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APPLICATION OF THE AMYR CALCULATING METHOD ON QUINOXALINE, 3-CHLOROQUINOXALINE, AND 3-METHYLQUINOXALINE IN THE INTERACTION WITH n WATER MOLECULES (n VARIES FROM 1 TO 6)**A. El Assyry¹, B. Benali¹, A. Boucetta¹, B. Lakhrissi²**¹*Laboratoire d'Optoélectronique et de Physico-chimie des Matériaux, Université Ibn Tofail, Faculté des Sciences, Département de Physique, Kénitra, Morocco*

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AMYR is a computer program for the calculation of molecular associations using Fraga's pairwise atom-atom potential. The interaction energy is evaluated through a $1/R$ expansion. A pairwise dispersion energy term is included in the potential and corrected by a damping function. The program carries out energy minimizations through variable metric methods. The new version allows for the stationary point analysis of the intermolecular potential by means of the Hessian eigenvalues. AMYR model is used for the first time in a calculation of quinoxaline, 3-chloroquinoxaline, and 3-methylquinoxaline molecules interacting with some water molecules. Intermolecular interaction energies are obtained and the stable conformation is determined in each case. The change conformation was considered at $\alpha \cong$ (CNC) angle when the solute molecules are surrounded by n water molecules ($1 \leq n \leq 6$).

Key word: quinoxaline, 3-chloroquinoxaline, 3-methylquinoxaline, AMYR, interaction energies, conformations.

INTRODUCTION

The quinoxaline chemistry is the subject of intense interest since this compound shows a remarkable biological activity [1–4]. Quinoxaline derivatives are biologically interesting compounds, and have been used in various pharmaceutical applications. For example, in colon cancer therapies [5] they interact with α -aminobutyric acid A (GABAA) and benzodiazepine receptor [6]; they inhibit aldose reductases [7], and they are potent angiotensin II receptor antagonists [8]. The quinoxaline biodisponibility can be improved by their grafting on the monosaccharide moiety [9]. Although a great number of quinoxalines was reported in the literature, relatively few crystal structures were given [10–14]. However, and in absence of spectroscopic data of these molecules in the bibliography, we considered useful to undertake a theoretical study aiming at their interaction with a certain number of surrounding water molecule. This work thus brings a contribution to the study of the interaction energy and the conformational structure of the complexes (aqueous solution — solvent (S)) from quinoxaline (Q) and two of its derivatives: 3-chloroquinoxaline (3-CQ) and 3-methylquinoxaline (3-MQ) (Fig. 1) in the interaction with solvent molecules (water in our case). We considered the interactions up to 6 water molecules, because the 7th water molecule does not affect the most stable conformation of the complex in three cases. This theoretical study is based on the semi-empirical AMYR calculation method [15–18]. AMYR is a program for the calculation of molecular associations using the atom-atom potential of Fraga by pairs. The interaction energy is evaluated by an extension of $1/R$. The most

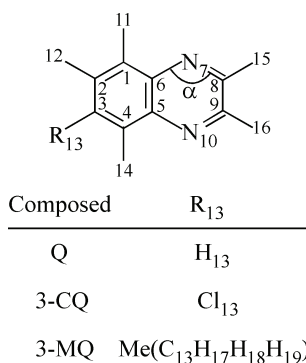


Fig. 1. Structure of quinoxaline and its derivatives

stable conformation of the molecular association is found by the minimization of the interaction energy between the two molecules. The energy is evaluated by means of $1/R$ (with limits R-1, R-4, R-6, and R-12) and of the coefficients obtained by the adjustment of SCF [19]. The geometrical structures of isolated molecules are obtained by the AM1 (Austin Model 1) calculation [20]; the results obtained are used in the AMYR program.

The main idea of this work is to determine the maximum interaction energy in absolute value and the most stable conformation between the molecular pharmaceutical product when diluted in the blood and water molecules that are the major compound of blood.

THEORY

The interaction energy ΔE between two rigid molecules A and B can be brought closer: $\Delta E = \sum_a \sum_b \Delta E_{ab}$ [21]. In terms of the interaction energy (pair potentials) between all possible pairs of atoms in the complex, the summation on a and b is prolonged respectively with the atoms in A and B.

This energy can be brought closer by [19]

$$\Delta E = \sum \sum \left\{ c_{ab}^{(1)} / R_{ab} + c_{ab}^{(4)} / R_{ab}^4 + c_{ab}^{(6)} / R_{ab}^6 + c_{ab}^{(7)} / R_{ab}^7 + c_{ab}^{(8)} / R_{ab}^8 + \dots \right\}.$$

An approach was proposed and employed in practice to avoid two difficulties obstructing the application practices of this formulation [19]. Thus, the total interaction energy between the molecule of Q (a) (where one of its derivative is 3-CQ and 3-MQ) and the water molecule (b) can be written as

$$E_{\text{inter}} = \sum_{a \in A} \sum_{b \in B} \left(C_{ab}^{(1)} / R_{ab} + C_{ab}^{(4)} / R_{ab}^4 + C_{ab}^{(6)} / R_{ab}^6 + C_{ab}^{(12)} / R_{ab}^{12} \right),$$

where the addition indices are prolonged with all the atoms a and b of the two molecules A and B. Thus, the total energy is the sum of interactions between all possible pairs of atoms of the beam. In this expression, one can easily identify the electrostatics, induction, dispersion, and repulsion limits of the traditional methods of the pair potential. The coefficients of this expression were parameterized by Fraga by the formulas

$$\begin{aligned} C_{ab}^{(1)} &= Q_a Q_b, \\ C_{ab}^{(4)} &= -\frac{1}{2} \left(f_b \alpha_b Q_a^2 + f_a \alpha_a Q_b^2 \right), \\ C_{ab}^{(6)} &= -\frac{3}{2} f_a \alpha_a f_b \alpha_b \left(\frac{f_a \alpha_a}{\sqrt{n_a}} + \frac{f_b \alpha_b}{\sqrt{n_b}} \right), \\ C_{ab}^{(12)} &= g_a g_b. \end{aligned}$$

The indices (a, b) indicate the class designation of each atom acting on one another, taking into account its molecular environment in agreement with the classification suggested by Clementi [22, 23] and prolonged by Fraga *et al.* [17, 18]. The values for the electronic load Q_x , the polarizability static α_x , the effective number of electrons n_x , and the parameters f_x and g_x for an atom pertaining to the class x were tabled in detail in [17—19, 21].

We adapted the Amyr potential to determine the interaction energy compared to the internal movements of Q and its two derivatives 3-CQ and 3-MQ (in particular, changes in the geometry). In all reported calculations, the geometries of the subsets of A and of B were calculated.

The total energy of a beam E_T^{Syst} can be written as a sum of the intramolecular energy $E_{\text{Intra}}^{\text{Soluté}}$ of (Q, 3-MQ or 3-CQ), the intramolecular energy $E_{\text{Intra}}^{\text{Solvent}}$ of a solvent molecule, and the intermolecular energy E_{Inter}

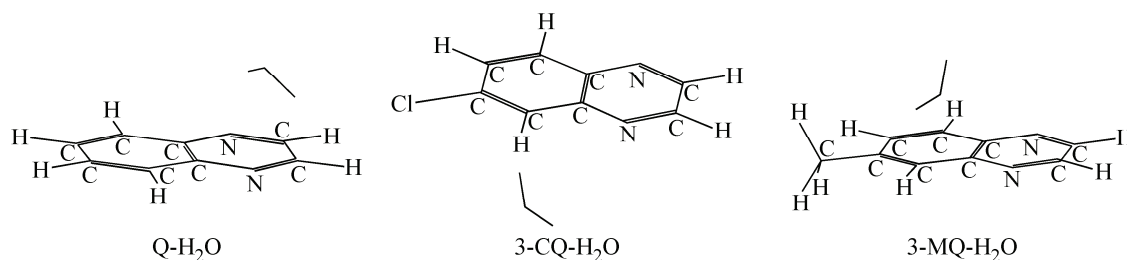


Fig. 2. Optimized structures of quinoxaline, 3-chloroquinoxaline, and 3-methylquinoxaline

$$E_T^{\text{Syst}} = E_{\text{Intra}}^{\text{Soluté}} + E_{\text{Intra}}^{\text{Solvent}} + E_{\text{Inter}}$$

In our calculations alone the effect of the angle $\alpha \cong (C_6N_7C_8)$ on the system energy was taken into account

$$E_T^{\text{Syst}}(\alpha) = E_{\text{Intra}}^{\text{Soluté}}(\alpha) + E_{\text{Intra}}^{\text{Solvent}} + E_{\text{Inter}}(\alpha),$$

where $E_{\text{Intra}}^{\text{Soluté}}(\alpha)$ represents the energy of (Q, 3-MQ or 3-CQ) for the coordinate (α), $E_{\text{Intra}}^{\text{Solvent}}$ does not depend on (α), and $E_{\text{Inter}}(\alpha)$ is the intermolecular energy of the system.

RESULTS AND DISCUSSION

Determination of the quinoxaline interaction sites. A theoretical simulation of the solvent effect on the geometrical conformation of quinoxaline and its two derivatives (3-chloroquinoxaline and the 3-methylquinoxaline) is carried out by means of the Amyr formalism. This method of the intermolecular interaction consists in the determination of various stable conformations of the system between the aqueous solution molecule and some solvent molecules such as water. The first stage of the calculation resides in the determination of the preferential interaction site of the studied molecule when it interacts with a water molecule (Fig. 2). Then, we study the variation of the interaction energy according to the intracyclic angle ($C_6N_7C_8$), considered most likely to react with the surrounding medium when the aqueous solution molecule is surrounded by one or more solvent molecules (to six water molecules, in our case).

Various values of total interaction energies (E_t) of the complexes (**1—n**) are gathered in Tables 1, 2, and 3 for various angles α of quinoxaline and two its derivatives. One considers the supermolecules whose absolute values of the total interaction energy are large, i.e. the forms where the water molecules interact between them and with the aqueous solution molecule.

The result obtained using the Amyr formalism under the most stable conformation of quinoxaline in the interaction with a water molecule shows that the double connection $N = C$ is the most favorable site. Indeed, the water molecule is located in a plane perpendicular to the plane of the heterocycle; one of hydrogen atoms interacts with the π electrons of the double connection $N = C$ and another hydrogen

Table 1

Total interaction energy E_t (kcal/mol) of complexes **1—1** to **1—6** according to the angle α (deg.) of quinoxaline

α	115	116	117	118	119	120	121
1—1	-11.983	-11.997	-10.846	-10.998	-12.037	-12.049	-12.062
1—2	-23.570	-23.552	-38.943	-39.306	-37.916	-38.042	-23.554
1—3	-39.569	-48.042	-50.958	-51.654	-49.271	-49.284	-39.725
1—4	-40.725	-50.823	-73.853	-74.470	-51.531	-49.652	-41.247
1—5	-42.796	-51.727	-73.989	-74.947	-68.159	-53.581	-47.888
1—6	-43.309	-53.513	-77.077	-75.012	-69.293	-53.585	-56.980

atom is pointed towards the hexagonal cycle. Thus, the values of the interaction energy (-10.84 kcal/mol) and of the interatomic average distance (2.6 \AA) show that it is about a specific interaction by a hydrogen bond of the type $\text{OH}\dots\pi$.

Intermolecular quinoxaline—water interaction. The calculation of the interaction energy with the surrounding water molecule(s) was undertaken in a systematic way. The complexes (quinoxaline — n water molecules) correspond to energy minima. The research of the various minima is carried out for various values of the angle α ; these minima are gathered in Table 1.

The analysis of this table shows that the interaction induced by only one water molecule is insufficient to support a well defined conformation. We planned to study the complexes (quinoxaline — n water molecules) with ($n = 2, 3, 4, 5,$ and 6) for various values of the intracyclic angle α of quinoxaline. Complex (1—2) is formed by the addition of a second water molecule to complex (1—1). In this case, two forms of supermolecules are essential that are different in the provision of two water molecules compared to the aqueous solution molecule. Total interaction energies of the forms (a) and (b) (Fig. 3) are about -38.943 kcal/mol and -13.757 kcal/mol respectively. According to these two values, one notes that the supermolecule having the form (a) is energetically most stable. However, it is advisable to announce that in the form (a) the interaction between the two water molecules is maximum. The lowest total interaction energy corresponds to the complexes (quinoxaline—2 water molecules) having close values of the angle α of $117^\circ, 118^\circ, 119^\circ,$ and 120° . These supermolecules are thus statistically equiprobable since one cannot support a complex compared to the other.

The addition of a third water molecule to complex (1—2) for various values of the angle α indicates that the supermolecules having angles of 117° and 118° are almost isoenergetic and correspond to the most energetically stable conformations (Fig. 4).

By adding a fourth, fifth, and sixth water molecule to each conformation of the supermolecule (1—3), one finds the same conformations of balance of complex (1—3) (Table 1). Therefore, the interactions induced by the fourth, fifth, and sixth water molecule are not distinct from those induced by the third molecule. The variation of the interaction energy of the water molecules, between complexes (1—3) and (1—4) with the angle of 117° , is about 23 kcal/mol.

These calculations of the intermolecular interactions thus suppose that once quinoxaline is in solution in protic solvents, two forms of supermolecules ($\alpha = 117^\circ$ and 118°) can coexist with close sta-

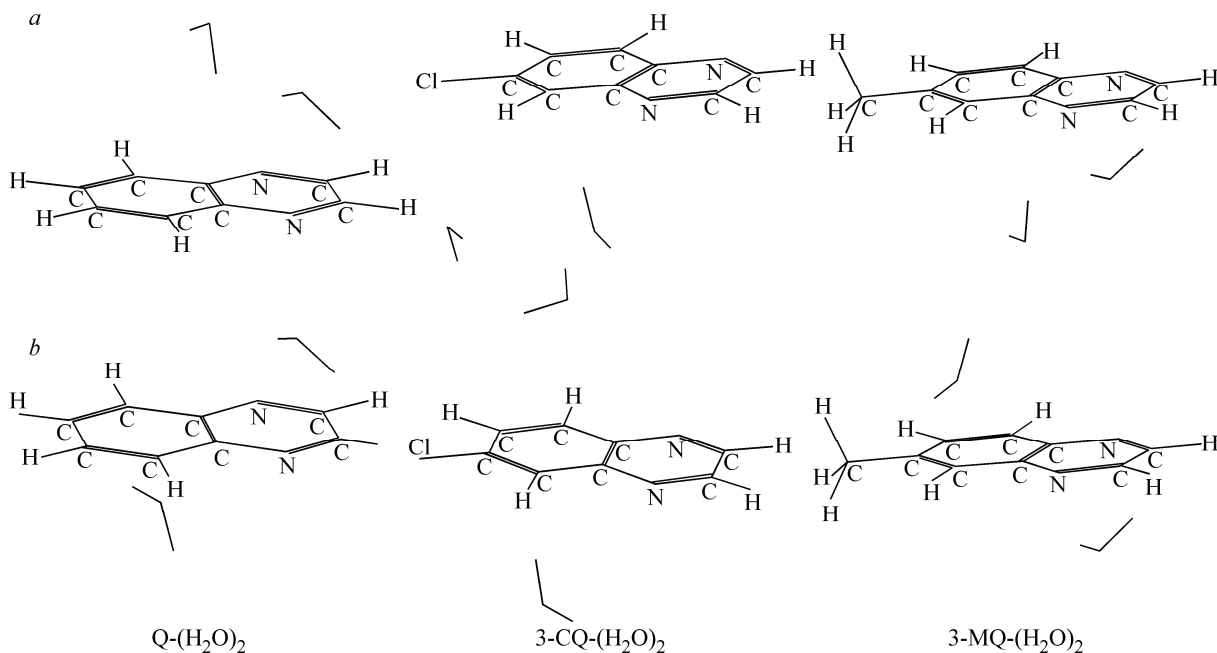


Fig. 3. Two forms (a) and (b) of the interaction of quinoxaline and its derivatives with two water molecules

Table 2

Total interaction energy E_t (kcal/mol) of complexes **1—1** to **1—6** according to the angle α (deg.) of 3-methylquinoxaline

α	113	114	115	116	117	118	119	120
1—1	-12.343	-12.357	-12.370	-12.383	-12.397	-12.409	-12.422	-12.435
1—2	-12.978	-12.994	-13.007	-13.020	-13.034	-13.046	-13.059	-13.074
1—3	-29.758	-29.349	-30.101	-30.366	-30.387	-29.400	-29.404	-29.416
1—4	-35.763	-37.607	-39.744	-40.651	-39.886	-36.937	-32.648	-31.755
1—5	-48.034	-45.378	-56.032	-55.299	-52.960	-48.894	-48.932	-49.384
1—6	-54.313	-56.193	-58.686	-50.706	-51.623	-50.990	-49.626	-49.793

tistical proportions and they are stabilized primarily by the interaction of water molecules between them, which become rather important.

Intermolecular 3-methylquinoxaline—water interaction. The minima of the total interaction energy (E_T) obtained for various values of the angle α varying from 11° to 120° with a step of 1° are gathered in Table 2.

This table shows that interactions induced by one or two water molecules are insufficient to support the well defined conformation, and that in the interaction of the molecule with three and four water molecules, the most energetically stable conformations are those that correspond to the complexes for which the angle $\alpha = 115^\circ$, 116° , and 117° . This table also states that when the 3-methylquinoxaline molecule interacts with five water molecules, the most energetically stable conformations are those that correspond to the angles $\alpha = 115^\circ$ and 116° . The interaction induced by five water molecules does not support a quite precise conformation. The most energetically stable conformation corresponds to the angle $\alpha = 115^\circ$ (Fig. 4, *b*) and to the supermolecule of complexes with six water molecules. Therefore, the increase in the interaction energy of the water molecules between them more stabilizes the supermolecule.

Intermolecular 3-chloroquinoxaline—water interaction. Table 3 gathers the values of the minima of the total interaction energy (E_T) obtained in the cases of interactions of a 3-chloroquinoxaline molecule with n ($n = 1, 2, 3, 4$, and 5) water molecules for various values of the angle α located at the level of the intracyclic nitrogen atom.

The analysis of the above table shows that the interactions induced by one and two water molecules are insufficient to support a well defined conformation, and that complex (**1—3**) having the angle of 116° presents an interaction energy more favored than complex (**1—3**) having angles of 114° , 115° , and 117° . These four supermolecules are thus statistically equiprobable and energetically most stable. The interaction induced by three water molecules on the 3-chloroquinoxaline molecule is insufficient to support a well defined conformation.

The values of this table indicate that in the interaction of the 3-chloroquinoxaline molecule with four water molecules the most energetically stable conformations are those that correspond to the

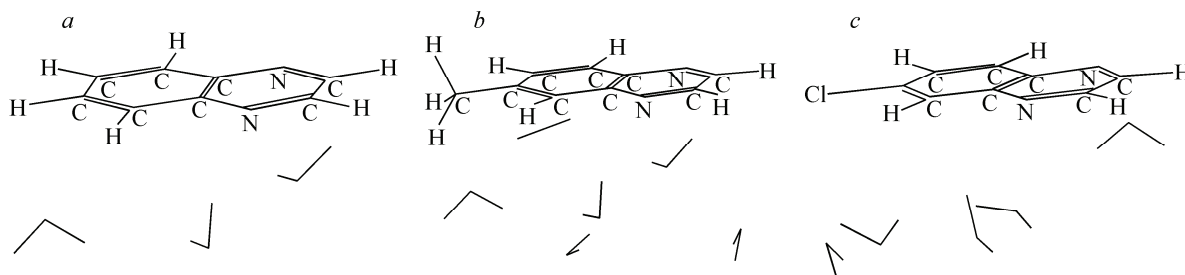


Fig. 4. Most stable conformation of the $Q-(H_2O)_n$ complexes (*a*), $3-MQ-(H_2O)_n$ complexes (*b*), $3-CQ-(H_2O)_n$ complexes (*c*)

Table 3

Total interaction energy E_i (kcal/mol) of complexes **1—1** to **1—5** according to the angle α (deg.) of 3-chloroquinoxaline

α	113	114	115	116	117	118	119	120
1—1	-4.655	-4.651	-4.650	-4.653	-4.648	-4.648	-4.646	-4.639
1—2	-13.830	-13.851	-13.867	-13.881	-13.892	-13.906	-13.925	-13.938
1—3	-25.986	-26.028	-26.009	-26.097	-26.037	-25.964	-25.938	-25.921
1—4	-41.567	-41.719	-41.813	-43.015	-42.799	-41.768	-41.745	-41.468
1—5	-44.297	-44.698	-45.786	-48.709	-46.452	-45.370	-45.349	-44.396

complexes where $\alpha = 116^\circ$ and 117° . Therefore, the interaction induced by a fourth water molecule is also insufficient to support a quite precise conformation.

One is primarily interested in conformations where the interaction between water molecules is maximum. The Table 3 data show that when the 3-chloroquinoxaline molecule interacts with five water molecules, the most stable conformation corresponds to the angle α of 116° (Fig. 4, c). The energy brought by the fifth water molecule compared to complex (**1—4**) is about -5.7 kcal/mol.

CONCLUSIONS

We carried out the calculations of the intermolecular interaction using the Amyr formalism to simulate the effect of the medium and to locate the site (s). Indeed, for the quinoxaline molecule we found that π systems of two hexagonal cycles are implied in the interaction with the water molecule. The intermolecular calculation of the interaction envisages also possibilities of the interaction per hydrogen bond and a conformational change when this one interacts with solvent (water) molecules ready to be complexed with the aqueous solution molecule. Concerning the 3-methylquinoxaline and 3-chloroquinoxaline molecules only the hexagonal cycle (which contains the substituent) constitutes the interaction zone.

Concerning quinoxaline, the calculation of the interaction energy of complex (**1—3**) for various values of the angle α indicates that the supermolecules with the angles of 117° and 118° are almost isoenergetic (-50.958 kcal/mol and -51.654 kcal/mol) and correspond to the most stable conformations. In the case of 3-methylquinoxaline, the analysis of the results shows that the most energetically stable conformation corresponds to the angle $\alpha = 115^\circ$ with an energy of -58.686 kcal/mol and for the supermolecule of complexes with six water molecules. When the 3-chloroquinoxaline molecule interacts with five water molecules, the most stable conformation corresponds to an angle α of 116° with an interaction energy of about -48.709 kcal/mol.

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