Biophysical Chemistry 137 (2008) 1–6

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

Construction of simplified models to simulate estrogenic disruptions by esters of 4-hydroxy benzoic acid (parabens)

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ARTICLE INFO

Article history:
Received 12 February 2008
Received in revised form 1 June 2008
Accepted 2 June 2008
Available online 12 June 2008

Keywords:
Parabens
Estrogenic activity
Antibacterial activity
Conformational analysis
Density Functional Theory

ABSTRACT

Four parabens (methyl, n-butyl, benzyl and isobutylparaben) were theoretically studied in order to evaluate their estrogenic activity through simplified models. The experimental structure of the human estrogen receptor ligand-binding domain in complex with 17β-estradiol was used as the starting point to construct the models. The complex between 17β-estradiol and three fragments of the estrogenic receptor (Arg, Glu and His), resulted in a reasonable simplified model of interaction. The replacement of 17-β-estradiol by parabens was evaluated by conformational analyses and interaction energy calculations at BHandHLYP/cc-PVTZ(-f)+ level of theory. According with the calculated interaction energies, methylparaben is the paraben with higher estrogenic activity, which is in agreement with experimental studies of extraction and quantification of parabens in tumors. The antibacterial activity of parabens was also explored considering the formation of potassium salts in the phenolic OH groups. From the obtained relative energy values, methylparaben is the most active preservative.

1. Introduction

The diagnosis and treatment of cancer have been, for many years, two matters of interest of multidisciplinary research groups and one of the main issues has involved the understanding of the anomalous mechanisms triggered by daily-use chemical products. Parabens (esters of 4-hydroxy benzoic acid, Fig. 1) are substances frequently used as antibacterial preservatives in many personal care products (e.g. deodorants and cosmetics) as well as in pharmaceutical formulations and food products [1].

The recurrent use of parabens has been justified due to their broad range of antibacterial activity [2] and chemical stability, besides their low-cost. Specific studies on propylparaben in Escherichia coli [3] showed an important activity, producing an abnormal gradient of potassium and consequent cellular death. Recently the parabens were stressed as potentially harmful chemicals [4] since, in addition to their antibacterial activity, they also exhibit estrogenic activity, that is, they are mimics of estrogens (hormones; see Fig. 2) with the potential to alter either in a beneficial or harmful manner, target tissues like breast and uterus.

To understand the implications around the mimicking of estrogens, it is important to mention what is the role of these natural hormones. After the interaction with specific estrogen receptors (ERs) [5], the end product of estrogens is the cellular growth and division by a process called cell proliferation. Once the estrogen-receptor complex is formed, it binds to co-activator proteins, triggering the gene activation. Molecules of messenger RNA are formed, which conduct to the synthesis of specific proteins involved in the cell proliferation (Fig. 3). If the cellular DNA is damaged by an abnormal gene activation due to estrogenic molecules (mimics of estrogen), mutations can appear and, if these mutant cells proliferate the result is cancer [6].

Experimental analyses (by HPLC detection) have shown parabens in some breast tumors [7,8] in concentrations of 20.6±4.2 ng per gram of tissue [9]. According to the comparative quantification of different parabens, methylparaben was present at the highest level, while benzyl and isobutylparabens were founded in smaller quantities. These findings were cause of concern given that today parabens can be found in more than 13,000 cosmetics and deodorant formulas. From studies of structure-activity relationships of different natural and synthetic substances like parabens, it was established that specific structural features are directly related to the estrogenic activity [10,11]. The 17β-estradiol, with a phenolic OH group and a 17β-hydroxyl group (molecule A in Fig. 2), is one of the most active estrogens for ER binding and, according to the crystal structure of the complex 17β-estradiol-ER, these OH groups interact with ER as H-bond donor and H-bond acceptor respectively. The crystal structure also showed that the presence of the phenolic OH is more important than the 17β-OH since the former interact by H-bonds with amino acid fragments of the ER (glutamate (Glu) and arginine (Arg) and one molecule of water, while the later only interacts with the histidine fragment (His) (only one H-bond is observed). Relative binding affinities (RBA) [12] showed that the elimination or modification of either of these two groups reduces

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doi:10.1016/j.bpc.2008.06.001

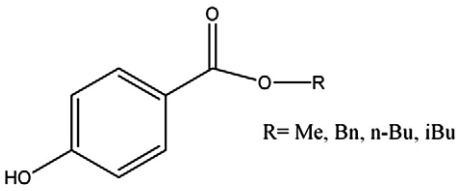

Fig. 1. Esters of 4-hydroxy benzoic acid (Parabens).

appreciably the binding affinity for the receptor ER. The aromatic ring of the 17β-estradiol also interacts with the receptor by weak interactions and, even though this group contributes less than phenolic OH [13], its contribution to the binding free energy is not negligible at all.

Estrogens and parabens are structurally similar since both contain phenolic OH groups and hydrophobic fragments. In case of parabens, the relationship between ER binding activity and hydrophobicity is linearly correlated (see reference [7]). Therefore, parabens are considered as potential substitutes of 17β-estradiol in the interaction with the receptor ER. The generalized consensus of the potential estrogenic activity of parabens is supported by many structure-activity studies reported so far [14]; however, a numerical value corresponding to the interaction energy between parabens and ER has not been assigned. Since the size of the whole molecular systems are banned in theoretical calculations, the design of simplified models is necessary to quantify such interactions.

In terms of models design, as was previously mentioned, the phenolic ring is directly involved in the estrogenic activity (more than 80% of the chemicals containing at least one phenolic ring showed estrogenic activity); thus, this molecular moiety should be included in the models in order to simulate the estrogenic interactions. The available crystal structure of the human estrogen receptor ligand-binding domain in complex with 17β-estradiol [15] permits the localization of the main ligand-receptor interactions.

Bearing the above information in mind, the aim of the present study is to carry out a theoretical study (from an energetic and conformational point of view) of the interaction between ER and parabens, using simplified models but high levels of theory, to establish a relative quantification of the interaction of each paraben with ER fragments. With comparative purposes, the interaction between 17β-estradiol and the ER fragments was also studied. Finally, the interaction of potassium cation with parabens, forming potassium salts, is also examined, in order to present a preliminary discussion about the properties of the parabens as antibacterial agents.

2. Methods

2.1. Construction of models

To evaluate the conformational and energetic effects entailed in the 17β-estradiol replacement by parabens inside the receptor domain (ER), paraben-ER complexes were theoretically constructed, taking as starting point the crystal structure of the human estrogen receptor ligand-binding domain in complex with 17β-estradiol (obtained from Protein Data Bank [16] as entry 1a52). The molecular environment

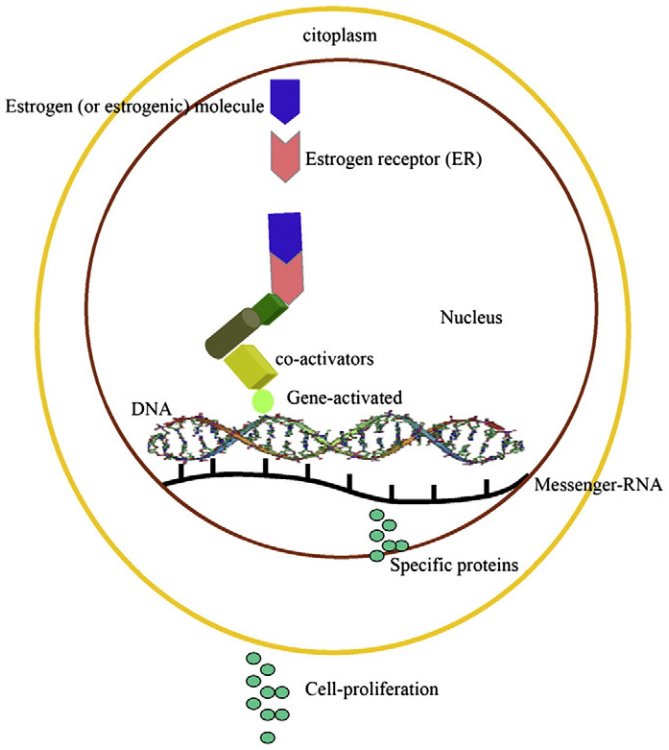

Fig. 3. Estrogen-receptor interaction to trigger gene activation and cell proliferation.

circumscribed in 12 Å, from the 17-β-estradiol toward the periphery, was arbitrarily selected using DeepView/Swiss-Pdb-Viewer v3.7 [17]. The resulting "truncated" structure was used for a first validation of the chosen conformational search method. To use higher levels of theory, simplified models, enclosing only three amino acid fragments interacting with 17β-estradiol (or with each paraben), were defined. When the natural 17β-estradiol is replaced by parabens, two questions come to discussion: a) what are now the conformers of minimum energy? and b) is the magnitude of the paraben-ER interaction energy comparable to that obtained for the natural complex 17β-estradiol-ER?. In order to find an answer to these questions, two levels of theory were used: Conformational analysis by force fields and Density Functional Theory (DFT).

2.2. Conformational analysis

The Monte Carlo statistical method [18], with an algorithm of multiple minima (MCMM) with no limits on the number of variable torsions [19,20] and the OPLS-AA force field [21], considered as the best parameterized for condensed-phase simulations of peptides and proteic systems, were used to perform global searching of the potential energy surfaces (PES) to generate initial structures of minimal energy for further analyses. The conformational analyses were carried out by Macromodel v.7 package [22]. A first validation was made by the treatment of the truncated experimental structure of the human

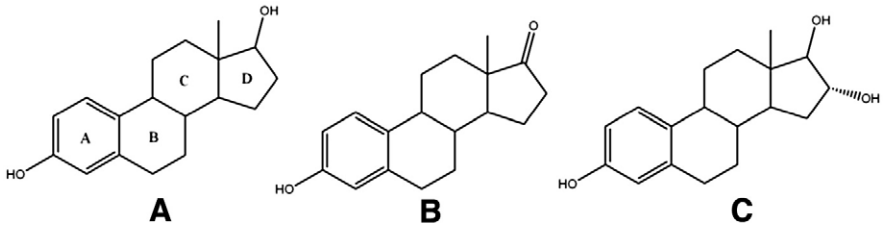

Fig. 2. Estrogens: A: 17β-estradiol; B: estrone; C: estriol.

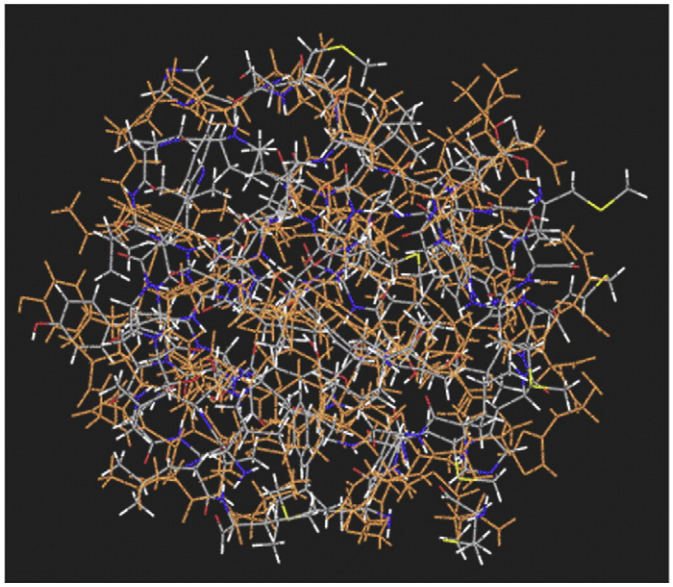

Fig. 4. Cut off structure of Human estrogen receptor ligand-binding domain in complex with 17-β-estradiol. Superposition of crystal structure and minimal energy conformer (orange structure).

estrogen receptor ligand-binding domain in complex with 17β-estradiol. The conformational search calculation was carried out in vacuum. The superposition of both, the conformer of minimum energy and the experimental structure gave a RMSD (root mean square deviation) of 3.7 (see Fig. 4. experimental structure in orange).

In view of the acceptable agreement, MCMM/OPLS-AA level (number of steps = 1500, energy window = 20 kJ/mol) was used to generate all minimum energy conformers for further calculations, including the replacement of 17-β-estradiol by parabens.

2.3. Interaction energy calculations by DFT

The energies of interaction of 17β-estradiol-ER and parabens-ER complexes, were evaluated at higher levels of theory, therefore, simplified models were constructed. The simplified model of interaction shown in Fig. 5 includes an arginine fragment positively charged, a glutamine fragment negatively charged and a neutral fragment of histidine, all of them in contact with 17β-estradiol. In case of parabens, all the interacting complexes were constructed from the complex of Fig. 5, via the replacement of the molecule of 17β-estradiol by each paraben of Fig. 1. The phenolic group and the amino acid fragments were immovable during the construction. The model of Fig. 5 was itself the input corresponding to the 17β-estradiol-ER complex. Even though the 17β-hydroxyl-histidine interaction of estradiol is not present in parabens (due to the lack of ring D), the histidine fragment was maintained in the models to evaluate the assimilation of this fragment in some other region of these estrogenic molecules by any interaction, including H-bonds, as presumably happens when the 17β-estradiol is replaced.

Table 1
Performance of large basis sets to describe the water dimer

Basis set	Interaction energy (kcal/mol)
6-31+G **	−6.99
cc-PVTZ (-f)	−6.53
cc-PVTZ(-f)+	−5.3
Experimental	−5.0±0.1

Once the complexes were constructed, their structures were equilibrated by MCMM/OPLS-AA, to obtain minimal energy conformers for posterior DFT calculations.

Single-point calculations of all the structures previously equilibrated were performed at DFT level with BHandHLYP as functional [23] given that it properly describes the H-bonds [24,25]. The selection of the basis set was made considering the water dimer as a reference, since the experimental energy of interaction by H-bonds is available [26]. The performance of three large basis sets was explored and the results are shown in Table 1.

As can be seen, the result obtained with the correlation-consistent basis set cc-PVTZ(-f)+ [27,28] is in very good agreement with the experimental value. Hence, the single-point calculations to obtain total energies were carried out at BHandHLYP/cc-PVTZ(-f)+ level of theory. Both, the BHandHLYP functional and the basis set cc-PVTZ(-f)+ are included in the program Jaguar 5.5 [29].

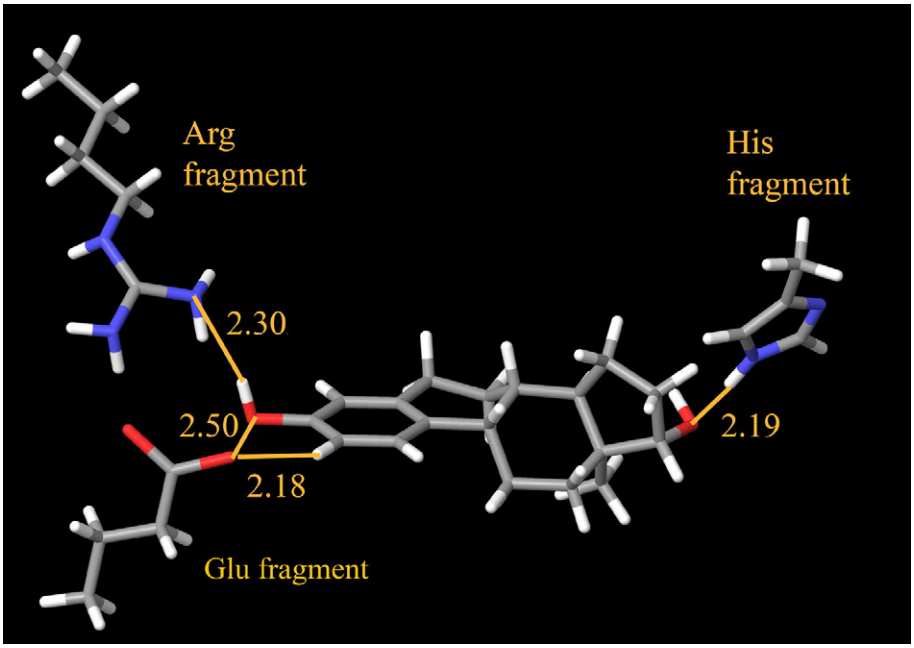

Fig. 5. Simplified model of interaction of 17-β-estradiol with ER fragments (arginine, glutamine and histidine fragments).

The variational method [30] was used to calculate the energies of interaction. The energy of interaction (ΔE) is defined as follows:

$$\Delta E = E_{\text{complex}} - \left(E_{\text{estrogenic molecule}} + E_{\text{fragments}}\right). \quad (1)$$

The term *fragments* in Eq. (1) refers to arginine, glutamine and histidine residues.

2.4. Antibacterial activity of parabens

According with the scheme showed in Fig. 6, all the structures, with *R*=rest of the molecule of the 17β-estradiol or parabens, were built with and without potassium.

The energy of each molecule was obtained following the same procedure described before. Since the base set cc-PVTZ(-f)+ is not defined for potassium, the LACV3P*+ basis set was used for all the molecules instead. The LACV3P basis set is a triple-ζ contraction of the LACVP basis set (see reference [23]), which includes effective core potentials (ECP) on heavy atoms and for the rest of the atoms use 6-311G basis set.

3. Results and discussion

3.1. Binding sites by conformational search

The interacting complex 17β-estradiol-ER (fragments: His, Arg, Glu; Fig. 5) was equilibrated by MCMM/OPLS-AA to obtain the minimal energy conformer showed in Fig. 7.

Even though a very simplified model was constructed, the interacting pattern is preserved after the conformational search, with the same atoms involved in the interaction; nevertheless, the number of H-bonds between the 17β-estradiol and ER fragments is increased and some of them are shorter (e.g. OH–His, from 2.19 Å to 1.7 Å), indicating that, due to the simplified environment, there is an adjustment to re-stabilized the system. Albeit these conformational changes, the total energies of both complexes, experimental and equilibrated, differ only by 12.8 kcal, according with single-point energy calculations at BHandHLYP/cc-PVTZ(-f)+ level of theory.

The same interacting environment was considered for the four parabens under study: methylparaben, n-butylparaben, isobutylparaben and benzylparaben. The input structures were constructed as described in Section 2.2 and conformational analysis calculations were carried out. The minimal energy conformers are shown in Fig. 8 A,B,C, and D.

From Fig. 8A-D is clearly observed that the interaction between phenolic OH groups of parabens and ER fragments, via H-bonds, is very important and is always present no matter what paraben is implicated. These results confirm why the presence of phenolic groups is one of the main reasons to suspect about the estrogenic activity of some chemicals like parabens. Comparing the interaction patterns exhibited by all the parabens with that observed for the 17β-estradiol, they are practically the same. As it was expected, due to the absence of the estrogenic oxygen in 17 position, all the parabens interact with the His fragment in different ways, involving also the phenolic group, but in general, there is a markedly resemblance of 17β-estradiol by parabens.

3.2. Interaction energies

Since one of the aims of the present study is assign a value to the estrogenic activity of parabens, using simplified models but high levels

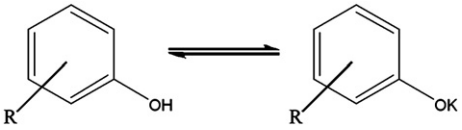

Fig. 6. Antibacterial activity of parabens. Formation of potassium salts.

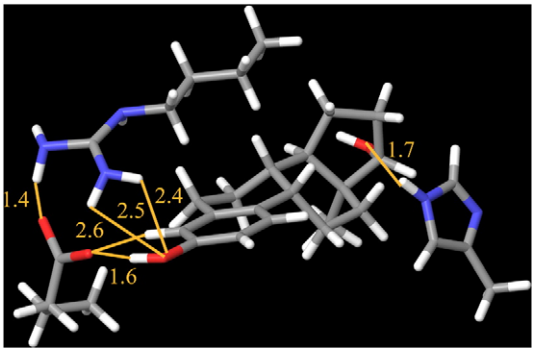

Fig. 7. Minimal energy conformer of 17-β-estradiol-ER complex.

of theory, single-point calculations at BHandHLYP/cc-PVTZ(-f)+ level were carried out, using structures previously equilibrated as inputs. Total energies of all the complexes and molecular fragments were obtained and these energies were used to calculate interaction energies (ΔEs) by means of the variational method (Eq. (1)). The results are shown in Table 2.

From Table 2, the level of theory was able to reproduce the expected scenario in which the interacting complex between 17β-estradiol and ER fragments resulted in the most favorable one. Furthermore, also was reproduced the order of interaction of parabens, taking as a reference the experimental observations obtained by Darbre et al. (see reference [9]), where methylparaben was present at the highest level and benzylparaben was not detected in any tumour extract. From the chromatograms presented by the authors, the peak corresponding to isobuthylparaben is the less intense. Thus, connecting the theoretical results with the experimental observations, the most favorable is the interaction energy between parabens and ER fragments, the higher their estrogenic activity will be.

From the theoretical interaction energies, the order of estrogenic activity of parabens is: methylparaben > nButylparaben > benzylparaben > isobutylparaben, being methylparaben 1.2 times more estrogenic than isobutylparaben.

At least in a relative way, these theoretical results could be useful to assign labels of estrogenicity of other parabens or chemicals with similar structure by interpolation of calculated interaction energy values, through simple models. In this context, molecules with interaction energy values >200 kcal, surrounded by the same environment (the same ER fragments), could be considered highly suspicious as estrogenic molecules.

It is noticeable from Table 2 that the interaction energy of the complex 17-β-estradiol-ER fragments is particularly high in comparison with the rest of the complexes (around 64 kcal). In this respect, two interpretations can be done: 1) The energetic difference corresponds to a real picture where the chance of replacement by mimics of estrogens is very low; and 2) Such energetic difference is the result of the simplified model itself, where the 17β-estradiol, as the most voluminous molecule, takes advantage of the less crowded surrounding, reducing the sterical hindrance, which is energetically favorable for the formation of the complex 17β-estradiol-ER fragments.

Since the presence of parabens in tumors has been certainly confirmed, the overestimation of the interaction energy can be adjudge to the model, in spite of the good agreement with the tendency experimentally observed.

3.3. Antibacterial activity of parabens

As it was mentioned before, parabens are not only estrogenic mimics, but also act as preservatives, disrupting the normal potassium gradient at cellular membrane level [2,3]. In order to explore the relative energies involved in the formation of potassium salts by parabens, the molecules

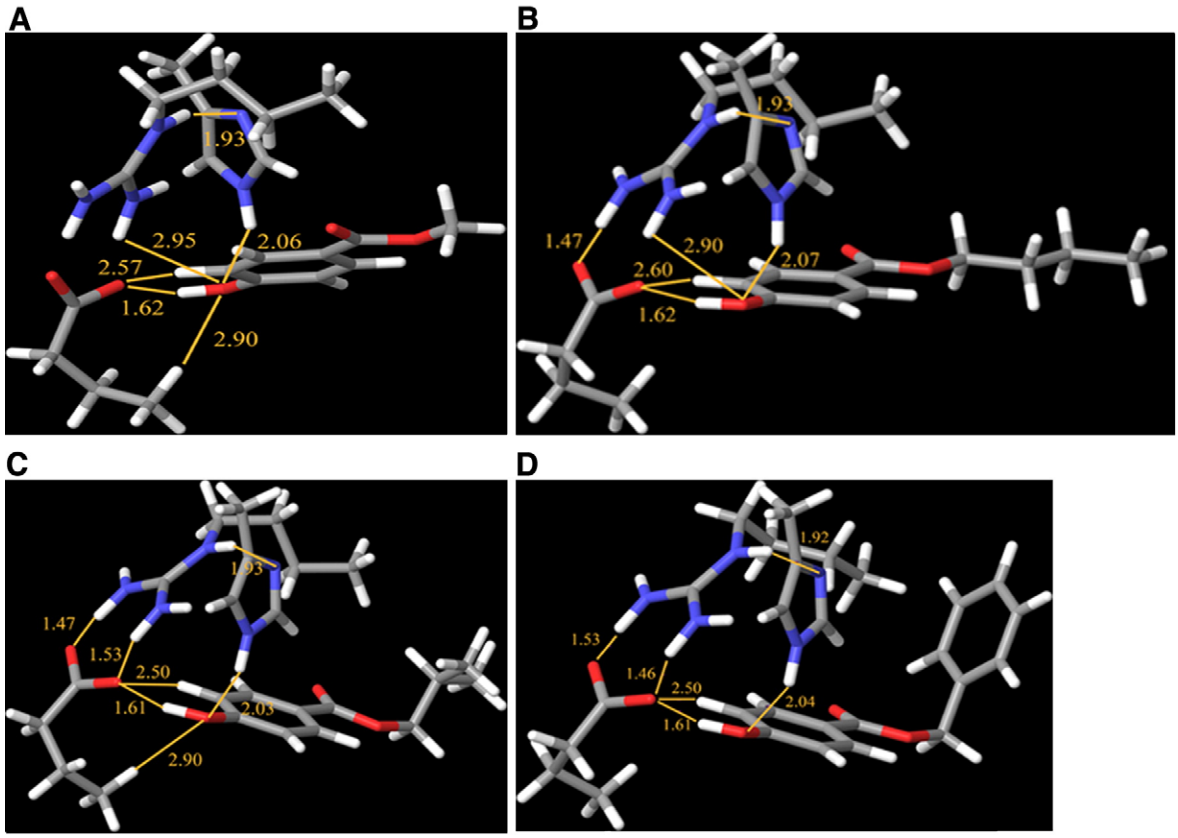

Fig. 8. A Minimal energy conformer of methylparaben-ER complex. B Minimal energy conformer of nbuthylparaben-ER complex. C Minimal energy conformer of isobuthylparaben-ER complex, D Minimal energy conformer of benzylparaben-ER complex.

with and without potassium were calculated. After the equilibration with MCMM/OPLS-AA, total energies were obtained by single point calculations at BHandHLYP/LACV3P*+ level of theory (see Table 3). These calculations were carried out in vacuum since only a first evaluation of relative energies was aimed. Further thermo chemical calculations in aqueous media will be address in future studies. According to the optimized structures, the formation of potassium salts at phenolic OH groups do not perturb the planarity (aromaticity) of the aromatic rings. A rapid exploration of possible sites of potassium-coordination was made, considering the structures A and B showed in Fig. 9.

Table 2
Single-point energy calculations at BHandHLYP/cc-PVTZ(-f)+ level of theory

Complex	Interaction energy (kcal)
17-β-estradiol-ER fragments[a]	−276.729
Methylparaben-ER fragments	−212.391
n-Butylparaben-ER fragments	−211.713
Benzylparaben-ER fragments	−183.961
Isobutylparaben-ER fragments	−169.738

a: fragments: Arg(+), Glu(−), His.

Table 3
Relative energies of potassium salts formation

R-Ph-OH[a]	R-Ph-Ok[a]	ΔE (Ha)[b]
17-β-estradiol −842.176	17-β-estradiol-K −868.888	−26.7
Methylparaben −530.400	Methylparaben-K −557.271	−26.8
n-Butylparaben −647.014	n-Butylparaben-K −673.696	−26.6
Benzylparaben −759.058	Benzylparaben-K −785.770	−26.7
Isobutylparaben −647.025	Isobutylparaben-K −673.738	−26.7

a) Single point energy calculations at BHandHLYP/LACV3P*+level of theory.
b) 1 Ha=627.15 kcal.

All the structures in the form A were more stable than structures B by more than 9 kcal/mol.

From Table 3, regardless of the overestimated values of energy, it is observed that all the molecules, including 17β-estradiol, form potassium salts at very similar energetic cost; however, the salt formation by methylparaben is more feasible.

4. Conclusions

The approach applied in the present study – simplified models-high levels of theory – allowed us to reproduce the experimental order of estrogenic activity observed for some parabens (methyl-, nbutyl-, isobutyl- and benzyl paraben). The importance of the results is that, by simple calculations of interaction energies, the estrogenic activity of other chemicals could be estimated by interpolation, to determine if it is more or less estrogenic than methylparaben for instance. Both, the Monte Carlo method for conformational analyses and the force field OPLS-AA showed very good performance to search minimal energy conformations of the molecular systems under study. The use of the DFT functional BHandHLYP, recommended to treat H-bonding

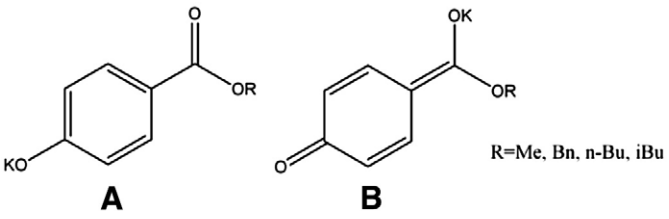

Fig. 9. Possible sites of potassium-coordination with parabens.

complexes, is justified since that kind of intermolecular interaction, via phenolic groups, was the most important.

According with all the results, the methylparaben is the most active of the parabens, not only in the interaction with fragments of the ER (estrogenic receptor) but also in the formation of potassium salts; that is, methylparaben is the most estrogenic and the best antibacterial agent among the other parabens.

Acknowledgment

This research was carried out with the support of grant IN-100906 from DGAPA to the acquisition of software and hardware.

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