on (S)-propranolol and Methacrylic Acid Complex” by Shaurya Swami, Karina Kapusta, Glake A. Hill, and Julia Saloni resubmitted to the Journal of Molecular Modeling. Authors would like to thank the reviewers for their insightful comments and note that the manuscript have been revised according to reviewers’ suggestions. Please see below for the answers to the reviewers’ comments:

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Reviewer 1:

Comment 1: Consider changing "…however, no theoretical study…" to "…however, to the best of our knowledge, no theoretical study…"
Reponse1: Suggested change has been made. Please see line 62.

Comment 2: Authors should use better functions such as M06-2X or wb97-xd that incorporate dispersion energy instead of using B3LYP.
Response 2: Systems have been reoptimized using M06-2X functional. Please see lines 93-96.

Comment 3: How is the Binding energy calculated?
Response 3: As shown in lines 111-112, binding energy, BE, has been calculated by utilizing a formula: 〖BE=∆E〗_Complex-∆E_Template-∆E_Monomer

Comment 4: Is the BSSE taken into account?
Response 4: Yes, BSSE has been considered in the BE evaluation. Please see Table 2.

Comment 5: Provide more details about designed complexes.
Response 5: As requested authors expanded description of the designed complexes. Please see lines: 107-112 and 131-146.

Reviewer 2:
Comment 1: Calculations have been performed with the B3LYP functional. The inability of B3LYP and other GGA functionals to properly describe dispersive interactions is well-known. For this reason, the state-of -the-art when computing interactions as such described in the paper entail the use of dispersion-corrected functionals or adding empirical corrections (as Grimme done) to the common GGA functionals (B3LYP-D3). Calculations mut be redone (including optimization) with a functional including dispersion effects.
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We hope that provided changes fully satisfied your concerns and queries. We are thankful for the valuable comments which we hope made our research article more valuable and understandable for the readers.
Thank you for your time and consideration.
Sincerely,
Dr. Julia Saloni on behalf of the other authors.

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Response to reviewer's comments
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February 26, 2021

Manuscript ID: JMMO-D-20-00861

To the Editor of the Journal of Molecular Modeling

Dear Professor Clark,

Please find attached revision of the manuscript entitled "Computational Studies on Binding, Solvent, and pH Effects on (S)-propranolol and Methacrylic Acid Complex" by Shaurya Swami, Karina Kapusta, Glake A. Hill, and Julia Saloni resubmitted to the Journal of Molecular Modeling.

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Sincerely,

Dr. Julia Saloni on behalf of the other authors.

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Computational Studies on Binding, Solvent, and pH Effects on (S)-propranolol and Methacrylic Acid Complex.

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Declarations:

Funding: The NSF EPSCoR (grant # OIA – 1757220) and an HBCU-SAFRA title III grant project 2018-2019.

Conflicts of Interest/Competing Interests: The authors confirm that there are no known conflicts of interest associated with this publication.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: All the co-authors are aware of and approve of the submission of the article to the Journal of Molecular Modeling.

Availability of Data and Material: The authors confirm that data and materials associated with his publication is available upon request.

Code Availability: Not applicable.

Author's Contributions.

S. Swami: calculations and literature study.

K. Kapusta: MEP calculations and visualization and IR spectra analysis.

G. A. Hill: editorial and language corrections.

J. Saloni: calculations, data analysis, manuscript preparation.

Abstract

Density functional theory methods have been applied to understand binding of (s)-propranolol, a template, to a methacrylic acid molecule acting as a functional monomer using basic 1:1 model. The model has been expanded to study an effect various pH by adding hydronium and hydroxide ions solvated by water molecules to the template-monomer system, to mimic acidic and basic environments, respectively. This could be considered as a model study towards a potential use of molecular imprinting method for the design of a transdermal patch for a topical and direct delivery of (s)-propranolol to hemangiomas.

In addition, this study provides detailed binding sites analysis of the template and functional monomer verified by the theoretical IR spectra analysis, as well as solvent and pH effects on template-monomer binding energy.

Key words: S-propranolol, MAA, Molecularly Imprinted Polymers, pH, IR spectra, solvent study

Introduction

Propranolol [1] is a commonly used substance to treat high blood pressure. It has also been found to significantly reduce the size of infantile hemangiomas, commonly known as birth marks or strawberries [2]. Hemangiomas in infants possess certain dangers to the child due to their rapid growth and unfavorable locations such as on the eyelid or nose where they can limit vision or obstruct the airways. Typical propranolol treatment requires oral administration of the drug. However, there are several serious side effects present with this type of drug delivery such as low blood pressure, slow heart rate, over reactivity of the airways and low blood sugar levels [3].

Since hemangiomas are local grows of blood vessels it would be preferred to administer medication locally, to prevent mentioned above side effects. Topical ointments may not be the best option for the young patients, since they need to be frequently reapplied to ensure delivery of the required dosage of the medication. Additionally, ointments can be easily wiped off or spread to another, undesired, areas of the body, such as the eyes. Because of that, we propose another way for the topical delivery of propranolol-via a transdermal patch. A transdermal patch is, in essence, a sophisticated band-aid saturated with desired medication that is slowly released to the body. Several experimental studies have been conducted to synthesize the transdermal patch [4-7]; however, to the best of our knowledge, no theoretical study has been performed on that subject. We propose that (s)-propranolol would first be encapsulated within a polymeric matrix, then, after application on the changed tissue, it will slowly be released directly to the hemangioma.

Polymeric matrix that encapsulates (s)-propranolol can be synthesized by application of molecular imprinting method. Molecularly imprinted polymers, MIP, are designer polymers that allows preparation of polymer matrix containing very specific, target oriented cavities [8]. Target, a molecule of interest, is non-covalently bonded to the cavity made of functional monomers and crosslinking agents. MIPs are used for a variety of applications that include selective extraction [9], detection of dangerous substances or analytical separation, just to name a few [10].

In recent years molecularly imprinted polymers are used for selective drug delivery [11]. Alizadeh et al. [12] published a combined experimental and theoretical work on a new chiral functional monomer for the synthesis of MIP for racemic propranolol. Haginaka and Sakai [13] reported very detailed experimental study on molecularly imprinted material for (s)-propranolol. In their work, methacrylic acid and ethylene glycol dimethacrylate, MAA-EDMA, based material was reported as the best for molecular imprinting (s)-propranolol due to its enantioselective recognition properties.

In our research, we propose the use of material based on molecularly imprinted (s)-propranolol in transdermal patch that could deliver (s)-propranolol directly to the changed skin tissues caused by hemangiomas, the delivery method that could significantly reducing existing side effects on human organism [14]

Presented work, utilizes basic computational model of MAA-(s)-binding scheme to the (s)-propranolol that includes recognition of the binding sites as well as the solvent effect on template-MAA interactions [15]. This computational approach can not only be used to study monomer template systems but also can be applied for basic analysis of variety organic-solvent systems, such as dye-solvent complexes.

Additionally, to the basic study we have extended our simple model to study interactions between template and monomer caused by acidic and basic environment by introducing hydronium and hydroxide ions to the interacting system.

Methodology

Methods and Basis Sets. This study has been performed using Density Functional Theory Methods [16-19] with the application of B3LYP hybrid functional [20] and M06-2X hybrid meta exchange-correlation functional [21] combined with standard gaussian basis set that includes polarization functions. Combination of B3LYP functional with 6-31G (d,p) basis set [22] has been proven to be sufficient for basic MIP calculations, and provides satisfactory results with the minimum computational cost [23, 24]. Additionally, all optimizations have been recalculated with M06-2X functional to incorporate dispersion effects on studied systems. Counterpoise corrections [25] has been applied to binding energy between monomer and template calculated utilizing both B3LYP and M06-2X functionals. Solvent study calculations have been conducted with the conductor-like polarizable continuum model, CPCM [26]. Charge distribution has been performed by using NBO analysis [27]. All the calculations have been performed utilizing Gaussian 09 suite of programs [28].

Basic Model. Basic model consists of one methacrylic acid monomer interacting with one (s)-propranolol template molecule. This model has been developed and validated in our previous studies on DNT and TNT imprinting [15, 23]. Four different binding sites on (s)-propranolol have been evaluated in order to find the complex with the largest binding energy. Out of the four possible binding positions, that have been analyzed, the energetically preferred one is located near secondary amine and hydroxyl groups of (s)-propranolol, as shown in Figure 3. There is no observed binding activity between monomer and template on naphthalene ring of (s)-propranolol.

Binding energy, BE, has been calculated by utilizing a formula:

$$BE = \Delta E_{Complex} - \Delta E_{Template} - \Delta E_{Monomer}$$

Basis set superposition error, BSSE, has been included into the binding energy value for the gas phase calculations and presented in Table 2.

Proposed model provides detailed structural, and binding characteristics in a gas phase as well as includes solvent studies completed for the following solvents: chloroform, dimethyl sulfoxide (DMSO), ethyl alcohol, and water. Theoretical IR spectra analysis of the MAA, the template and template-MAA system has been completed.

Additionally, to mimic skin surface environment, moist and acidic, and to study influence of the low pH on template-monomer binding, hydronium ion, solvated with five water molecules, has been introduced to the basic model.

To provide the complete picture of pH effects on (s)-propranolol-MAA binding scheme, studies have been extended by analysis of the impact of the high pH on the template-monomer binding by introducing hydroxide ion, solvated with five water molecules, to the basic model. All structural changes caused by the change of the pH, have been observed, described, and verified by calculated IR spectra.

All calculations have been performed with no symmetry constraints.

Results and Discussion

Binding of MAA to (S)-propranolol.

Four possible binding sites for MAA monomer on (s)-propranolol template have been evaluated to find the lowest energy system. Investigation shows that MAA prefers to bind to the aliphatic chain of the template and it omits aromatic naphthalene ring. Studied complex, optimized at both B3LYP and M06-2X levels of theory (where an Asterix * indicates M06-2X method) is formed through two hydrogen bonds. First hydrogen bond is connecting amino group of (s)-propranolol with carbonyl group of MAA, while second links hydroxyl group of (s)-propranolol with hydroxyl group of methacrylic acid.

As shown in Table 1 and Figure 1, the bonding distances are reported as 2.21 Å (2.25 Å*) and 1.71 Å (1.66 Å*) for corresponding N-H…O=C and O-H…O-H hydrogen bonds. M06-2X calculations shows N-H…O=C to be slightly elongated by 0.04 Å, while O-H…O-H is shortened by 0.05 Å, when compared to B3LYP results. The pure hydrogen bonding interactions between (s)-propranolol and MAA, without presence of solvent, amounts 16.03* kcal/mol and 13.77 kcal/mol for M06-2X and B3LYP, respectively. Total binding energy between monomer and template has been corrected by applying basis set superposition error, BSSE, calculated in the gas phase. BSEE lowers the binding energy to 14.06* kcal/mol and 11.67 kcal/mol for M06-2X and B3LYP calculations, respectively.

Addition of the solvent to the interacting system lowers the binding energy between (s)-propranolol and MAA. Binding energies listed in Table 2 shows the decreasing trend of the binding energy value calculated with the presence of solvent. Additional computations revealed that, interestingly, both water and ethanol position themselves in between methacrylic acid and the (s)-propranolol forming a direct hydrogen bonding to both. As a result, no direct hydrogen bonding between MAA and (s)-propranolol can be observed (see supporting materials Figure 14 and 15).

Theoretical IR spectra for studied systems in gas phase have been calculated with both M06-2X and B3LYP functionals. Spectra obtained with the use of both methods are similar in trends, the differences are seen with a slight shift of the peaks but not with their intensities. As shown in Figure 6, calculated IR spectrum confirms binding between MAA and (s)-propranolol. Figures 4 and 5 present calculated spectra of isolated MAA and (s)-propranolol molecules, respectively. Comparison of the calculated spectra of monomer, template and complex, leads to the following observations: there is a slightly increased intensity of the vC=O (MAA), vNH ((s)-propranolol), and vOH ((s)-propranolol) peaks, and a significant increase with intensity of the vOH (MAA) in the spectrum of the complex. Mentioned above peaks represent C=O…N-H and O-H…OCH hydrogen bonding within the complex. It can also be observed that those characteristic peaks are shifted towards lower frequency when compared to the spectra of pure MAA and (s)-propranolol.

Effect of the pH.

Low pH. The (s)-propranolol-MAA complex has been introduced to the acidic environment, by addition of the hydronium ion, H_3O^+, initially located above the hydrogen bonds formed by (s)-propranolol and MAA molecules. After the full optimization of the system, at B3LYP and M06-2X levels, performed with the presence of five water molecules, hydronium ion relocates to the position in between the (s)-propranolol and MAA molecules, additionally a single proton transfer is observed, as shown in Figure 7. The transfer occurs between hydrogen from the H_3O^+ ion and nitrogen of the N-H group of (s)-propranolol. A proton from the hydronium ion is attracted by the lone electron pair located on nitrogen on (s)-propranolol molecule. Newly formed H_2O molecule becomes a part of a hydrogen bonding network within (s)-propranolol and MAA system. Calculation shows that the five waters of solvation do not participate in the proton transfer. As shown in Figure 7, there are four hydrogen bonds in the product of the (s)-propranolol-MAA + H_3O^+ reaction: two direct hydrogen bonds between (s)-propranolol and MAA (N-H…O=C and CHO…HO with the distances of 2.20Å and 1.77Å respectively), and two

hydrogen bonding to newly formed H_2O molecule, each from (s)-propranolol and MAA (NH…OH (water) and (water) OH…O=C with the distances of 1.68Å and 1.78Å respectively). Average binding energy within product of the (s)-propranolol-MAA + $H3O^+$ reaction amounts 12.25 kcal/mol (9.39 kcal mol BSSE corrected) and 15.03kcal/mol (12.45 kcal/mol BSSE corrected) for B3LYP and M06-2X respectively, per h-bonding. There are no observed structural changes within MAA molecule.

Introduction of an acidic environment causes (s)-propranolol to change into cationic form, while hydronium ion due to observed proton transfer converts into the neutral water molecule. Comparison of the map of the electrostatic potential, MEP, between neutral (s)-propranolol-MAA system and the product of the (s)-propranolol-MAA + H_3O^+ reaction, presented in Figures 9 and 10, shows observable change within the electron distribution caused by the addition of the hydronium ion followed by a single proton transfer. In the neutral (s)-propranolol-MAA system, three nucleophilic centers can be observed (see Figure 9, marked in red). Two of them, on the oxygens from the hydroxyl groups on both (s)-propranolol and MAA, and the third on the carbonyl oxygen located on MAA molecule. Addition of the hydronium ion followed by the proton transfer that caused hydronium ion to convert into a water molecule, and (s)-propranolol to become positively charged, can easily be visible on the MEP of the product of the (s)-propranolol-MAA + H_3O^+ reaction. As presented on Figure 10 (marked blue), positive charge is shown to be located on the hydrogen atom of hydroxyl group and the nitrogen (where proton transfer occurred) both being a part of the (s)-propranolol molecule.

Figure 12 shows calculated IR spectra for the product of the (s)-propranolol-MAA + H_3O^+ reaction at B3LYP level. Water formed in the reaction, proton transfer to the secondary amine group on the template, and the hydrogen bonding between water and (s)-propranolol are indicated by the following peaks: vH-O-H (3874 cm^{-1}), vNH (3412 cm^{-1}) and vNH…OH (2906 cm^{-1}), respectively.

Additionally, vOH (MAA) and vOH((s)-propranolol) vibrations of the product of the (s)-propranolol-MAA + H_3O^+ reaction are shown to be right shifted when compared to (s)-propranolol-MAA complex reported on Figure 6.

High pH. To mimic basic pH and study its influence on the template-monomer system a hydroxide ion, OH^-, has been added to the (s)-propranolol-MAA complex above the two hydrogen bonds binding template with monomer. After conducting full optimization at both B3LYP and M06-2X levels of theory, with the presence of five waters of solvation, it has been observed that an introduction of the OH^- ion causes the simultaneous double proton transfer from (s)-propranolol to the hydroxide ion, and from MAA to the (s)-propranolol molecule, as presented in Figure 8. Hydrogen from the (s)-propranolol hydroxyl group is attracted by nucleophilic oxygen of hydroxide ion, causes a proton transfer and a formation of water molecule. As a result, (s)-propranolol becomes temporarily negative, with the extra electron localized on the oxygen atom (formally hydroxyl group) that causes second proton transfer from MAA hydroxyl group to the nucleophilic oxygen of (s)-propranolol. Consequently, MAA lacks a proton on the (former) hydroxyl group, and the two oxygens are connected via double bonds to the carbon (former carboxylic group). MAA system becomes negatively charged with extra electron localized on the outer oxygen atom of the former carboxylic group. The product of the (s)-propranolol-MAA + OH^- reaction is a system connected via four hydrogen bonds with average binding energy of 15.73 kcal/mol (13.11 kcal/mol BSSE corrected) and 15.94 kcal/mol (13.47 kcal/mol BSSE corrected) for B3LYP and M06-2X methods respectively, per each h-bonding. The first two h-bonds located between MAA and water (C=O…H-O), and MAA and (s)-propranolol (C=O…HO) have interacting distance of 1.95Å and 1.65Å, respectively. Remaining two interactions are formed between MAA's outer oxygen and (s)-propranolol (C=O…H-C), and water and (s)-propranolol (H-O…OHC). Their bond distances amount 2.24Å and 2.08Å, respectively.

Comparison of MEP, between neutral (s)-propranolol-MAA system and the product of the (s)-propranolol-MAA + OH^- reaction, presented in Figures 9 and 11, shows a change of electron distribution surrounding oxygen in COO^- group of MAA, in the product of the (s)-propranolol-MAA + OH^- reaction, when compared to neutral (s)-propranolol MAA MEP. In Figure 11, red area around the oxygen on MAA represents the accumulation of the extra negative charge that occurred after the proton transfer from the hydroxyl group of MAA to hydroxide ion.

Figure 13 shows B3LYP calculated IR spectra for the product of the (s)-propranolol-MAA + OH^- reaction. There are few interesting picks reported in this spectrum: βH-O-H, at frequency of 3670 cm^{-1}, that corresponds to the vibrations of the water molecule formed during the reaction of the monomer-template system with hydroxide ion. During that reaction, a proton has been transferred from MAA hydroxyl group to the attacking nucleophilic hydroxide group, and as a result, the COOH group of MAA has been converted to the O=C=O group, βO=C=O at 1979 cm^{-1}. There is no vOH (MAA) vibration represented in the spectrum (Figure 13) due to mentioned above proton transfer from MAA to the hydroxide ion.

It can be observed high intensity peak of vOH ((s)-propranolol) that corresponds to the hydrogen bonding between COO^- group of MAA with hydroxyl group of (s)-propranolol, see Figures 8 and 13. Additionally, there is low intensity peak between secondary amine group of the template and hydroxide group from water at 3451 cm^{-1} that indicates weak hydrogen bonding between the two species with bond distance of 3.26Å (as shown in Figure 8). Frequencies of vOH (MAA) and vNH ((s)-propranolol) are shifted to the left by around 120 cm^{-1} when compared to the spectrum of (s)-propranolol-MAA complex presented in Figure 6.

Figures 12 and 13 show calculated IR spectra for products of reactions with hydroxide and hydronium ions that has been obtained using B3LYP method only. As presented in Figures 4-6 M06-2X does not alters the intensities of the important peaks, just causes their slight shift to the left.

Based on the performed analysis change of the pH significantly alters the monomer template system, not only by changing structure, electron distribution but also the binding scheme.

Conclusions

Presented in this manuscript detailed analysis of binding energy scheme of monomer to the template provides a base line, introductory study for the solvent selection in the molecular imprinting process of (s)-propranolol in methacrylic acid towards its potential use as transdermal patch to treat hemangiomas. Included studies, can provide better understanding on binding and release processes of MIP-trapped (s)-propranolol as well as application of two DFT functionals B3LYP an M06-2X without and with dispersive interactions, respectively. For example, BE calculated in M06-2X functional is 2.26 kcal/mol higher than one calculated using B3LYP functional. Counterpoise correction lowers binding energy, calculated in the gas phase, by 1.97 kcal/mol form M06-2X and 2.1 kcal/mol for B3LYP method. Additionally, performed calculations demonstrated the trend of the solvent effect on the (s)-propranolol's binding to the functional monomer. Presented calculations shows that protic solvents (methanol and water) have much stronger effect on the binding that aprotic ones (chloroform and DMSO), they lower BE by 3.31 kcal/mol on average, while aprotic solvents lower BE by only 1.61 kcal/mol. Solvent effect is considered to be one of the crucial information for the future synthesis of the transdermal patch. Additionally, since a transdermal patch is to be working on the surface of the skin, and skin's typical pH is slightly acidic, the study of the pH effect on the MAA-(s)-propranolol's binding stability has been conducted as well. As presented in manuscript, the introduction of hydronium or hydroxide ions to the MIP interacting with (s)-propranolol causes the proton transfer within the system and reduced direct binding between monomer (a part of MIP drug delivery system/transdermal patch) and the (s)-propranolol (a medicine that would be delivered). Since computational research become a part of the initial stages of drug design this study of the

solvent selection, binding characteristic of the monomer and template system as well as pH effect on binding are necessary for the initial stages of basic research for the development of the transdermal patch for the delivery of (s)-propranolol via MIP to hemangiomas

Acknowledgements

Mississippi Center for Supercomputing Research at the University of Mississippi in Oxford, MS. This research is supported by Institute for Undergraduate Research (I UR). An HBCU-SAFRA title III grant project 2018-2019. Julia Saloni thanks the NSF EPSCoR (grant # OIA – 1757220) for providing start-up funds that facilitate completion of this project.

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382 **Tables**

383 Table 1. Selected bond distances in MAA, s-propranolol and (s)-propranolol-MAA complex.

Bond in Molecule	Distance, Å M06-2X	B3LYP	Bond in Complex	Distance, Å M06-2X	B3LYP
MAA			**MAA in Complex**		
C=O	1.21	1.21	C=O	1.22	1.22
O-H	0.97	0.97	O-H	1.00	1.00
C-OH	1.35	1.36	C-OH	1.33	1.34
S-propranolol			**S-propranolol in Complex**		
O-H	0.97	0.97	O-H	0.98	0.99
C-OH	1.41	1.41	C-OH	1.42	1.43
N-H	1.02	1.02	N-H	1.02	1.02
C-NH	1.46	1.47	C-NH	1.46	1.47

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386 Table 2. Binding energies for (s)-propranolol-MAA complex in solvent.

Solvent	BE in kcal/mol (M06-2X)	BE in kcal/mol (B3LYP)
no solvent	-16.03	-13.77
no solvent (BSSE corrected)	-14.06	-11.67
ethanol	-12.08	-10.03
water	-11.96	-10.62
DMSO	-12.00	-12.72
chloroform	-12.85	-11.60

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Figures

Figure1: Geometry of a methacrylic acid, MAA, the monomer.

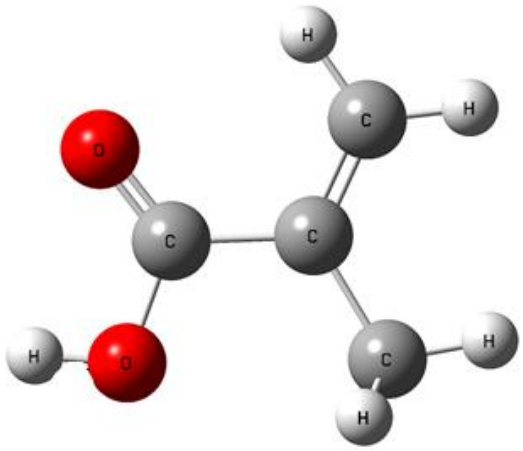
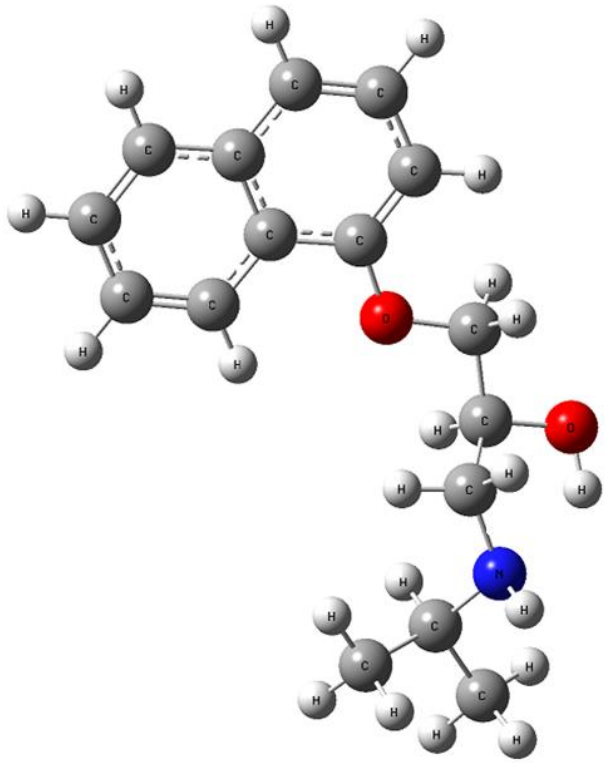


Figure 2: Geometry of a (s)-propranolol, the template.



405 Figure 3: Geometry of (s)-propranolol-MAA complex at B3LYP and * at M06-2X level.

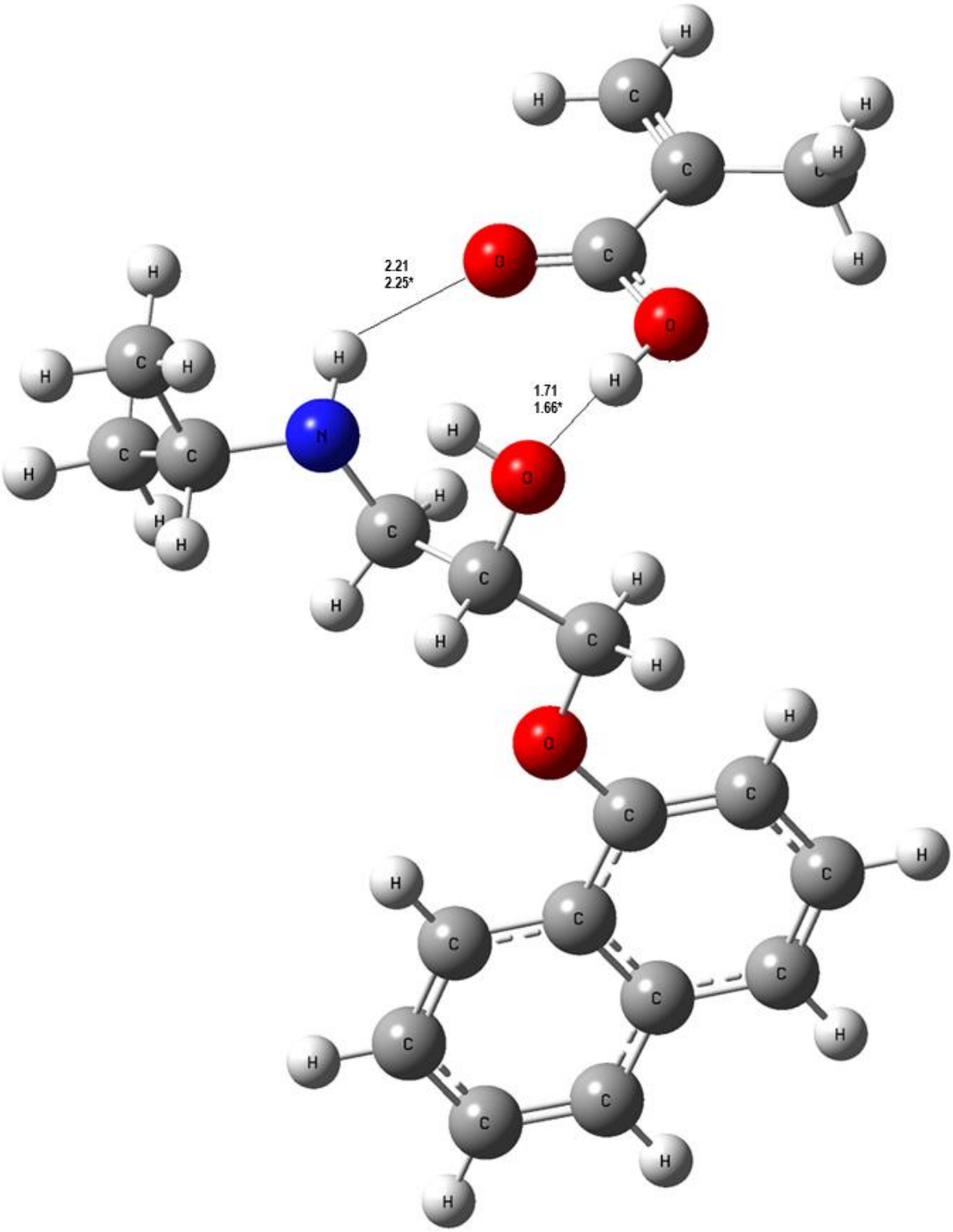


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Figure 4. Calculated IR spectra for methacrylic acid, MAA, the monomer, on x axis: frequency in cm^{-1} at B3LYP and * at M06-2X level.

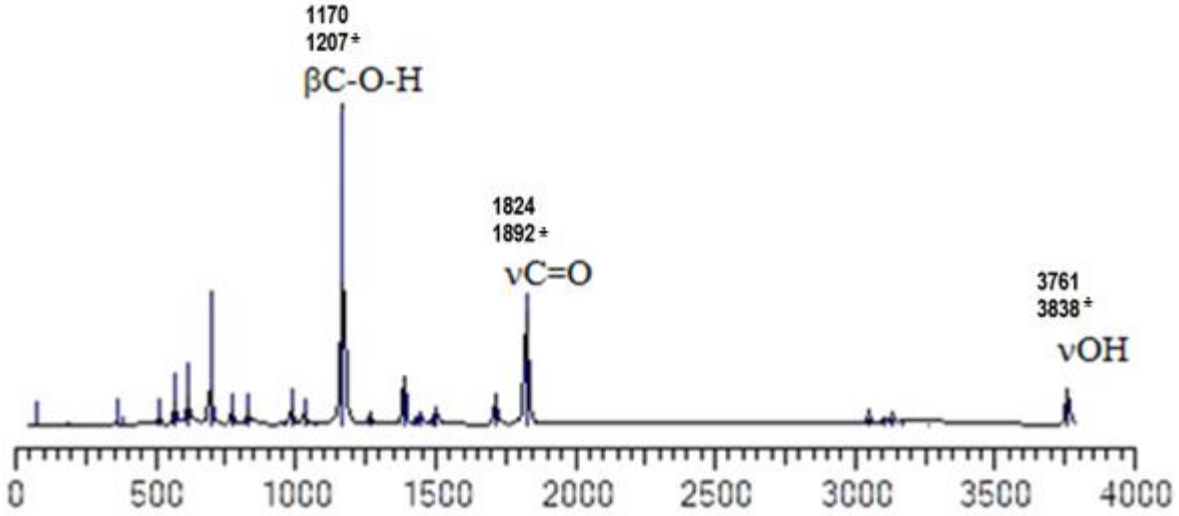


Figure 5. Calculated IR spectra for (s)-propranolol, the template, on x axis: frequency in cm^{-1} at B3LYP and * at M06-2X level.

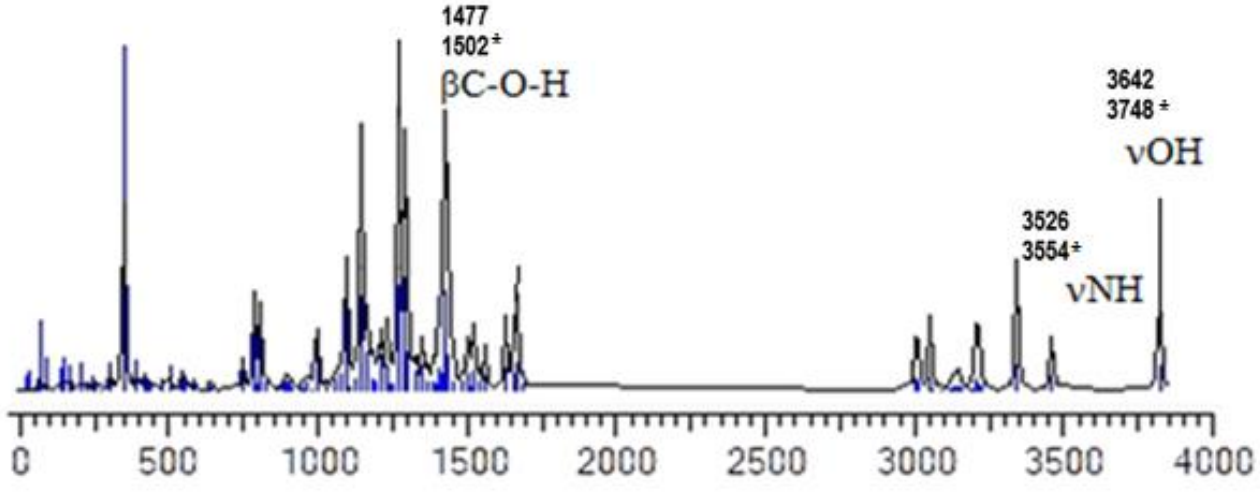


Figure 6. Calculated IR spectra for (s)-propranolol-MAA complex, on x axis: frequency in cm^{-1} at B3LYP and * at M06-2X level.

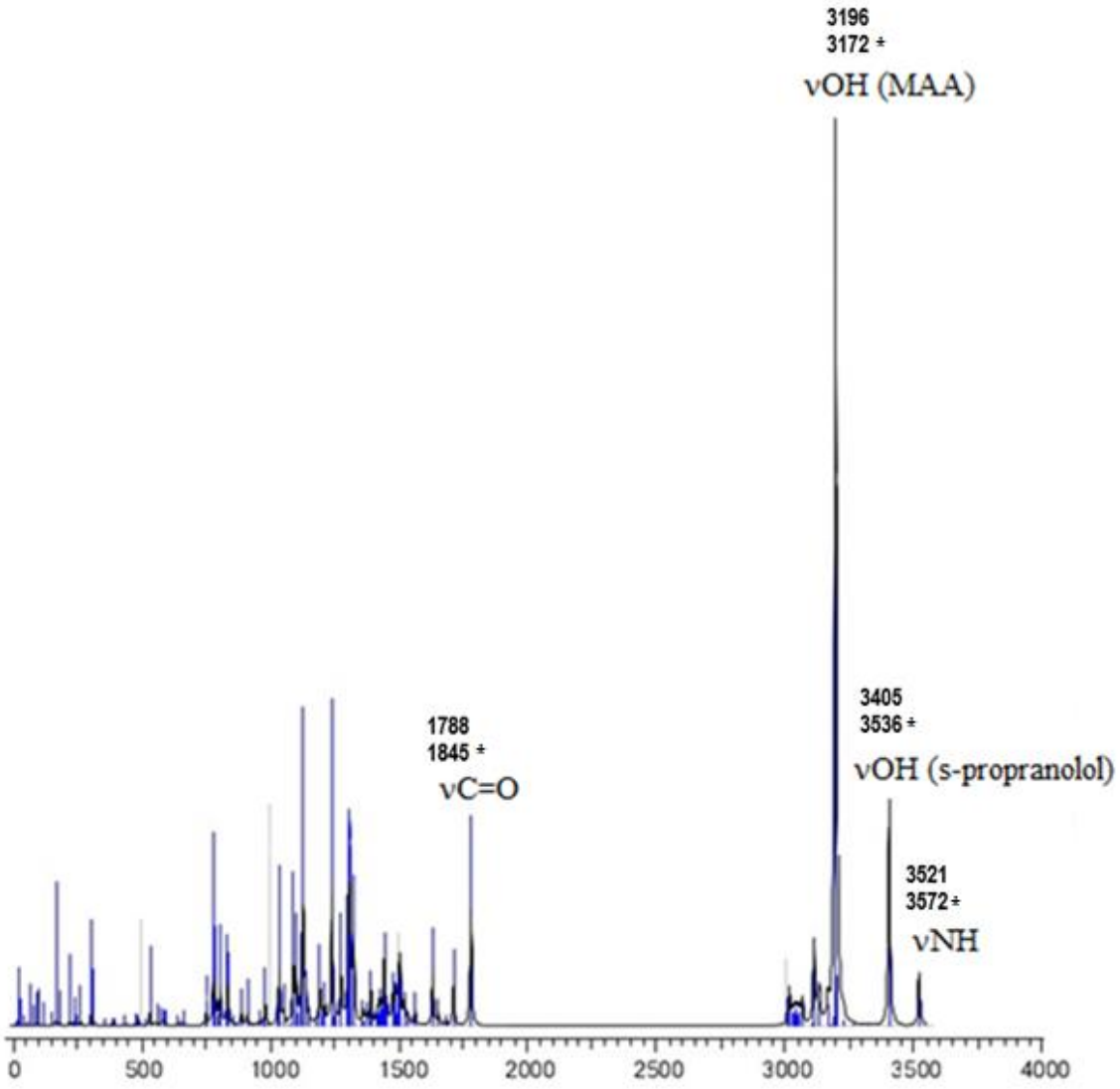


Figure 7. Schematic representation of the influence of hydronium ion, H_3O^+, on the (s)-propranolol-MAA complex.

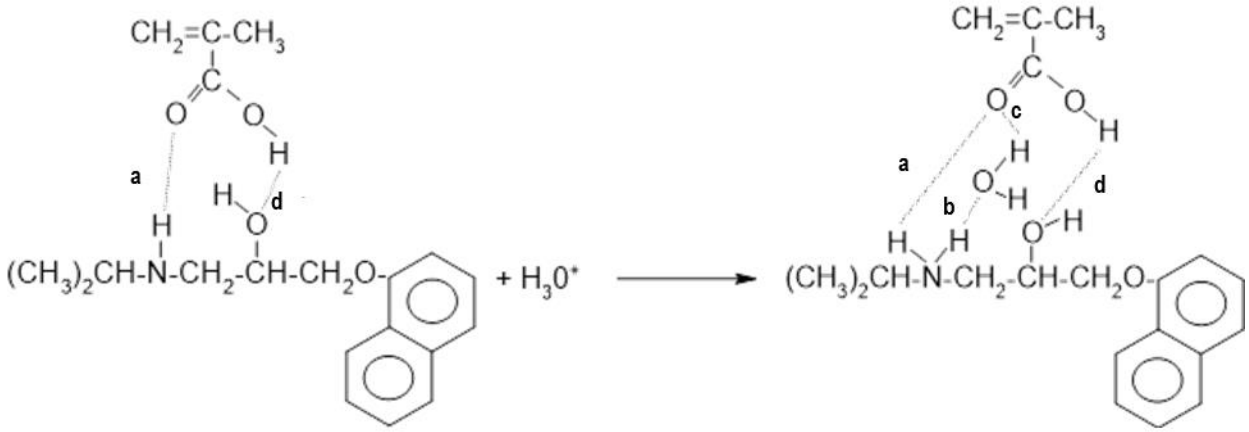


Figure 8. Schematic representation of the influence of hydroxide, OH-, group on the (s)-propranolol-MAA complex.

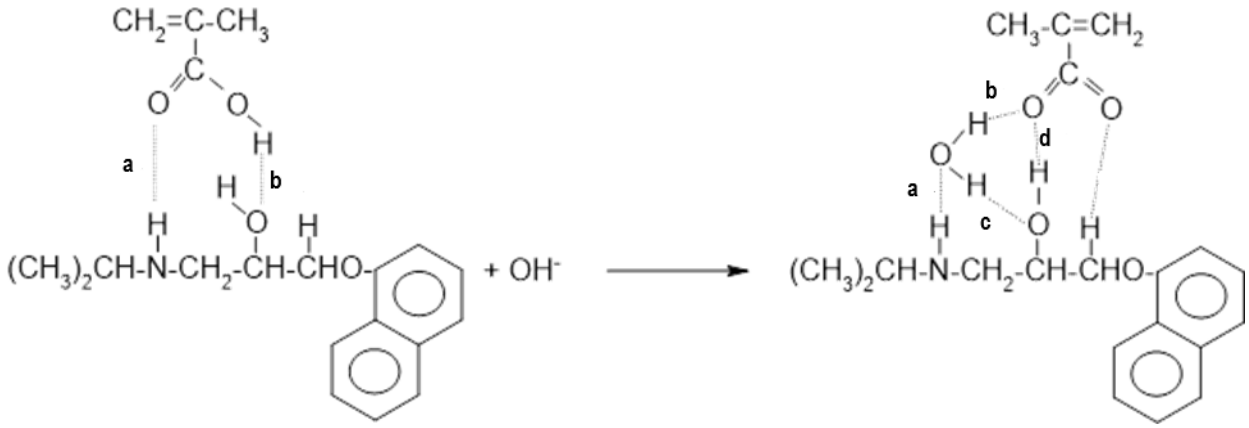


Figure 9. MEP of the (s)-propranolol-MAA system

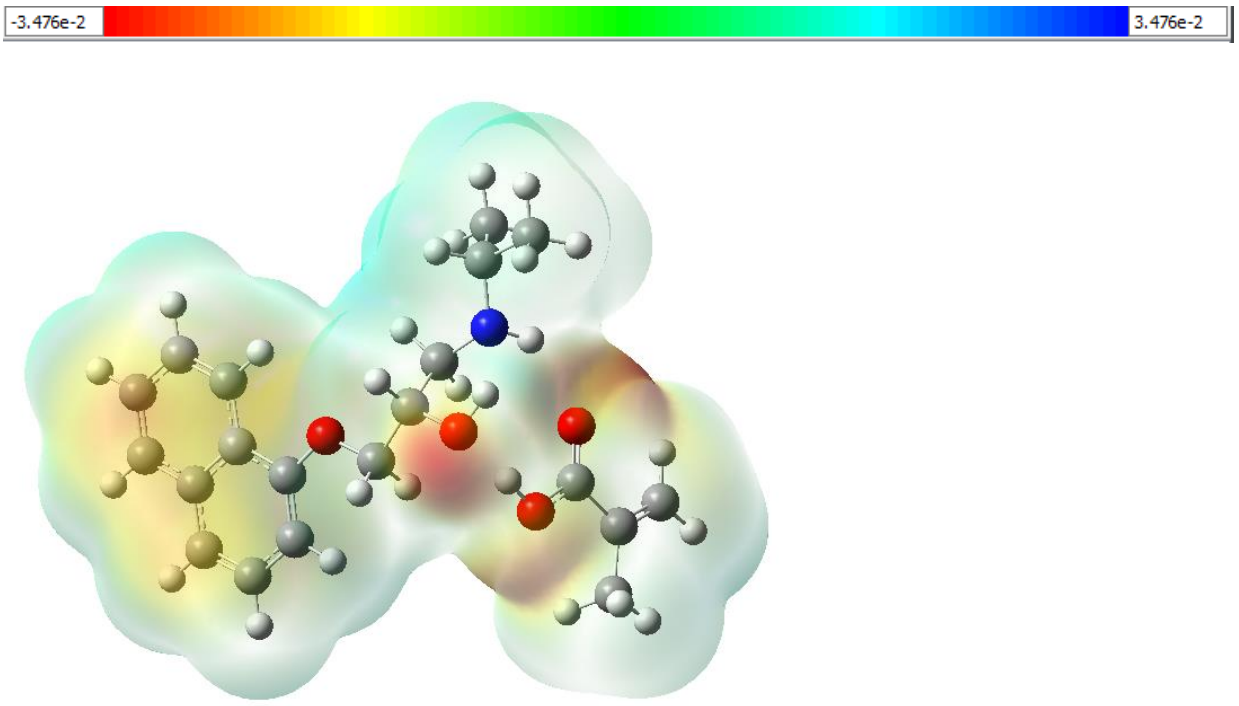


Figure 10. MEP of the product of the (s)-propranolol-MAA + H_3O^+ reaction.

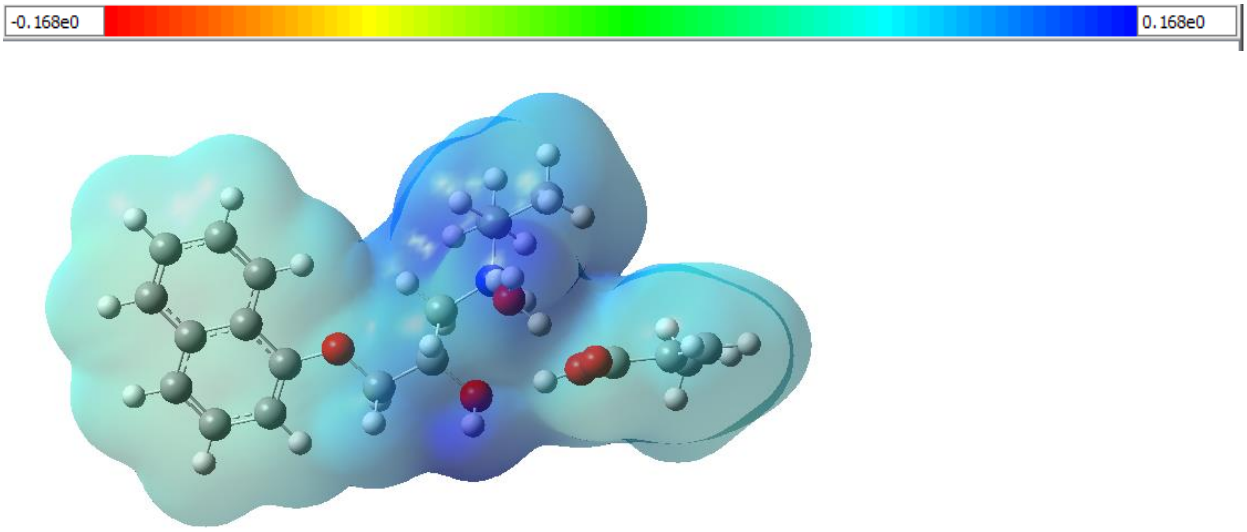
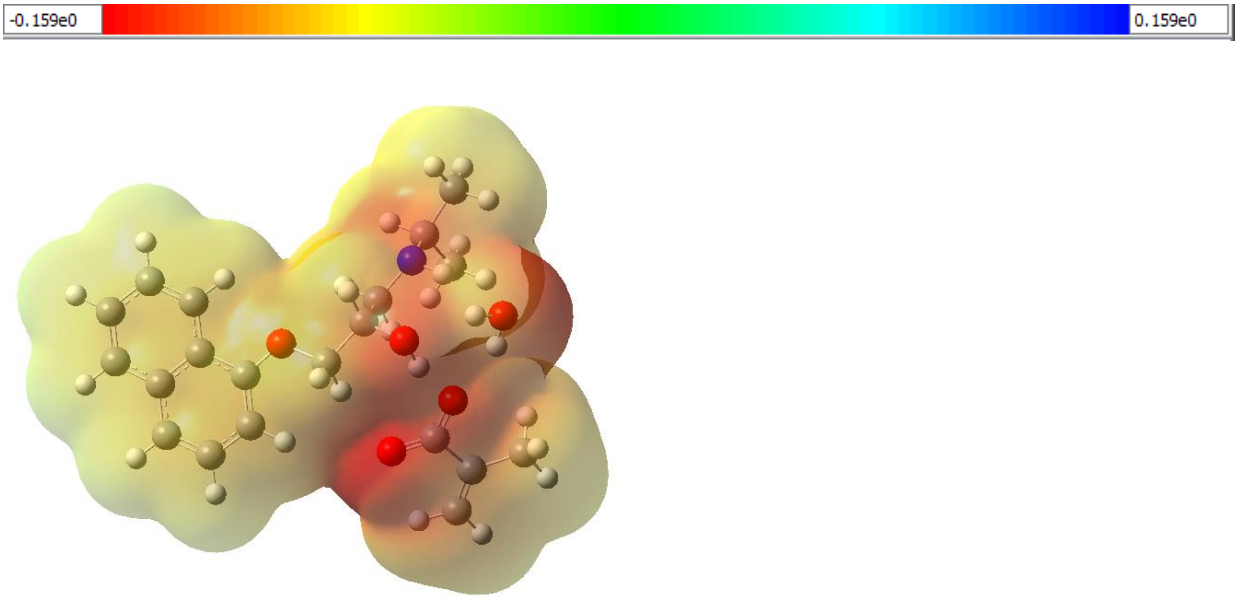


Figure 11. MEP of the product of the (s)-propranolol-MAA +OH^- reaction.



464 Figure 12. Calculated IR spectra for the product of the (s)-propranolol-MAA + H_3O^+ reaction, on

465 x axis: frequency in cm^{-1}.

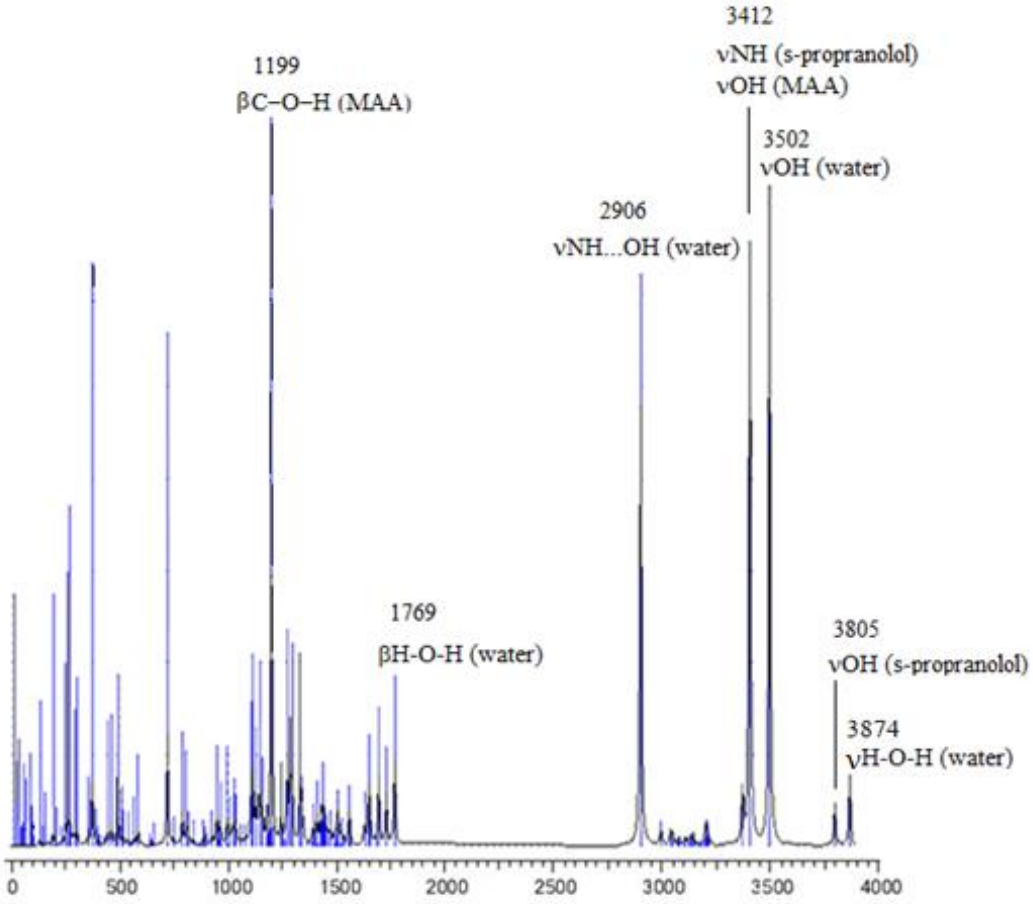


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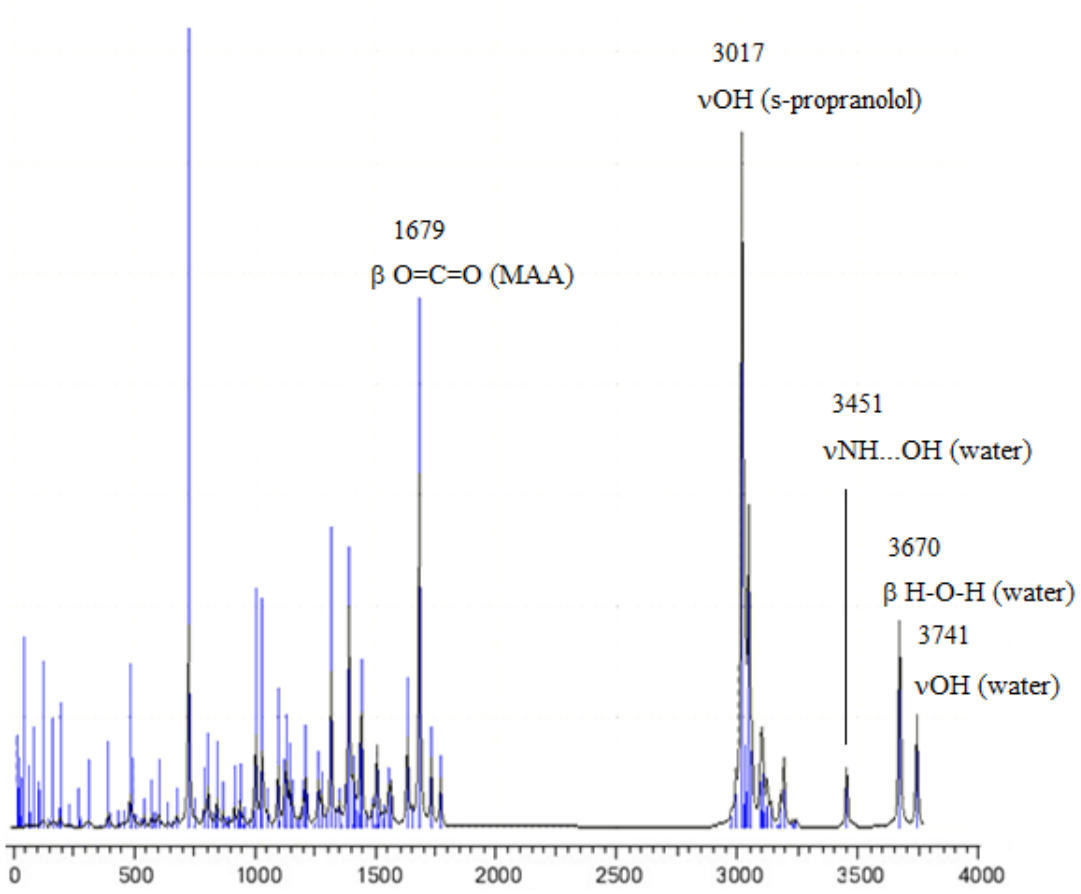
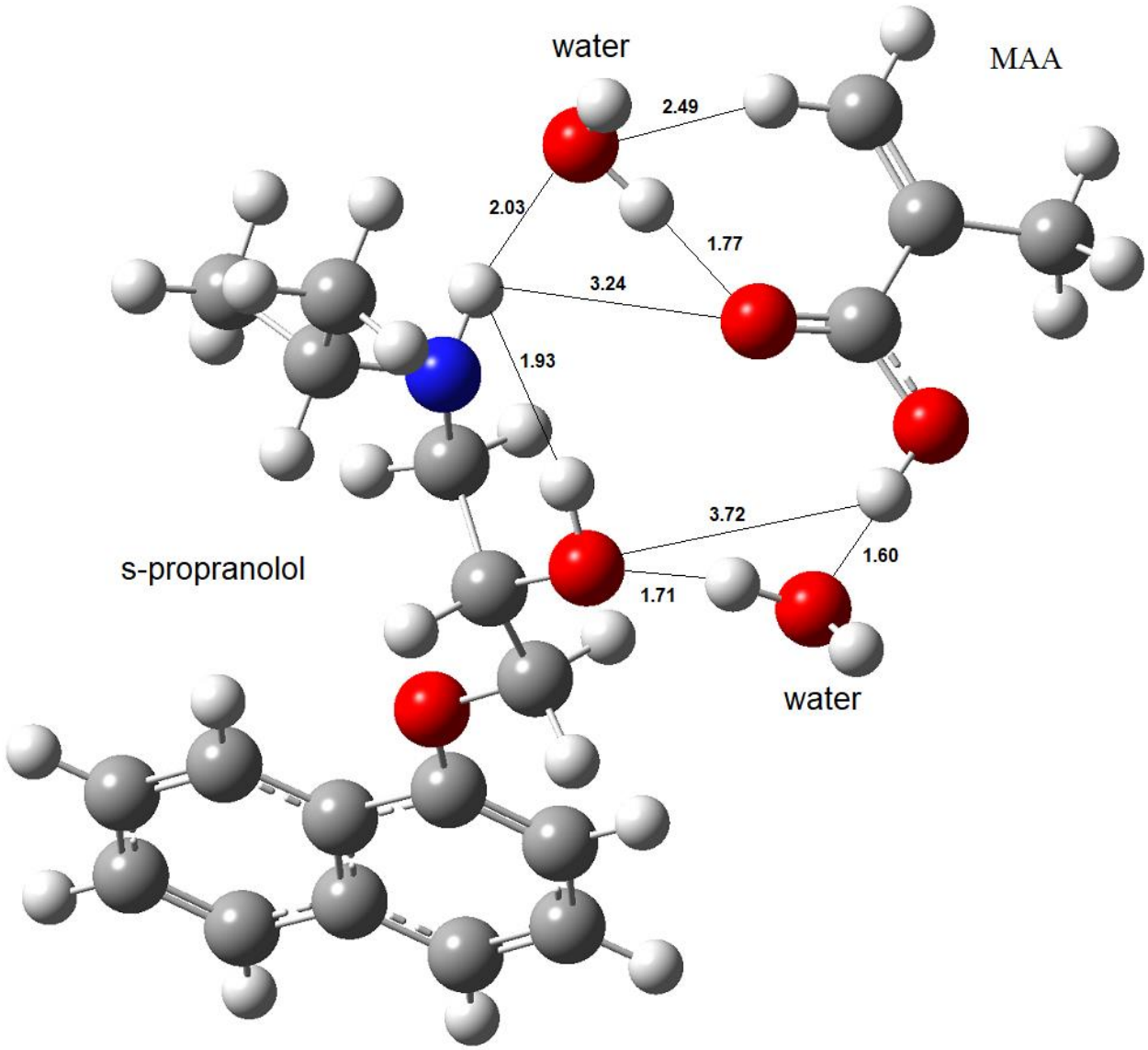
Figure 13. Calculated IR spectra the product of the (s)-propranolol-MAA + OH^- reaction, on x axis: frequency in cm^{-1}.



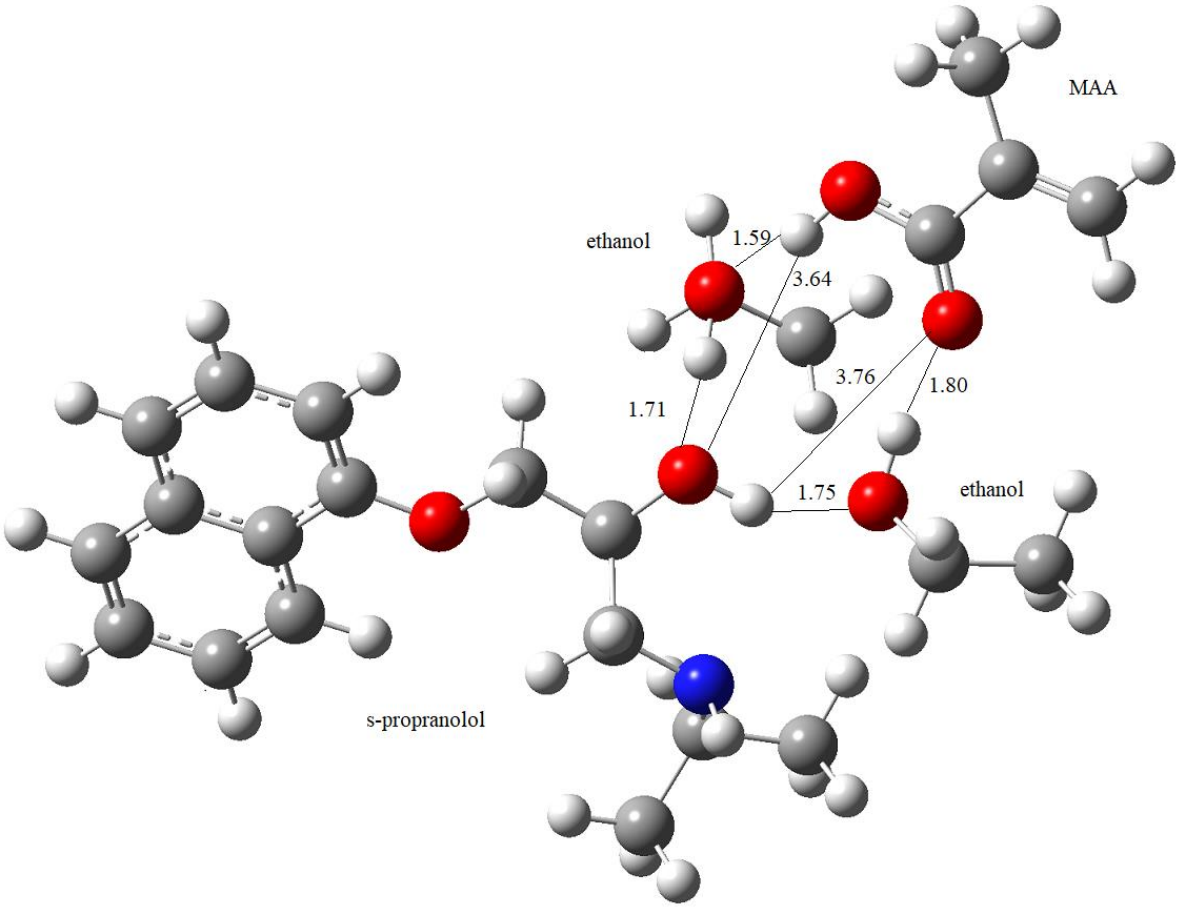
Supporting Materials:

Figure 14: Geometry of (s)-propranolol-MAA complex with two water molecules. B3LYP/6-31G(d,p) level of theory. Distances in angstroms, Å.



496 Figure 15: Geometry of (s)-propranolol-MAA complex with two ethanol molecules. B3LYP/6-

497 31G(d,p) level of theory. Distances in ang



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