EDA-NCI: A Scientific Software to Investigate Non-covalent Interactions Combining Classical Dynamic Simulations and QM/MM Calculations

Marcos Mandado(✉) and Nicolás Ramos-Berdullas

Department of Physical Chemistry, University of Vigo, Lagoas-Marcosende S/N, 36310 Vigo, Spain

{mandado,nicolas.ramos}@uvigo.es

Abstract. Simulations in biological environments such as proteins, DNA or lipids entail model systems that include a large number of atoms. Moreover, dynamic simulations, in which thermal effects are considered, sometimes require hundreds of thousands of calculations in order to reproduce a physicochemical process in a biological environment. Therefore, classical simulations based on widely parametrized force fields are employed instead of more accurate quantum methods, whose high computational requirements preclude their application. Disappointingly, although classical simulations could provide a proper sampling of the nuclear configurational space along a given process, they do not yield reliable microscopic information on the weight of different non-covalent interactions; namely, electrostatic, Pauli repulsion, induction (and charge transfer) and dispersion, in the total energy. This is mainly due to compensation of errors between different terms of the force field associated with the parametrization process, focused on getting good macroscopic properties instead of an accurate description of the interatomic interactions. As an alternative to classical and quantum methods, hybrid quantum mechanics/molecular mechanics schemes (QM/MM), where the target region is treated with a quantum method and the rest is represented by a classical force field, can be applied for large biological systems. These schemes combine the accuracy of quantum approaches and the small computational requirements of classical ones. In addition, a thorough analysis of intermolecular interactions can be carried out by means of an energy decomposition analysis (EDA), whose implementation within the framework of QM/MM schemes is known as QM/MM-EDA. In this paper, a methodology developed in our group to investigate intermolecular interactions, combining CMD simulations and a QM/MM energy decomposition analysis (QM/MM-EDA), and its implementation are presented. Finally, some applications to the study of ion solvation and membrane permeation processes are discussed.

Keywords: Non-covalent Interactions · Energy Decomposition Analysis · QM/MM · Molecular Dynamics

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1 Introduction

1.1 Classical Molecular Dynamics Simulations

Classical Molecular dynamics (CMD) simulations allow analyzing the behavior and evolution of a system (physical, chemical or biological) over time, calculating the forces between the atoms that make it up using the equations of Newton's motion [1–3]. Operationally, it is a method for generating the trajectories of a system composed of N particles by direct numerical integration of Newton's equations of motion, with specifications of an interatomic interaction potential of suitable initial and boundary conditions, also known as force field (FF). The functional form of a FF includes terms used to calculate the potential energy between atoms linked by covalent bonds (bonded terms) and between non-bonded atoms that represent the long-range electrostatic and van der Waals forces. Equation (1) represents the form of a typical polarizable FF used in CMD,

$$V\left(\mathrm{r^N}\right) = V_{bonded} + \sum_i \sum_j \left\{ \frac{q_i q_j}{R_{ij}} - \frac{1}{2} \frac{q_i \boldsymbol{\mu}_\mathrm{j} \mathrm{R_{ij}}}{R_{ij}^3} + 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{R_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{R_{ij}} \right)^{6} \right] \right\} \quad (1)$$

where the explicit form of the interatomic potential for covalently bonded atoms has been omitted since we are interested here in the non-covalent interactions. In Eq. (1), the first term included between braces corresponds to the electrostatic interactions between the atomic charges q_i and q_j separated by a distance R_{ij}, the second term is the polarization interaction between the atomic charges q_i and the induced atomic dipoles μ_j and the third term is the well-known Lennard-Jones potential, which accounts for dispersion and repulsion interatomic interactions. The Lennard-Jones parameters, ε_{ij} and σ_{ij}, as well as the atomic charges and the atomic electric polarizabilities used to calculate the induced atomic dipoles, are usually obtained from high-level quantum chemical calculations performed on simplified molecular models [4]. Simple point-charge based FFs have the same form but avoiding the second term of Eq. (1) corresponding to polarization interaction.

Different physicochemical properties of the system can be calculated by means of CMD, such as free energy, entropy, solubility, viscosity, pressure or phase change temperatures. In biological systems, it allows measuring the interaction strength between potential drugs and their biomolecular targets or receptors, and even describing the behavior of a protein and complex molecules under certain conditions. In addition, if, for example, the interaction of a drug with its receptor is analyzed, CMD makes it possible to observe conformational changes of the receptor and not only of the drug, which can yield crucial information for the design of new molecules for clinical use [5]. Another advantage is that it not only allows the simulation of the ligand-protein system, but it can also include the solvent that surrounds it (such as water), as well as possible ions present in the media, and allows the regulation of the temperature and pressure.

1.2 QM/MM Schemes

Unfortunately, the classical FFs employed in CMD simulations are sometimes not accurate enough to adequately represent the non-covalent interactions arising from non-bonded atoms, particularly dispersion and repulsion interactions. Therefore, more precise quantum chemical methods are required to describe, at least, the interaction region.

Since the computational requirements, in terms of time, memory or storage capacity, of quantum chemical methods are much higher than classical FFs, hybrid quantum/classical schemes, such as the popular QM/MM (Quantum Mechanics/Molecular Mechanics) methods, can be employed [6, 7]. The main idea behind QM/MM methods is the splitting of the system into two regions: the target and the surroundings, which are described at QM and MM levels of theory, respectively. Obviously, the QM region includes the most important part of the system, where the process takes place, whereas the MM region contains the remaining atoms. Therefore, the full Hamiltonian of the system gets separated into three parts: QM, MM and QM-MM, the latter accounting for the interactions at the interface between both regions. QM/MM methods can be grouped within two different schemes; additive [7] or subtractive [8]. In the additive scheme a term describing the interaction between the QM and MM regions is explicitly constructed, whereas in the subtractive scheme this term is avoided and the energy is calculated by combination of the energy obtained at MM level for the full system and the energies obtained at QM and MM levels for the QM region.

The methodology presented in this paper was developed to be applied in combination with additive QM/MM schemes, which are, by the way, the most widespread and accurate methods. The interaction at the interface between QM and MM regions can be represented using mechanical, electrostatic, polarizable or flexible boundary embedding schemes. The most employed embedding scheme is the electrostatic one due to its compromise between accuracy and computational cost [9, 10]. In an electrostatic embedding, the electrostatic potential created by the MM atomic charges (q) polarizes the QM region, however, the polarization of the MM region by the potential created by the QM region is not accounted for. Equation (2) represents the Hamiltonian terms corresponding to the QM-MM interaction in an electrostatic embedding, where subscripts i, k and j refer to MM atomic charges, electrons and nuclei of the QM region, respectively.

$$H^{elec}_{QM-MM} = -\sum_i \sum_k \frac{q_i}{|\mathrm{r}_{\boldsymbol{k}} - \mathrm{R_i}|} + \sum_i \sum_j \frac{q_i Z_j}{\mathrm{R_{ij}}} \tag{2}$$

In a polarizable embedding, the polarization of the MM region is also taken into account [11, 12]. Therefore, in addition to the electrostatic interaction with the MM atomic charges, the interaction of the electric potential of the QM region with the induced atomic dipole moments (μ) of the classical region is included in the Hamiltonian, so that the classical region must be described by a polarizable FF. Equation (3) represents the Hamiltonian terms corresponding to the QM-MM interaction in a polarizable embedding.

$$\begin{aligned} H^{pol}_{QM-MM} = &-\sum_i \sum_k \frac{q_i}{|\mathrm{r}_{\boldsymbol{k}} - \mathrm{R_i}|} + \sum_i \sum_j \frac{q_i Z_j}{\mathrm{R_{ij}}} + \frac{1}{2} \sum_i \sum_k \frac{\mu_i (\mathrm{r}_{\boldsymbol{k}} - \mathrm{R_i})}{|\mathrm{r}_{\boldsymbol{k}} - \mathrm{R_i}|^3} \\ &- \sum_i \sum_j \frac{Z_j \boldsymbol{\mu}_\mathrm{i} \cdot \mathrm{R_{ij}}}{R^3_{ij}} \end{aligned} \tag{3}$$

2 QM/MM Energy Decomposition Analysis (QM/MM-EDA)

2.1 Methodology

The energy involved in a non-covalent interaction between two molecules or molecular fragments A and B that form a complex AB is called interaction energy, E_{int}. At QM/MM level, this interaction energy can be calculated using the supermolecule approach as the difference between the energy of the complex and the sum of the energies of the separated molecules or fragments (Eq. (4)).

$$E_{int} = E_{AB}(\mathrm{AB}) - (E_A(\mathrm{AB}) + E_B(\mathrm{AB})) \tag{4}$$

In Eq. (4), (AB) indicates that the energies of the complex and separated molecules are all obtained with the geometry and basis set of the complex, the latter to compensate for the basis set superposition error (BSSE) within the QM region. This expression gives us the total energy involved in the interaction, but, as mentioned in the previous section, to properly test the performance of each potential energy term included in the FF it is advisable to analyze the different energy contributions separately, namely, electrostatic, Pauli repulsion and polarization. There are different interaction energy decomposition schemes proposed in the literature, also known as energy decomposition analysis (EDA), either based on variational [13] or perturbational approaches [14]. We have developed in our group a hybrid variational/perturbational methodology [15, 16]. In this method, the interaction energy is firstly partitioned into electrostatic, repulsion and polarization contributions by separating the one-electron density into isolated monomers' one-electron densities plus one-electron deformation densities associated with the repulsion and polarization interactions (Eq. (5)), and the xc-density (exchange-correlation density) into isolated monomers' xc-densities plus intermolecular x-density (exchange density) and deformation xc-density (Eq. (6)).

$$\rho(\mathrm{r}) = \rho_A(\mathrm{r}) + \rho_B(\mathrm{r}) + \Delta\rho_{Pau}(\mathrm{r}) + \Delta\rho_{pol}(\mathrm{r}) \tag{5}$$

$$\rho_{xc}(\mathrm{r}_1,\mathrm{r}_2) = \rho_{xc,A}(\mathrm{r}_1,\mathrm{r}_2) + \rho_{xc,B}(\mathrm{r}_1,\mathrm{r}_2) + \rho_{x,AB}(\mathrm{r}_1,\mathrm{r}_2) + \Delta\rho_{xc,pol}(\mathrm{r}_1,\mathrm{r}_2) \tag{6}$$

In a second step, the expression of the induction energy obtained from second order perturbation theory (PT) is employed to extract this energy from the polarization energy. For weak non-covalent interactions, where second order PT recovers most of the energy and higher-order terms are negligible, the rest of polarization energy corresponds to dispersion energy. Using this decomposition scheme, the interaction energy is partitioned as in Eq. (7),

$$E_{int} = E_{elec} + E_{Pau} + E_{ind} + E_{disp+res-pol} \tag{7}$$

where the last term of the rhs includes dispersion plus the rest of polarization energy coming from higher orders in PT.

This EDA scheme was first developed and implemented for its use in combination with pure QM methods [15, 16], either wave function based [15] or density functional theory (DFT) [16]. The method was then extended to hybrid QM/MM schemes; using

electrostatic embedding first and very recently with polarizable embedding [17, 18]. The fundamental difference with respect to pure QM methods is that the potentials corresponding to the fixed atomic charges and induced dipoles in the FF that characterizes the MM region are added to the corresponding Hamiltonians used to calculate the different energy terms of Eq. (7). Some additional details are given in the next subsection.

The reader can find full mathematical formulations of the method elsewhere, both for the pure QM version [15, 16] and the QM/MM extension [17, 18].

2.2 Implementation

The method described in the previous subsection has been implemented in a scientific software of free access (EDA-NCI) written in Fortran language [19]. The currently available version only supports pure QM calculations and QM/MM calculations using electrostatic embedding. A new version including polarizable embedding is currently in a testing stage, and some preliminary results are discussed in the next section. Moreover, the program is currently interfaced with the Gaussian 09 and Gaussian16 electronic structure software packages [20] and the AMBER20 classical molecular dynamics software [21]. The former is used to obtain the input one-electron densities of the QM region required for the EDA, whereas the latter provides the atomic charges and induced dipole moments of the MM region. Development of interfaces with other software packages, such as Terachem, ORCA and Gromacs are currently in progress.

The essential steps followed by the EDA-NCI software are summarized in the schematic flowchart shown in Fig. 1. It must be noticed that previously to the calculation of the QM electron densities with the external software (first step in Fig. 1), the corresponding input files for this software are automatically generated using a python script included in the MoBioTools toolkit [22]. For QM/MM calculations, this script also incorporates into the Gaussian input files the atomic charges and dipole moments of the MM region previously read from the topology file of AMBER.

The flowchart represents first a summary of the operations performed externally by the electronic structure software employed (currently Gaussian, versions 09 or 16). From these operations, the input information regarding the one-electron densities of the complex and the isolated molecules or fragments are generated in the form of density matrices (DMs). In the particular case of QM/MM calculations, the atomic charges and dipole moments, the latter represented by a model of two opposite point charges [18], are added to the input information required by EDA-NCI using the module charge.x, internally incorporated to the EDA-NCI program.

Once the external operations are ended, an input file containing minimal information is created to perform the EDA-NCI internal operations described at the bottom of Fig. 1. These operations include: i) diagonalization of the fragments' one-electron density matrices to obtain the eigenvectors (molecular orbitals, MOs) and eigenvalues (occupation numbers); ii) mutual orthogonalization of the MOs of the different fragments to obtain the Pauli one-electron density matrix and the intermolecular x-density matrix; iii) calculation of the polarization one-electron density matrix and the deformation xc-density matrix; iv) one- and two-electron integral evaluation for construction of the Hamiltonian matrices involved in each energy contribution; v) calculation of the different energy terms from the corresponding deformation and Hamiltonian matrices; and

finally, vi) generation of an output file containing information of the different operations and a summary of the results, and generation of separate files containing the deformation density matrices for visualization using external programs, such as Gaussview [23].

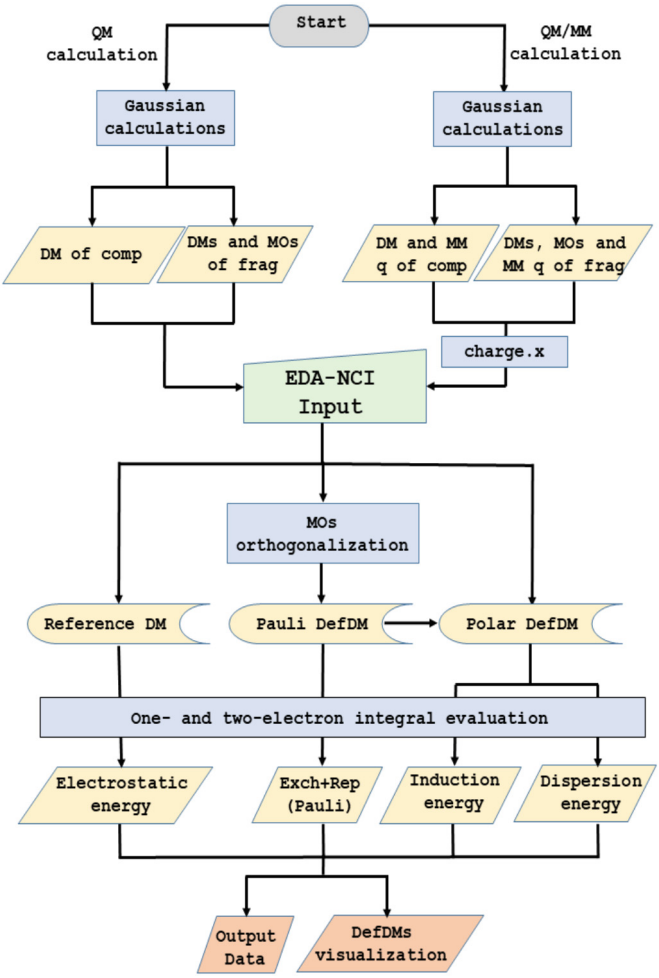

Fig. 1. Schematic flowchart of EDA-NCI

In Fig. 2, we can see on the left the representation of the Pauli and polarization electron densities obtained for an arbitrary geometry around the free energy minimum of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) within a lipid membrane, and on the right a summary of the EDA results included at the end of the output file.

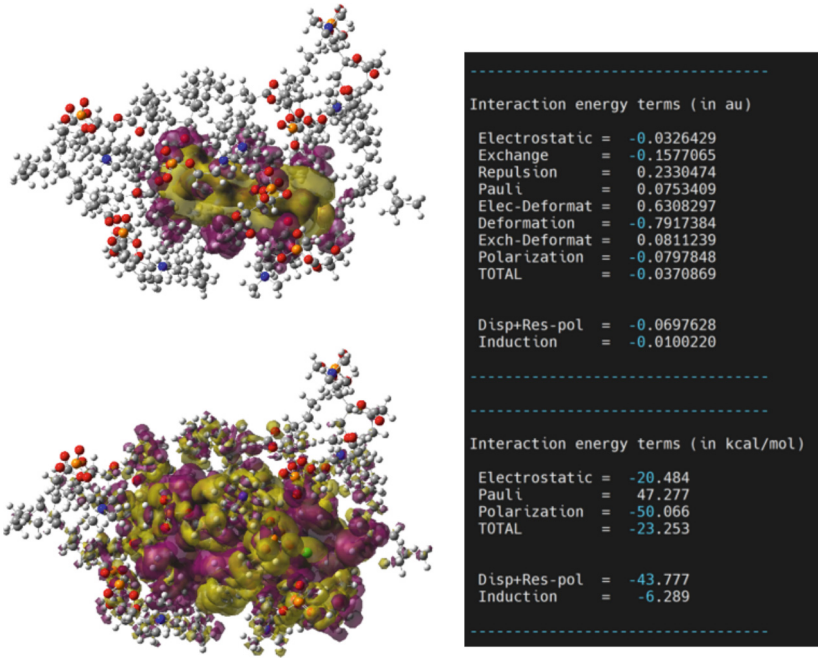

Fig. 2. Representation of the Pauli (top-left) and polarization (bottom-left) densities and the summary of the EDA results from the EDA-NCI output file (right) for the 2,3,7,8-tetrachlorodibenzo-p-dioxin embedded in a lipid membrane. A density cutoff of 10^{-5} is used, magenta and light brown colors represent positive and negative densities, respectively.

3 Examples of Application

In this section, some results of the QM/MM-EDA scheme obtained with the EDA-NCI software will be briefly summarized, namely, its application to the dynamic study of the solvation process of a zwitterion (glycine) [18] and to the dynamic study of the penetration of the TCDD pollutant through a lipid membrane [24].

3.1 Solvation of Glycine

These results presented here are part of a larger investigation where the intermolecular interactions responsible of the solvation of cationic, anionic and zwitterionic species were evaluated [18]. Zwitterions are probably the most interesting systems because, although they are globally neutral, they possess large formal positive and negative charges located on opposite sides of the molecule.

The target system was formed by a glycine molecule in its zwitterionic form ($^{+}NH_3$-CH_2-COO^{-}) surrounded by a water environment. As we intended to investigate the full dynamic process instead of a static situation, previous to the QM/MM calculations, classical molecular dynamics (CMD) simulations were carried out to generate an ensemble of geometries to subsequently perform a statistical analysis of the different interaction

energy terms. CMD simulations were run with AMBER20, a simulation box containing a total of 3250 water molecules was used. The Generalized Amber Force Field (GAFF) was employed for the glycine molecule, the simple point-charges based TIP3P and polarizable POL3 models were employed for the water molecules. Details about the results obtained from the CMD simulations can be found elsewhere [18], herein we will focus on the subsequent QM/MM-EDA analysis. The QM region was treated at DFT level, using the M062X functional and the 6-31G(d) basis set.

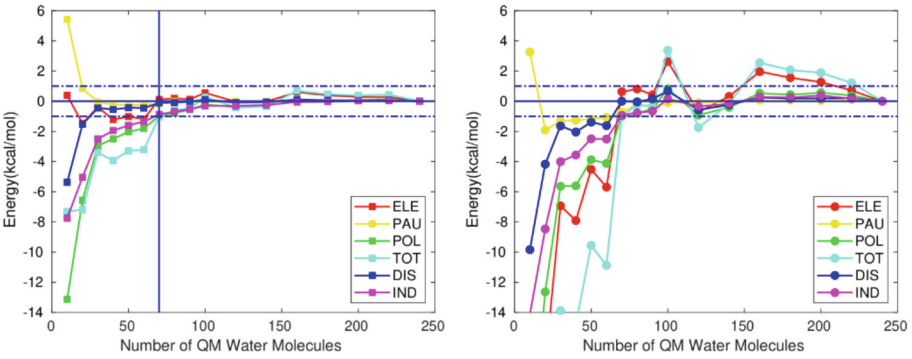

Fig. 3. Convergence of the different interaction energy terms with the number of water molecules in the QM region for hybrid QM/MM-EDA (left) and pure QM-EDA (right) calculations.

Before the statistical analysis, a geometry was randomly selected and QM/MM-EDA calculations using different QM region sizes were performed to characterize the minimum number of water molecules required for the QM region to get the EDA results converged. This is a crucial step since in the literature one can find many QM/MM calculations carried out without previous checking of the optimum QM region, with the consequent risk that the results may not be accurate enough. In Fig. 3, a representation of the interaction energy as well as its different contributions versus the number of water molecules included in the QM region is shown. In order to understand the important role played by the MM potential in the calculations, the same comparison is made by removing the MM region and keeping only the core of the glycine-water interaction represented by the QM region. As can be observed in Fig. 3, the different interaction energy terms reach convergence (within the range of 1 kcal/mol) with a QM region of 70 water molecules, being the repulsion and dispersion energies those that show a faster convergence. On the contrary, the convergence of all the energy terms is significantly slower without the MM region, with a remarkable effect on the electrostatic energy, which is not fully converged even for 200 water molecules.

Once the optimum size of the QM region was found, 200 equispaced geometries along CMD simulations carried out with the TIP3P and the POL3 models were selected to perform the statistical analysis of the relative contributions of the different energy terms. First, the statistical analysis reflected that a sample containing 20 or more geometries was sufficiently converged, as fluctuations of the sample means were in the ± 1 kcal/mol range with respect to the reference when 20 or more geometries were sampled. Therefore, Fig. 4

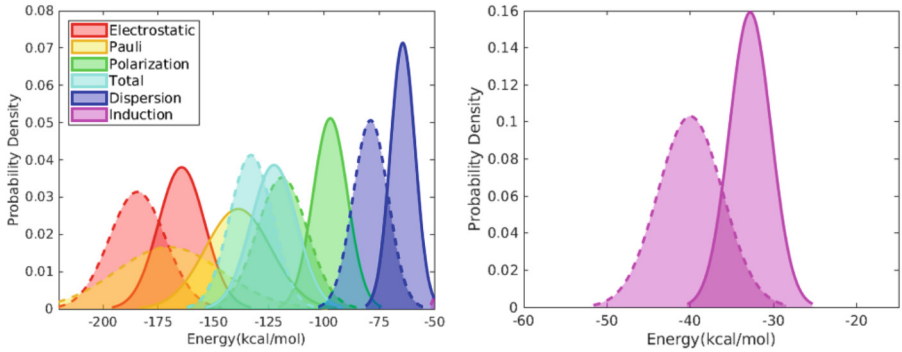

Fig. 4. Normal probability distributions for each interaction energy term obtained from a sample of 20 equispaced geometries from a CMD simulation of the solvation process of glycine carried out with the TIP3P (continuous line) and the POL3 (dashed line) models. Pauli repulsion is represented with opposite sign.

represents the normal probability distributions obtained with a sample of 20 geometries considering a QM region containing 100 water molecules.

As can be extracted from Fig. 4, the most important contribution to the stability of the zwitterion in water is by far the electrostatic energy. This energy is very large (around −190 kcal/mol and −170 kcal/mol with the POL3 and TIP3P models, respectively), reflecting the collective charge-dipole interaction established between the positive and negative charges of glycine and the dipoles of the surrounding water molecules. Regarding the polarization energy, both induction and dispersion contribute significantly, although the latter has a larger weight. On the other hand, the Pauli repulsion shows the broadest distribution among all the energy terms. This is due to the short-range character of this term, which makes it more sensitive to changes in geometry. Finally, the simple point-charge based model of TIP3P reflects a slightly lower stability of solvated glycine than the model POL3, which is based on point-charges and induced atomic dipoles. This is the expected result, as the inclusion of polarization in the CMD simulation and in the MM region for the QM/MM calculations helps to stabilize ionic and zwitterionic forms of molecules.

3.2 Membrane Permeation of TCDD

The second example of application that will be discussed is the process of penetration of polychlorinated dioxins through a cell membrane [24]. The most toxic form of polychlorinated dioxins is the TCDD, which is the one that will be analyzed here.

As in the previous example of solvated glycine, we will first perform the CMD simulation of the penetration process using a membrane model. The membrane model chosen was a lipid bilayer formed by two leaflets of 64 1,2-dioleyl-sn-glycero-phosphocholine (DOPC) molecules. This bilayer has a total thickness of 50 Å. Each DOPC molecule has a hydrophobic chain and a hydrophilic tail and the two layers are confronted each other with the hydrophobic chains pointed at the center of the bilayer. Thus, taken into

account the non-polar and aromatic character of TCDD, it is expected that the intermolecular interaction between the TCDD molecule and the lipid bilayer evolves from a small electrostatic interaction to a large dispersive one as the molecule migrates from the outer hydrophilic region to the inner hydrophobic one.

Details about the results obtained from the CMD simulation can be found elsewhere [24]. Herein, we will just mention that the penetration process was found to be thermodynamically favored and that two free energy minima (one on each side of the membrane) were found at 9 Å from the center of the membrane and a local energy maximum, very close in energy to the minima, was found at the center. As the previous example, we will focus on the QM/MM-EDA calculations. The QM region was treated at DFT level, using the M062X functional and the 6-31G(d) basis set. The first step was the characterization of the optimum size for the QM region. In Fig. 5, a representation of the interaction energy as well as its different contributions versus the number of DOPC molecules included in the QM region is shown for a geometry randomly chosen close to the energy minima. As can be observed, the convergence for all the energy terms is reached when the number of DOPC molecules in the QM region is 7. This entails a large number of atoms in the QM region since each DOPC molecule contains 54 heavy atoms and 84 hydrogens, and the TCDD molecule contains 18 heavy atoms and 4 hydrogens.

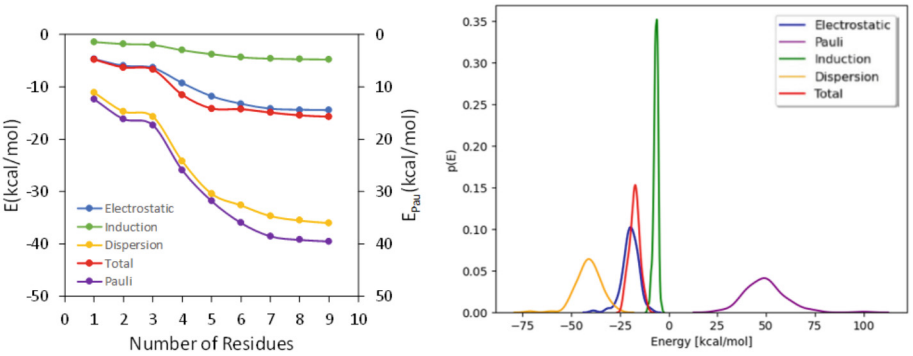

Fig. 5. Convergence of the different interaction energy terms with the number of DOPC molecules in the QM region for hybrid QM/MM-EDA calculations (left) and normal distributions of the interaction energy and its different components on 100 equispaced geometries selected from the free energy minima of the CMD simulation of the penetration process of TCDD through a lipid membrane (right).

In Fig. 5, the normal distribution of the interaction energy and its different components around the free energy minima is shown. In this case, up to 100 equispaced geometries were selected for the statistical analysis. As a remarkable difference with respect to the previous example of zwitterionic glycine in water, the dispersion energy is clearly the most important contribution. This is an expected result taken into account the non-polar character of TCDD and the hydrophobic nature of the DOPC chains. Thus, the stabilization of the TCDD molecule inside the lipid bilayer at the energy minima is due to a large dispersive interaction with these hydrophobic chains from the DOPC molecules. On the contrary, the induction energy has a residual contribution in this case.

4 Conclusions

In this short paper, a methodology to theoretically and computationally investigate the intermolecular interactions involved in biological processes and its implementation in the EDA-NCI software are presented. To illustrate its performance, some results recently published are briefly summarized. This methodology is applied in combination with CMD simulations and QM/MM electronic structure calculations. The power of this methodology is twofold: on the one hand, it allows obtaining the optimal QM size for QM/MM studies of intermolecular interactions in terms of accuracy and computational cost; on the other hand, it allows monitoring the intermolecular interactions along a dynamic process in terms of its strength and nature. Both electrostatic and polarizable embeddings can be used with the current implementation of this QM/MM-EDA scheme.

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