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Theoretical design of dendrimeric fractal patterns for the encapsulation of a family of drugs: salicylanilides

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Abstract—Four dendrimeric fragments (FPs) were designed to encapsulate a family of drugs known as salicylanilides (importantly acaricides/anthelminthics), mainly by H-bonding. The experimental system: PAMAM–DBNP (2,6-dibromo-4-nitrophenol) was also calculated as a reference. The efficiency of encapsulation is related to the presence of functional groups like amide and alcohol, the flexibility of the aliphatic chains, and efficient pre-organization before the encapsulation. All the geometry optimizations were carried out at DFT/LAV3P* level of theory. Two hybrid functionals were tested: B3LYP and BHandHLYP. The last one shows improved performance in describing close contacts as well as better agreement with experimental observations for the complex PAMAM–BDNP.

1. Introduction

Dendrimers, studied so far and for more than two decades, are described as well-defined, highly branched macromolecules. Several research groups have discussed the great potential of dendrimers as advanced materials in many different areas including medicine[1,2] and catalysis,[1–3] among others. Particularly, the use of dendrimers as drug delivery vehicles has attracted much attention. Due to their globular structures and internal cavities, dendrimers resemble the globular proteins observed in nature with a remarkable difference: the internal cavities of proteins are the natural consequence of self-stabilization processes, while in the case of dendrimers, such cavities can be designed in a rational way. Such possibility of designing has been a starting point of numerous studies, trying to find 'the best' fractal patterns† for specific applications.[4]

In the pharmaceutical area, the most important characteristic of any drug is its medical efficiency and, unfortunately, it often drops because, even though the drug reaches the target site, it occurs in very small amounts mainly due to solubility problems.[5] Therefore, the development of drug carriers has been of great importance and many works have been done so far in an interdisciplinary way.

Some polymers and copolymers, as well as micelle vehicles, have been already used as drug delivery systems; however, they have had limited applications due to their polydispersities, poor stability, and aggregation problems when the solvent is not the appropriate one.[6] In this sense, features like monodispersity and inherent micelle-like structure of dendrimers, among other properties, justify their attractiveness in pharmaceutical and medicinal applications.[7]

One of the most studied dendrimers, so-called PAMAM (poly(amidoamine)),[8] has been already tested as host for some biologically important molecules like quinoline, quinazoline, and nicotine, as well as for a variety of drugs.[9] Since favorable biological properties like low in vitro and in vivo toxicities, low immunogenicity (degree to which a substance induces an immune response), and known biodistribution were observed for PAMAM starburst dendrimers,[10] this family of molecules has been systematically chosen to be tested as drug delivery systems. Thus, amine- and ester-terminated PAMAM dendrimers were used to increase the solubility of drugs like ibuprofen,[5] nifedipine, salicylic acid, and 2,6-dibromo-4-nitrophenol.[11] PEG-attached PAMAM dendrimers of third and fourth generations were designed to encapsulate anticancer drugs like adriamycin and methotrexate,[12] with an efficiency depending on the dendrimeric generation and the flexibility of the chains of the poly(ethylene glycol) grafts. Other drugs like piroxicam,[13] anti-inflammatory drugs such as ketoprofen, diflunisal, and naproxen[14] as well as nicotinic acid[15] have been also encapsulated by PAMAM dendrimers.

Beyond the PAMAM family, so far explored, the challenge now is the designing of new and more specific dendrimeric

Keywords: Dendrimers; Salicylanilides; DFT calculations; H-bonding; Host–guest complexes.
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† Fractal pattern in this context is defined as each repetitive unit forming the branches of a dendrimer.

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fractal patterns to be used as hosts, including a more detailed structural description of the inclusion complexes and the interactions involved in their formation. Interesting examples of different designs of delivery systems can be found in the literature.[16]

1.1. Specific problem to be solved

In veterinary, a set of high-spectral drugs, known as salicylanilides (Fig. 1), are used as acaricides and antihelmithycs. These drugs are highly active against adult flukes and immature flukes[17] such as *Fasciola hepatica* and *Fasciola gigantica* as well as cestode infection.

In spite of their activity, these hydrophobic drugs lose effectiveness due to their low solubility; therefore, an encapsulation process appears as a very attractive alternative. Basically three ways of interaction have been described considering dendritic hosts: (i) physical entrapment, (ii) covalent attachment onto the dendrimeric surface (dendrimer–drug conjugates), and (iii) non-covalent binding of drug molecules inside the dendrimers by H-bonding and/or hydrophobic interactions. It has been observed that the host designs involving this last option (H-bonding) represent the most suitable way, considering not only the ease to form complexes but also the convenience for the posterior delivery process,[18] since no covalent bonds have to be broken.

The computational chemistry applied to the host's design emerges as an excellent tool to evaluate different combinations of functional groups and lengths of fractal patterns, which can be used later as building blocks to construct dendrimeric hosts, more specific to encapsulate particular guests.

In the present study, taking advantages of computational tools, different fractal patterns (molecular fragments) were rationally designed to encapsulate molecules of salicylanilides, considering H-bonding as one of the main interactions. The interaction energies were evaluated in order to find 'ideal' fractal patterns for the posterior construction of dendrimeric architectures. The conformations of the designed fractal patterns (FPs) were obtained in gas-phase as well as in aqueous medium to explore the pre-organization condition of these hosts (prior to encapsulation processes) in a more realistic environment. For comparative purposes, the encapsulation system formed between a PAMAM derivative and 2,6-dibromo-4-nitrophenol (*DBNP*) (antifungal/antibacterial agent),[19] was considered here as an experimental reference system (see Section 3.2).

2. Computational details

All the initial structures (FPs, drugs, and the inclusion complexes formed between them) were equilibrated by conformational search (Force Field OPLS2001),[20] using the Monte Carlo statistical method[21] included in the Macromodel software. The algorithm of Monte Carlo Multiple Minima (MCMM)[22] without limits on the number of variable torsion allowed in the search was used. In all the cases redundant conformers (two to four splice structures) were found to have the lowest energy, hence they were grouped to be taken as single minimal energy conformers to carry out subsequent calculations. The rejected second conformers (clearly different in structure) have higher energy (3–4 kcal/mol). The geometry optimization of all minimal energy conformers was carried out at B3LYP/LAV3P* level of theory. The LAV3P* basis set, included in the Jaguar 5.5 program,[23] considers effective core potentials (ECPs) generated to replace the innermost core electrons for third-row (K–Cu), fourth-row (Rb–Ag), and fifth-row (Cs–Au), integrating relativistic effects (important for heavy atoms) and reducing in this way the computational efforts comparing with all-electron calculations.[24] Natural charges were calculated in gas phase by Natural Bond Orbital analysis.[25] For comparative purposes (see Section 3.6), another hybrid functional, BHandHLYP (exchange: 50% exact HF exchange, 50% Slater local exchange functional; correlation: Lee–Yang–Parr local and non-local functional[26]) was used instead of B3LYP, for the calculation of interaction energies, considering only one of the host molecules and its interaction with all the guests under study.

The conformational search, as well as the geometry optimization of the designed hosts was also carried out in aqueous medium to evaluate the conformational changes due to the environment. The solvated molecules were calculated using the self-consistent reaction field method with its own Poisson–Boltzmann solver,[27] which represents the solvent as a layer of charges at the molecular surface (providing in this way a dielectric continuum boundary). These solvent point charges are returned to a SCF algorithm to calculate

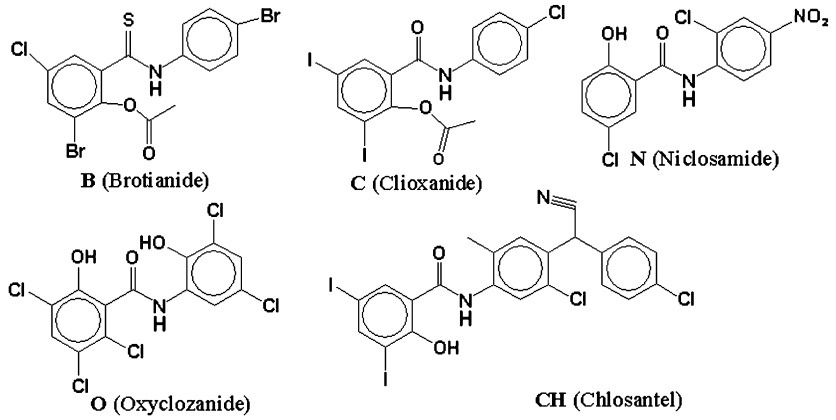

Figure 1. Salicylanilides (capital letters in bold style will be used as labels).

again the wave function incorporating the solvent charges. The process is repeated until the convergence is achieved.

3. Results and discussion

3.1. Design of fractal patterns

Twenty different fractal patterns (FPs) were designed, incorporating some polar functional groups (e.g., –NHCO, –NHR, ROH, –NHOH, etc.) into their chains, in order to induce the non-covalent interactions like H-bonds. The length of the aliphatic chains was also modified since it was observed earlier that the flexibility is a critical factor to take into account when encapsulation hosts are designed.[4]

All the constructed fractal patterns, as well as their complexes with the salicylanilides, were minimized by conformational analysis (MCMM). A first discrimination of fractal patterns was carried out, based on the number and directionality of H-bonds formed with the encapsulated drugs in a range of distances from 1.5 to 2.5 Å. It was observed that, as the aliphatic chains in the FPs become more flexible, the formation of H-bonds is favored. The most efficient functional groups were the amide, alcohol, and sulfonic acid interacting with the drugs forming H-bonds. Thus, after rational elimination, four of the most suitable FPs to encapsulate the drugs under study are illustrated in Figure 2.

For further analyses (including the calculation of host–guest interaction energies), the geometry optimizations of the FPs, the salicylanilides, and the host–guest complexes formed between them were carried out at B3LYP/LAV3P* level of theory. The interaction energies were calculated according to the variation method,[28] as the difference between the energy of the host–guest complex and the sum of total energies of their isolated parts ($\Delta E = E_{complex} - (E_{fractal\ pattern} + E_{drug})$).

Table 1 shows the interaction energies (in kcal/mol) between FPs and drug molecules.

From Table 1, the efficiency of encapsulation of FPs follows the next general order: FP1>FP2>FP3>FP4.

All the interaction energies between FPs and drugs are schematically plotted in Figure 3. With the exception of the complexes FP4-**B** and FP4-**N**, all the interactions resulted favorable. In general, the flexibility and chemical nature of

Table 1. Interaction energies (kcal/mol) calculated at B3LYP/LAV3P* level of theory

FP	1	2	3	4
Brotianide	−17.431	−11.721	−0.383	8.130
Clioxanide	−23.255	−9.973	−5.626	−11.424
Chlosantel	−31.121	−25.364	−18.465	−10.450
Niclosamide	−24.304	−30.668	−9.627	0.090
Oxyclozanide	−50.362	−43.438	−34.276	−36.501

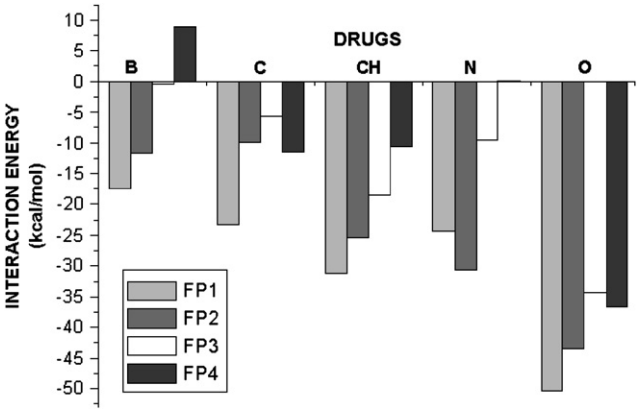

Figure 3. Interaction energies of FPs–drugs.

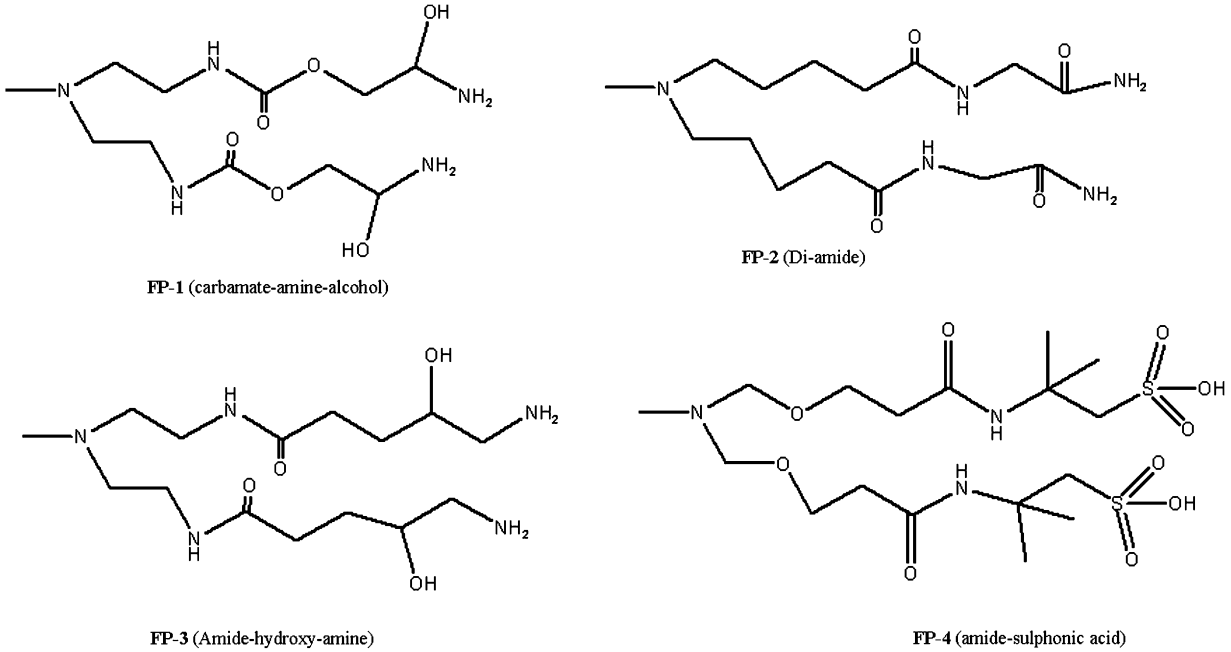

Figure 2. Suitable fractal patterns (FPs) to interact with salicylanilides.

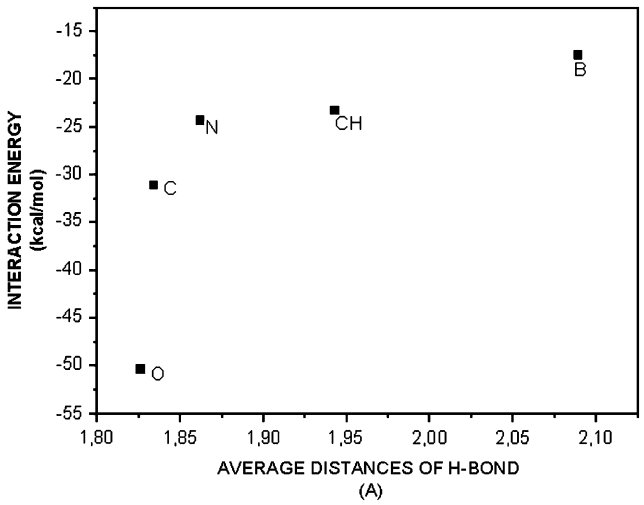

Figure 4. FP1–drug complexes (**O**: oxyclozanide; **C**: clioxanide; **N**: niclosamide; **CH**: chlosantel; **B**: brotianide).

the designed FPs were appropriate to shelter the salicylanilides in a specific way.

A clear relationship was observed between the H-bonding distances and the interaction energies. The average H-bond distances versus the interaction energies of the FP1–drugs complexes are plotted in Figure 4. Even though a linear relationship was not observed, the tendency is straightforward: the shorter is the distance, the more favorable is the interaction energy between the host and the guests.

The correlation observed in Figure 4 is an evidence of the important role of H-bonding as a driving force for the complex formation. Due to their high directionality and the amplest range of strength of interaction (e.g., $[F–H–F]^-$ and $NH_3–H–Cl^-$; ~40 and ~15 kcal/mol, respectively), the H-bonds are present in many examples of molecular tectonics where the formation of molecular assemblies is directed by them.[29] The assemblage by H-bonding is illustrated in Figure 5 where the encapsulation of the drugs by the fractal pattern FP1 is shown.

An additional important remark about the H-bonding is that the H-bond length is more important than their number.

Considering such short distances, in any host–guest complex there is, to some extent, a superposition of molecular orbitals. These orbitals are theoretically described by a basis set. Since the complete description of each orbital of each part of the complex by a basis set is operationally difficult, a superposition of basis sets to achieve the complete description occurs, resulting in the error known as the basis set superposition error (BSSE), which overestimates the interaction energy.

In order to illustrate the magnitude of the BSSE, it was calculated only for the complexes formed between FP1 and the drugs. The standard estimation was done by the counterpoise correction of Boys and Bernardi.[30] In Table 2 are shown the corrected interaction energies (final column) and the magnitude of the error due to the superposition of the basis when the complexes are formed.

Even when the calculated BSSE values are significant (for comparison see Ref. 31), the stability order of the complexes is maintained since the error is quite similar in all the cases, and, even considering this error, the interaction energies are still favorable.

In Section 3.2 an experimental encapsulation system reported in the literature is described and the host–guest interaction energy calculations are presented in order to validate the used theoretical methods.

3.2. Experimental reference system: PAMAM–DBNP

In 2003 Twyman et al. (see Ref. 19a) reported a set of neutral water-soluble PAMAM derivatives with hydroxyl terminal groups (e.g., Fig. 6) as potential drug carriers.

Some water-insoluble molecules were tried to be encapsulated, particularly by the dendrimer with 24 terminal OH groups (Gen 1.5). The insoluble antifungal/antibacterial compound 2,6-dibromo-4-nitrophenol (DBNP) was encapsulated and totally solubilized. The binding mechanism proposed by the authors involves ion-pairing interactions with the internal tertiary nitrogens.[32] No H-bonding interactions were observed.

Trying to reproduce the unambiguous complexation manifested by the infinite solubilization of DBNP (independent of the interaction mechanism), a fragment of the PAMAM dendrimer (without hydroxyl terminal groups, not involved anyway in the encapsulation process) was constructed and its host–guest complex with DBNP was considered. To avoid interactions with amino-terminal groups, the terminal amines were di-substituted with methyl groups. The same theoretical methodology described above for the designed fractal patterns and their complexes with salicylanilides was used to calculate the reference system. Figure 7 shows the structure of the model inclusion complex in vacuum (pure host–guest interaction): B3LYP/LAV3P* model (Table 3) was able to reproduce the encapsulation of the DBNP by the PAMAM fragment since favorable interaction energy (−4.442 kcal/mol) was obtained. To compare the encapsulation efficiencies, the FP1–DBNP complex is also calculated and the interaction energy is included in Table 3. The FP1 interacts more efficiently with DBNP than the PAMAM fragment does, by H-bonding, which is desirable in terms of facilitation of the posterior release of the guest molecules. The difference observed in energies of interaction can be taken as an indication for the presence of more interacting sites in the designed fractal pattern.

Taking into account the presence of aliphatic amines (terminal-primary amines and internal-tertiary amines) as part of the fractal patterns FP1, FP2, and FP3, and also present in the PAMAM reference system, their possible protonation in aqueous media, thus competing with the encapsulation process, is an issue that will be discussed below. In the case of the fractal patterns FP1, FP2, and FP3, the primary amines as terminal groups are irrelevant since all these fractal patterns were designed as simple models to be eventually incorporated, as building blocks, in a dendrimeric framework, hence, such terminal groups will be totally substituted to give rise to dendrimeric drug carriers. As in the PAMAM

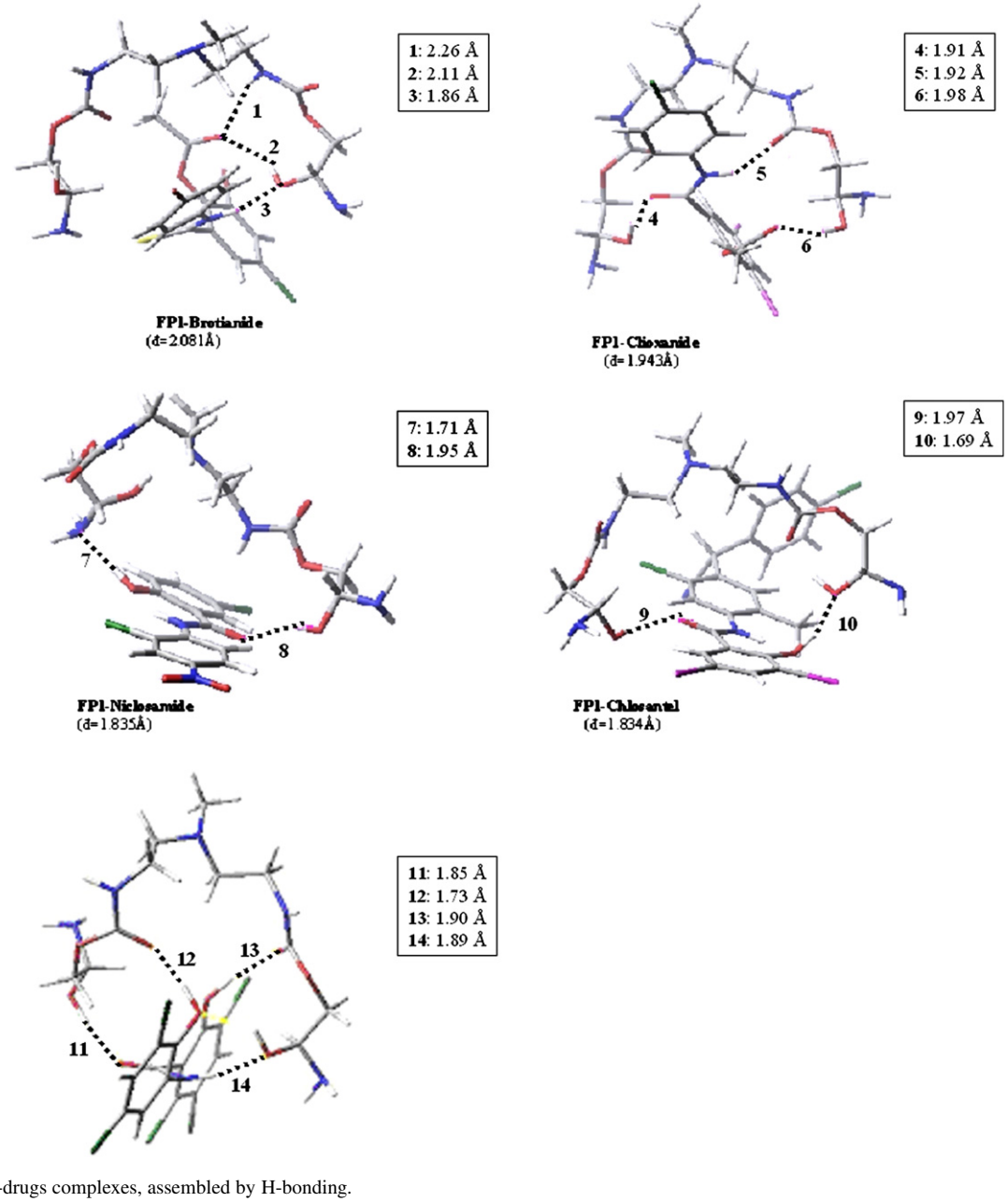

Figure 5. FP1-drugs complexes, assembled by H-bonding.

Table 2. BSSE and corrected interaction energies (kcal/mol) for FP1–drugs complexes

FP1–drug	BSSE (kcal/mol)	E_{corr} (kcal/mol)
Brotianide	−10.17	−7.25834731
Clioxanide	−10.32	−12.93569904
Niclosamide	−6.65	−17.65654303
Chlosantel	−9.53	−21.59453124
Oxyclozanide	−12.01	−38.35508542

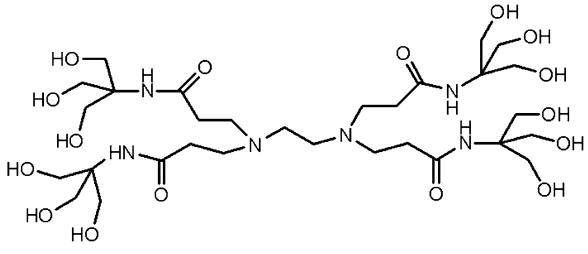

Figure 6. PAMAM derivative.

reference system, as it was mentioned above, the terminal amino groups were methyl-substituted in order to avoid any possible interaction. Thus, the remaining aliphatic amines, inside the dendrimer, in both FPs and PAMAM reference systems, are all tertiary amines. In order to ensure that the protonation of these internal amines by water can be discarded as possible competing event, the equilibrium concentration of protonated amines was estimated using pK_a values of the conjugated acids of tertiary amines (pK_a data compiled by R. Williams) as well as the ionic product K_w. As a result (pK_a value of the conjugated acid of trimethylamine (pK_a=9.76) and $K_w=10^{-14}$), the fraction of free tertiary amine in aqueous solution is more than 99%. It is

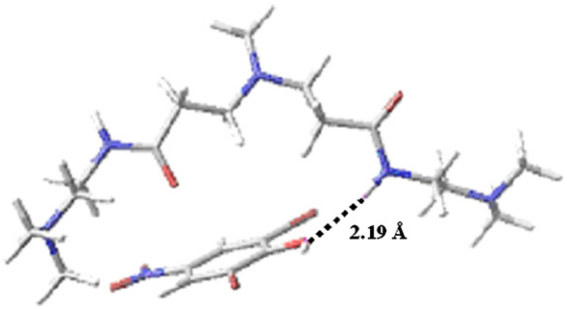

Figure 7. Reference system: model inclusion complex PAMAM–DBNP in vacuum.

Table 3. Reference system calculated at B3LYP/LAV3P* level of theory

Reference system	Interaction energy (kcal/mol)	BSSE (kcal/mol)	E_{corr} (kcal/mol)
PAMAM–DBNP	−9.5716	−5.1290	−4.4425
Comparison			
FP1–DBNP	−18.2102	−4.4400	−13.7702

important to mention that, as the dendrimeric drug carriers achieve globular structures at higher generations, the discussion about possible protonations becomes even less important due to the reduction of solvent accessibility. Soluble globular macromolecules with a hydrophobic interior, to shelter the hydrophobic drugs are the most probable scenario.

3.3. Electrostatic maps

Since H-bonding is involved, the electrostatic potential in aqueous medium was mapped onto a surface of electron density to get a description of the electrostatic characteristics of both drugs and FPs (Fig. 8a and b, respectively). The colors toward blue and red represent positive and negative regions, respectively.

Regarding the results of interaction energies from Table 1, brotianide and clioxanide were the worst drugs to encapsulate by the hosts and they are actually the drugs whose electrostatic potential surfaces show little 'variety of regions' to interact: clioxanide exhibits mainly well defined negative zones and brotianide does not even exhibit defined regions at all. The other three drugs have both, negative and positive well defined regions, which increase the interaction possibilities from the electrostatic point of view.

A similar situation was found in the case of the FPs (Fig. 8b). The FP4 was the poorest host for the salicylanilides and it is precisely the one with fewest variety of regions at the electrostatic surfaces.

Thus, specially when H-bonding (electrostatic in nature) is involved, the calculation of the electrostatic surfaces can be very useful to visualize the sites of interaction in both hosts and guests in order to predict their affinities.

3.4. Pre-organized conformations

When a host–guest complex is formed, there are several operating factors that modulate the affinity of the interaction. The shape, size, conformation, and charge distribution of the host entities are key 'controllers' to take into account when a design is carried out. In this sense, it is very important to examine the pre-organization of the designed fractal patterns, before the complexation occurs, starting from their conformations.

The optimized conformations of the FPs in both gas phase and solution (water) phase are shown in Figure 9a and b.

This schematic comparison shows that in the cases of FP1 and FP2 there are no big differences in conformation when the solvent is present, upholding their cavity shapes to shelter the guest molecules.

An orientation of the carbonyl groups is observed in the case of solvated FP2, pointing the oxygen atoms toward the interior of the cavity, but still maintaining the enough room to encapsulate one drug molecule. This behavior is convenient in terms of encapsulation in aqueous media since the host conformations do not change drastically, preserving a relative independence of the environment. Undoubtedly the drugs, hydrophobic in nature, will prefer any environment less polar than water, such as the interior of the FPs.

Analyzing the other two FPs (Fig. 9b), particularly the FP3 showed a notable change when the structure is exposed to solvent, evidencing its affinity to polar environments. The FP4, similar to FP1 and FP2, essentially maintains its conformation in both media. Thus, the inspection of the conformations leads to an intuitive idea of the accessibility inside the cavities of the designed fractal patterns, which coincides with the efficiency of encapsulation stated before in terms of the energy of interaction. The fractal pattern labeled as FP3 showed a solvated structure with the lowest level of pre-organization and the energetic trade off for that is reflected in the unfavorable interaction energies with some of the drug molecules, compared with other fractal patterns. Therefore, a compromise between the number of sites of interaction and the pre-organization conditions must be settled in order to have better hosts for specific applications.

The flexibility of the dendrimeric architectures has to be highlighted (Fig. 9a and b), which is notoriously different from that observed for conventional host systems like cyclodextrins, cyclophanes, calixarenes, etc.

3.5. NBO analysis

From the analysis of the atomic charges (NBO calculations) it is possible to locate, not only the donor sites of the host molecules but also the hydrogen atoms with a deficit of charge, susceptible to form H-bonds with some electronegative atom from the guest molecules (salicylanilides in this case), increasing in this way the sites of interaction between the drugs and the fractal patterns (see Fig. 10).

Thus, well pre-organization, suitable electrostatic environment, flexibility, and the negative charge distribution lying on the heteroatoms are some of the features founded in the designed FPs. Specially the fractal pattern FP1 brings together most of the favorable features and it is the host interacting with the highest efficiency with the salicylanilides.

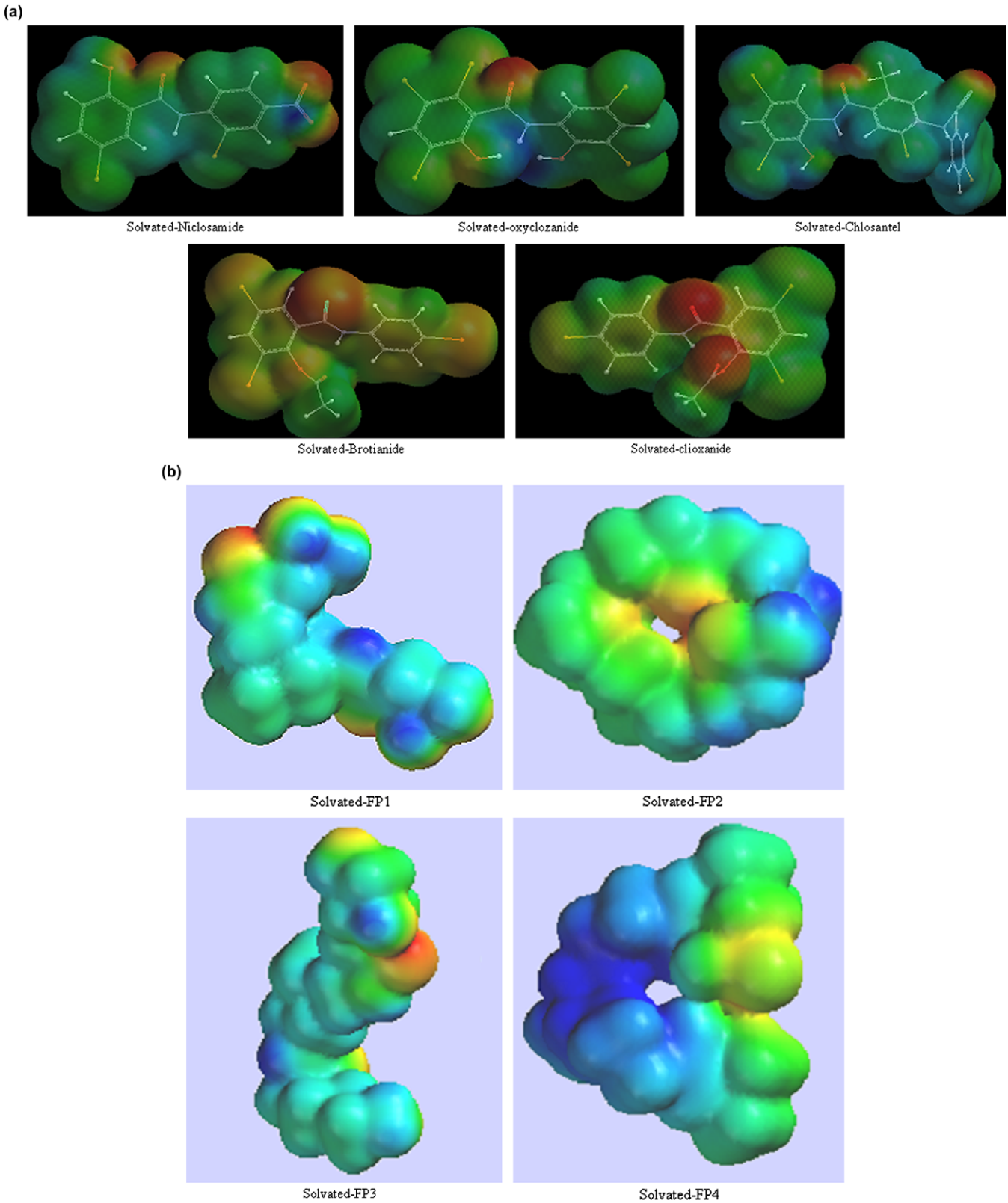

Figure 8. Electrostatic potential surfaces of (a) solvated salicylanilides; (b) solvated FPs.

3.6. DFT functionals: B3LYP versus BHandHLYP describing H-bonding

The theoretical treatment of non-covalent interactions has been widely discussed and some methods have been very successful reproducing both weak and strong interactions.[33] Within the DFT framework, the hybrid functional labeled as BHandHLYP, developed in 1993, shows good performance, in describing the non-covalent interactions with an important electrostatic contribution.[34] This functional, with higher

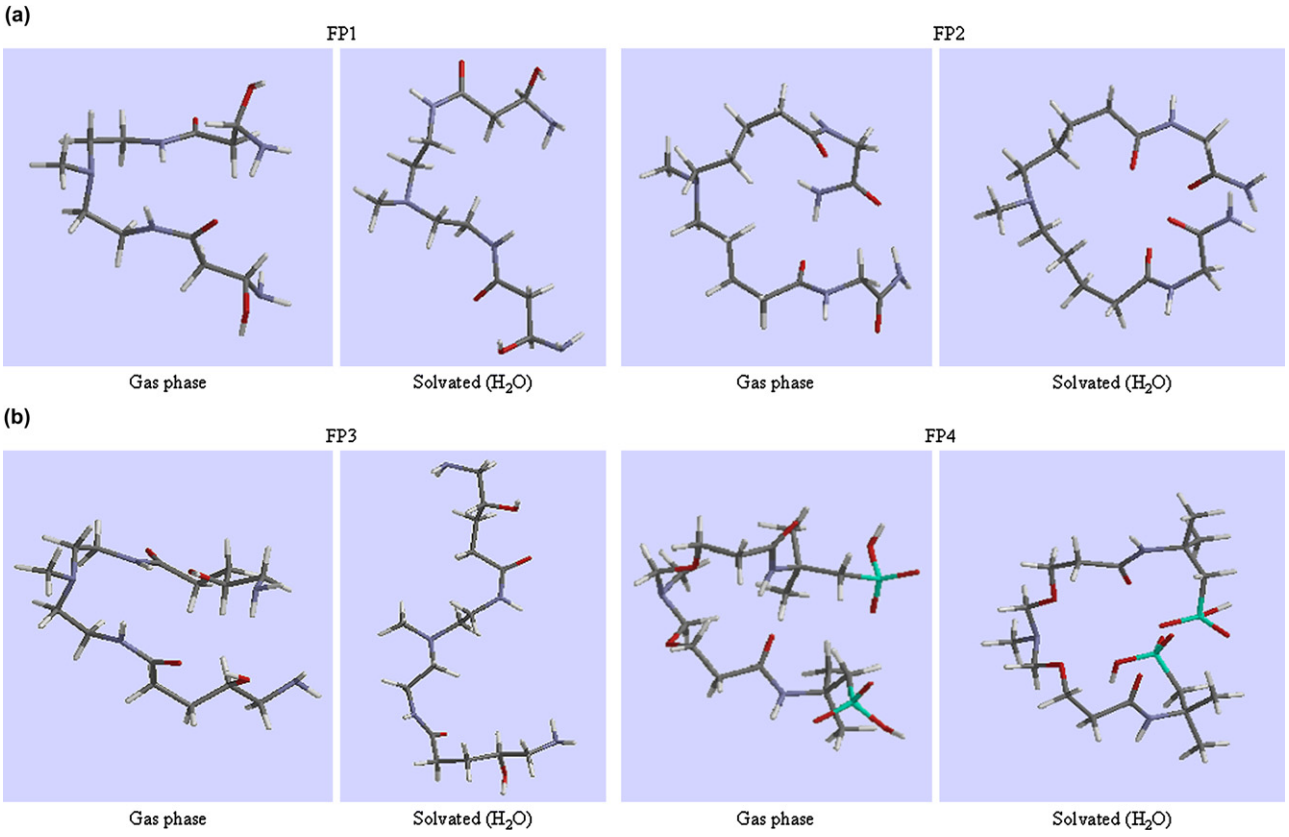

Figure 9. Conformations of fractal patterns in gas phase and aqueous phase: (a) FP1 and FP2; (b) FP3 and FP4.

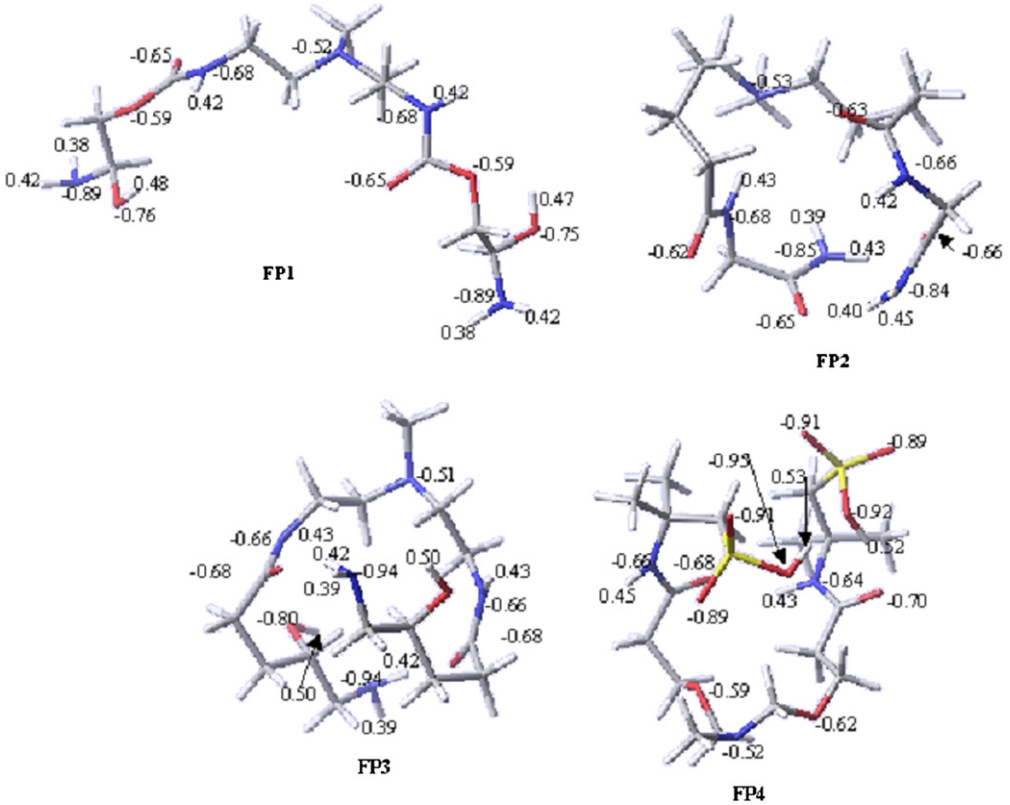

Figure 10. Atomic charges from the NBO analysis.

percent of Hartree–Fock (exact) exchange contribution (50%) has shown superior, in comparison with other hybrid functionals like B3LYP (with 20%), particularly reproducing H-bonding interactions. A comparison of these two hybrid functionals (B3LYP and BHandHLYP) was carried out by the calculation of interaction energies of the host–guest systems formed between the fractal pattern FP1 and the studied drugs, using the same basis set as it is shown in Table 4 (BSSE correction was included). The corrected energies are those in parentheses.

Table 4. FP1–drugs interaction energies (kcal/mol)

	B3LYP/LACVP*	BHandHLYP/LACVP*
Brotianide	−17.431 (−7.258)	−28.515 (−19.052)
Clioxanide	−23.255 (−12.935)	−36.426 (−24.459)
Niclosamide	−24.304 (−17.656)	−38.233 (−28.864)
Chlosantel	−31.121 (−21.594)	−45.847 (−33.750)
Oxyclozanide	−50.362 (−38.355)	−35.542 (−23.534)
PAMAM–DBNP	**−9.5716 (−4.4425)**	**(−15.1215)**

In parentheses are included the corrected interaction energies.

As seen from Table 4, except for the complex FP1–oxyclozanide, the interaction energies become 30–40% more negative when the functional BHandHLYP is used (roughly the same percentage corresponding to the 'extra' Hartree–Fock exchange contribution considered in this functional). According to the results obtained for the experimental system PAMAM–DBNP (in bold style at the end of Table 4), the functional BHandHLYP reproduces the experimental observation even better than B3LYP since a more negative energy was obtained, which is more in accordance with the infinite solubility of the hydrophobic molecule of DBNP after its encapsulation. The H-bond distances are shorter when the BHandHLYP functional is used in the calculation, comparing with those obtained with the B3LYP functional (see Table 5). Clearly, the treatment of exchange-correlation contributions by the functional BHandHLYP is better than that obtained by B3LYP, since the short distances (below 3 Å) correspond to more favorable interaction energies.

The interaction energies of the FP1–drug complexes show a polynomial (second-order) fit as a function of the exchange-correlation contribution (XC). The plots in Figure 11

Table 5. Number of H-bonds and their average distances (Å) in FP1–drugs complexes

	B3LYP	BHandHLYP
Brotianide	(3) 2.089	(3) 1.933
Clioxanide	(3) 1.943	(3) 1.836
Niclosamide	(2) 1.862	(2) 1.779
Chlosantel	(2) 1.834	(2) 1.744
Oxyclozanide	(5) 1.889	(5) 1.824

In parentheses are expressed the number of H-bonds.

make evident that the treatment of the XC energetic term is the main difference between the two hybrid functionals BHandHLYP and B3LYP. While the functional BHandHLYP (Fig. 11a) enclose all the FP1–drug complexes with a very good fit (R^2: 0.997), the functional B3LYP (Fig. 11b) do not describe the complete series (oxyclozanide did not fit). The calculated interaction energies as a function of all other energetic contributions showed a good linear fit, regardless of the hybrid functional used.

Therefore, although both functionals describe nearly the same order of stability of the complexes under study, the functional BHandHLYP showed two important skills: a better description of close contacts and a wider spectrum of systems that it can depict.

4. Conclusions

Using computational chemistry tools, four dendrimeric fragments (fractal patterns, FPs) were designed as simple models to encapsulate a family of drugs known as salicylanilides (important acaricides/antihelmithycs), mainly by H-bonding. The incorporation of different polar functional groups as part of the FPs as well as the modification of the length of the aliphatic chains were both aspects taken into account to get good candidates as hosts for the drugs under study. There is a compromise between flexibility and sites of interaction by polar groups but generally speaking, as the aliphatic chains in the FPs become more flexible, the formation of H-bonds is favored. The pre-organization of any host is an essential attribute to participate in encapsulation events; a bad pre-organization of the hosts results in a poorer interaction with the guests. In this terms, the studied fractal

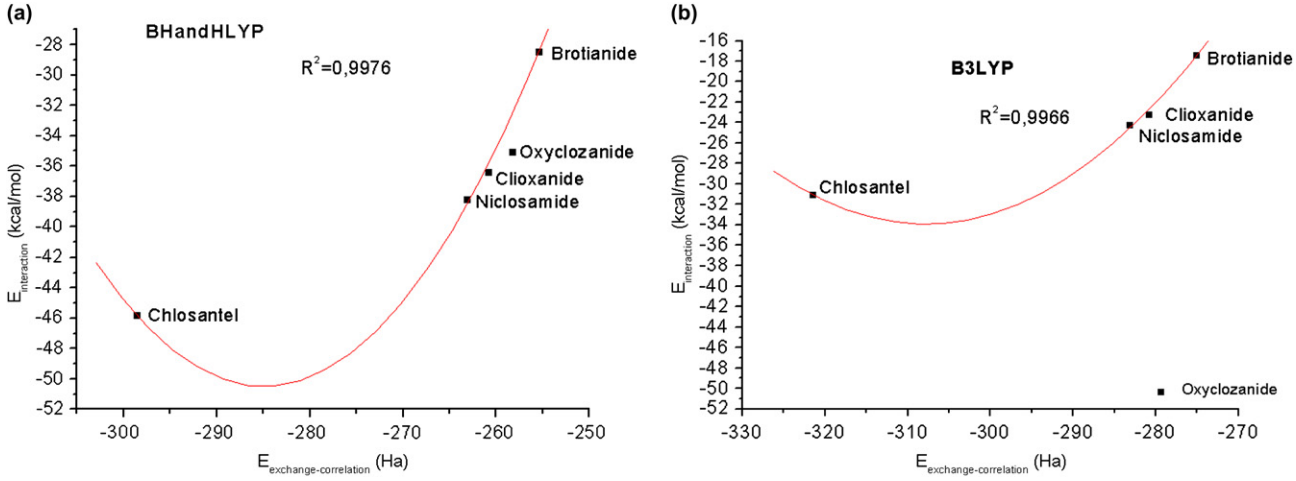

Figure 11. Interaction energy versus exchange correlation energy term: (a) BHandHLYP treatment; (b) B3LYP treatment.

patterns in both, gas phase and aqueous phase, exhibited generally good pre-organization to shelter the drugs as guest molecules, in accordance with the negative energies of interaction obtained theoretically. Two hybrid functionals, B3LYP and BHandHLYP, were used to calculate the interaction energies between FPs and salicylanilides. Both functionals describe nearly the same order of stability of the complexes under study; however, the functional BHandHLYP described in a better way the close contacts and also reproduced in a more realistic manner the favorable interaction between PAMAM and DBNP (reference system) observed experimentally.

In accordance with all the obtained results for the designed fractal patterns, the rational construction of hosts for specific guests seems to be useful to get major efficiency in encapsulation processes thus, this philosophy will be kept for further work.

Finally, both, the synthesis of the designed fractal patterns to corroborate their skills experimentally as well as the study of the salicylanilides delivery from the interior of the dendrimeric hosts are two important issues that will be address in future work. It is known that the primary action of salicylanilides as acaricides is the uncoupling of oxidative phosphorylation,[35,36] which means that they are the chemicals that decrease the efficiency of ATP production at mitochondrial level, causing the cellular death.[37,38] The carrier-mediated mechanism of transport follows a trans-membranal pathway; thus, once the carrier–drug complex reaches the target site (which is enclosed for the highly hydrophobic mitochondrial membrane), the release of the drug (hydrophobic in nature) is possible due to a major affinity, leaving the carrier (e.g., a dendrimer) behind, which is more alike to the aqueous environment mainly due to its globular shape. Theoretical and experimental works will be done about these subjects.

References and notes

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