



Theoretical investigation using AMYR calculations of five quinoxalinones in interaction with water molecules

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Abstract

Program AMYR, originally written by S. Fraga (University of Alberta, Canada), allows for the calculation of molecular associations using a pair-wise atom-atom potential. The interaction energy is evaluated through a $1/R$ expansion. Our improved version includes a dispersion energy term in the potential corrected by damping functions, the possibility of carrying out energy minimizations through variable metric methods, as well as the optional calculation of geometrical and topological indices. Program AMYR has been adapted also for high-performance computing and vectorization. An interactive version of the program carries out real-time molecular graphics showing simultaneously the energy profile of the calculations.

In this paper, AMYR model is used for the first time in calculation of five quinoxalinones [quinoxalin-2(1H)-one ($C_8H_6N_2O$), 6-chloroquinoxalin-2(1H)-one ($C_8H_5N_2OCl$), 6-bromoquinoxalin-2(1H)-one ($C_8H_5N_2OBr$), 6-méthylquinoxalin-2(1H)-one ($C_9H_8N_2O$) and 6-nitroquinoxalin-2(1H)-one ($C_8H_5N_3O_3$)] molecules interacting with water molecules. Intermolecular interaction energies have been obtained and the stable conformation was determined in each case. Changes of conformation were considered for the C–N–C angle α when the solute molecules were surrounded by n water molecules.

Keywords: quinoxalinone derivatives, water molecules, AMYR model, Interaction energy, Conformations.

1. Introduction

Quinoxalines are a versatile class of nitrogen containing heterocyclic compounds and they constitute useful intermediates in organic synthesis. Heterocyclic compounds represent an important class of biological active molecules. Specifically those containing quinoxaline derivatives have evoked considerable attention in recent years as these are endowed. Quinoxaline, also called a benzopyrazine, in organic chemistry, is a heterocyclic compound containing a ring complex made up of a benzene ring and a pyrazine ring and they are isomeric with cinnolones, phthalazines and quinazolines [1]. There are a number of processes available to generate quinoxaline but generally, they are synthesized by the condensation of 1,2-dicarbonyls with 1,2diamines in presence of suitable catalyst using various solvent systems.

They possess well known biological activities including AMPA/GlyN receptor antagonis [2], antihistaminic agents [3] anti-trypanosomal activity [4], anti-herps [5], antiplasmodial activity [6], Ca uptake/ Release inhibitor [7], inhibit vascular smooth muscle cell proliferation [8]. Quinoxaline derivatives constitute the basis of many insecticides, fungicides, herbicides, as well as being important in human health and as receptor antagonists. Although rarely described in nature, synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin, levomycin and actinomycin which are known to inhibit the growth of Gram-positive bacteria and also active against various transplantable tumours [9].

The quinoxaline chemistry has been the subject of intense interest, since this compound shows remarkable biological properties. Although a great number of quinoxaline was reported in the literature; recently the study of structural and energetic proprieties has been done by our group [10-13]. However, and in absence of spectroscopic and energetically data of these molecules in the bibliography, we considered to be useful to undertake a theoretical study aiming their interaction with a certain number of surrounding water molecule. This work thus brings a contribution to the study of interaction energy and conformational structure of the complexes (aqueous solution –

solvent (S) from quinoxalin-2(1H)-one (Q) and four of its derivative: 6-chloroquinoxalin-2(1H)-one (6-CQ), 6-bromoquinoxalin-2(1H)-one (6-BQ), 6-méthylquinoxalin-2(1H)-one (6-MQ) and 6-nitroquinoxalin-2(1H)-one (6-NQ) (fig.1) in interaction with molecules of the solvent (water in our case). We considered interactions with up to six water molecules, because the seventh water molecule does not affect the most stable conformations of the complexes for these five molecules. This theoretical study is based on the semi-empirical method of AMYR calculation [14-17].

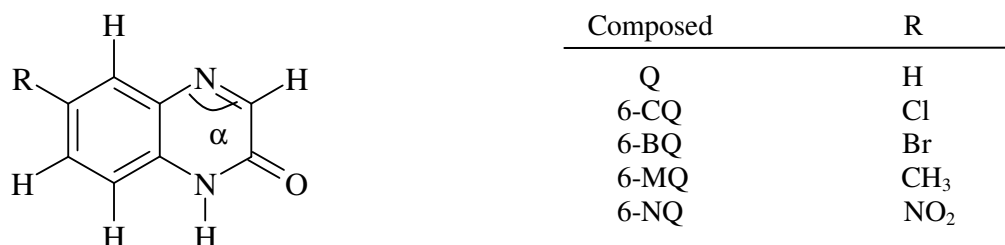


Figure 1: Structures of quinoxalin-2(1H)-one and its derivatives.

AMYR is a program for the calculation of molecular associations by using the atom-atom potential of Fraga by pairs. The interaction energy is evaluated by an extension of $1/R$. The most 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 [18]. The geometrical structures of isolated molecules are obtained by AM1 (Austin Model1) calculation [19]; the results obtained are used in AMYR program.

The main idea of this work was to determine the maximum absolute value of the interaction energy and the most stable conformation for a pharmaceutical molecule when diluted in blood, the major component of which is water.

2. Theoretical methodology

The interaction energy, ΔE , between two rigid molecules, A and B , can be expressed as $\Delta E = \sum_a \sum_b \Delta E_{ab}$ [20].

In terms of interaction energy (pair potentials) between all the possible pairs of atoms in the complex; the summation on a and b are prolonged, respectively, with the atoms in A and B .

This energy can be expressed as [18]:

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

An approach has been proposed and used to avoid two difficulties which obstruct the practical application of this formula [18]. All interaction energies between a molecule of Q (a) (either 6-CQ, 6-BQ, 6-MQ or 6-NQ) and the water molecule (b) can be written as:

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

where the addition indices are obtained for all the atoms a and b of the two molecules A and B . Thus, all the energy is the sum of the 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 pair potential. The coefficients of this expression were parameterized by Fraga by using the formulas:

$$C_{ab}^{(1)} = Q_a Q_b ; \quad C_{ab}^{(4)} = -\frac{1}{2} (f_b \alpha_b Q_a^2 + f_a \alpha_a Q_b^2)$$

$$C_{ab}^{(6)} = -\frac{3}{2} f_a \alpha_a f_b \alpha_b \left(\frac{f_a \alpha_a}{\sqrt{n_a}} + \frac{f_b \alpha_b}{\sqrt{n_b}} \right) ; \quad C_{ab}^{(12)} = g_a g_b$$

The indices (a , b) designate the class of each atom acting one on other, taking account of its molecular environment in agreement with the classification suggested by Clementi et al. [21,22] and prolonged by Fraga et al. [16,17]. The values for the electronic load Q_x , the polarizability statistic α_x , the effective number of electrons n_x , and f_x and g_x for an atom in class x were tabulated in detail in Refs [16 – 18, 20].

We adapted the AMYR potential to determine the interaction energy for the internal movements of Q and its four derivatives 6-CQ, 6-BQ, 6-MQ and 6-NQ (in particular, the changes of the geometry). In all reported calculations, the geometries of the subsets of A and of B were calculated.

All the energy of a beam E_T^{Syst} can be written as the sum of the intramolecular energy $E_{Intra}^{Soluté}$ of Q, 6-CQ, 6-BQ, 6-MQ or 6-NQ, of the intramolecular energy $E_{Intra}^{Solvent}$ of the solvent molecule, and of the intermolecular energy E_{Inter} : $E_T^{Syst} = E_{Intra}^{Soluté} + E_{Intra}^{Solvent} + E_{Inter}$.

In our calculations alone the influence of the angle α on the system energy was taken into account:

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

where $E_{Intra}^{Soluté}(\alpha)$ represents the energy of Q, 6-CQ, 6-BQ, 6-MQ or 6-NQ for the coordinate α , $E_{Intra}^{Solvent}$ does not depend on α , and $E_{Inter}(\alpha)$ is the intermolecular energy of the system.

3. Results and discussion

3.1. Determination of the interaction sites

Theoretical simulation of the solvent effect on the geometrical conformation of quinoxalin-2(1H)-one and its four derivatives (6-CQ, 6-BQ, 6-MQ and 6-NQ) was carried out by means of AMYR formalism. This intermolecular interaction method consists in determining variety of stable conformations of the system between the molecule in aqueous solution and solvent molecules, i.e. water. The first stage of calculation is 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 interaction energy according to intracyclic angle (α), considered most likely to react with the surrounding medium, when the aqueous solution molecule is surrounded by one or more solvent molecules (up to six water molecules in our case).

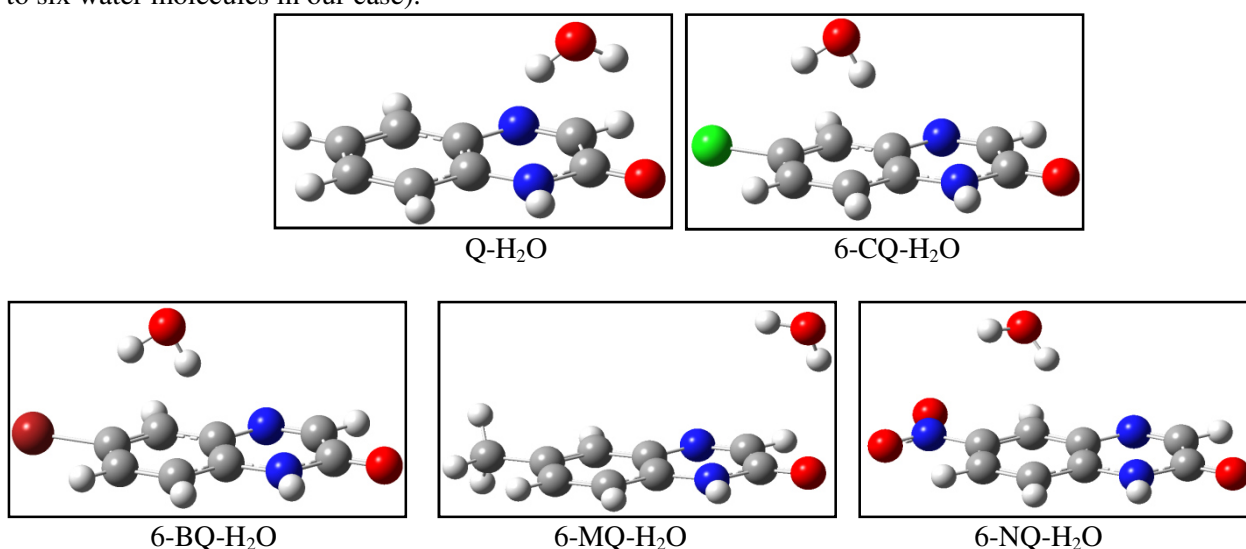


Figure 2: Optimized structures of quinoxalin-2(1H)-one, 6-CQ, 6-BQ, 6-MQ and 6-NQ on interaction with one water molecule.

The various values of total interaction energies (E_i) of complexes 1-*n* are gathered in tables 1, 2, 3, 4 and 5 for different values of angle α of quinoxalin-2(1H)-one and its four derivatives. One regards as supermolecules those whose absolute values of the total interaction energy are large, i.e. the forms in which the water molecules interact with them and with aqueous solvent molecules.

The result is obtained by using the AMYR formalism under the most stable conformation of quinoxalin-2(1H)-one in interaction with a water molecule; this shows that the N=C double bond is the most favorable site. Indeed, the water molecule is located in a plane perpendicular to the heterocycle plane, and one of hydrogen atoms interacts with the π electrons of the N=C double bond and other hydrogen is pointed toward the hexagonal ring. Thus the values of the interaction energy (-11.52 kcal/mol) and of the average interatomic distance (2.5 Angström) show that it is approximately a specific interaction by hydrogen bonding of the type OH... π .

3.2. Intermolecular interaction quinoxalin-2(1H)-one–water

Experimentally, the single-crystal structure of quinoxalin-2(1H)-one (C₈H₆N₂O) was determined at room temperature. The compound is orthorhombique, *P2₁2₁2₁* with *Z* = 4, the molecule is none symmetrical. The unit-cell dimensions are *a* = 21.318 (3) Å, *b* = 7.350 (1) Å, *c* = 4.350 (1) Å, *V* = 681.6 Å³ and *d* = 1.424 g.cm⁻³.

Calculation of interaction energy with the surrounding water molecule(s) was undertaken systematically. The complexes (quinoxalin-2(1H)-one – *n* water molecules) correspond to the energy minima. Research on different minima was performed for different values of the angle α ; these minima are listed in Table 1.

Table.1: Total interaction energy (*E_t*) (in Kcal/mol) of complexes (1-1) to (1-6) according to the angle α (in degree) of quinoxalin-2(1H)-one.

$\alpha(^{\circ})$	118	119	120,320	121	122	123	124
1-1	-12,660	-12,674	-11,523	-11,675	-12,714	-12,726	-12,739
1-2	-24,247	-24,229	-39,620	-39,983	-38,593	-38,719	-24,231
1-3	-40,246	-48,719	-51,635	-52,331	-49,948	-49,961	-40,402
1-4	-41,402	-51,500	-74,530	-75,147	-52,208	-50,329	-41,924
1-5	-43,473	-52,404	-74,666	-75,624	-68,836	-54,258	-48,565
1-6	-43,986	-54,190	-77,754	-75,689	-69,970	-54,262	-57,657

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 (quinoxalin-2(1H)-one – *n* water molecules) with (*n*=2,3,4,5 and 6) for different values of the intracyclic angle α of quinoxalin-2(1H)-one. Complex 1–2 is formed by addition of a second water molecule to complex 1–1. In this case, two forms of supermolecule are essential; those different by provision of two water molecules compared with the aqueous solution molecule. Total interaction energies of the forms (a) and (b) (Fig. 3) are, respectively, approximately –39.620 and –14.675kcal/mol. According to these two values, one notes that the supermolecule having the form (a) is energetically the 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 (quinoxalin-2(1H)-one – 2 water molecules) having similar values of the angle α = 120,320°, 121°, 122° and 123°. These supermolecules are thus statistically equiprobable because one cannot support a complex compared with the other.

Addition of a third water molecule to complex 1–2 for different values of the angle α indicates that the supermolecules having angles 120,320° and 121° are almost isoenergetic and correspond to the most stable conformations (Fig. 4).

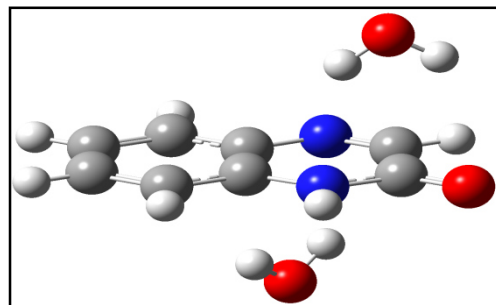
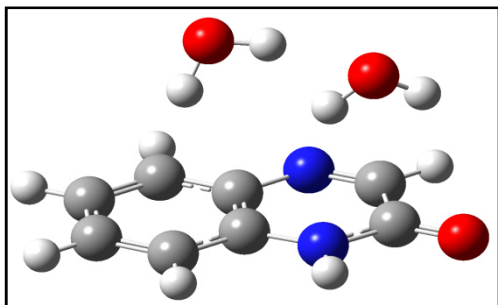
By adding a fourth, fifth, and sixth water molecule to each conformation of the supermolecule 1–3, one finds the same conformations of balance of the complex 1–3 (Table 1). Therefore, the interactions induced by the fourth, fifth, and sixth water molecules are not distinct from those induced by the third molecule. The variation of the interaction energy of the water molecules, between complexes 1–3 and 1–4 relating to the angle 120,320°, is approximately 23 kcal/mol. These intermolecular interaction calculations thus suppose, once quinoxalin-2(1H)-one is in solution in protic solvents, two forms of supermolecule (α = 120,320° and 121°) can coexist with close statistical proportions and are stabilized primarily by interaction of the water molecules between them, which become rather important.

3.3. Intermolecular interaction 6-chloroquinoxalin-2(1H)-one–water/ 6-bromoquinoxalin-2(1H)-one–water

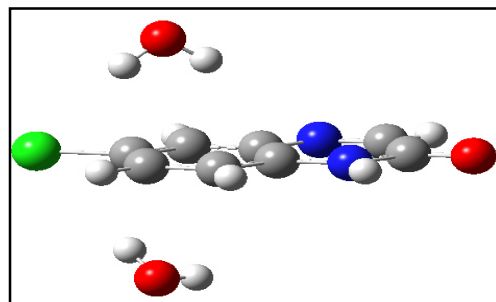
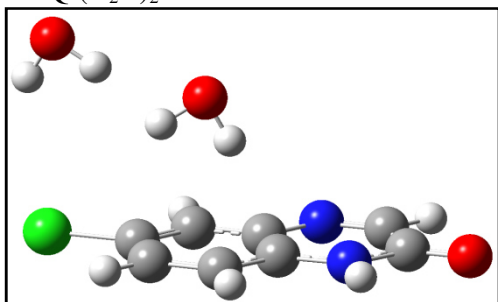
Experimentally, the single-crystal structure of 6-chloroquinoxalin-2(1H)-one (C₈H₅N₂OCl) was determined at room temperature. The compound is orthorhombique, *Cmca* with *Z* = 8, the molecule is none symmetrical. The unit-cell dimensions are *a* = 7.374 Å, *b* = 7.736 Å, *c* = 26.200 Å, *V* = 1495 Å³ and *d* = 1.605 g.cm⁻³.

Table 2 and 3 lists the minimum values of the total interaction energy (*E_t*) obtained for interactions of a 6-chloroquinoxalin-2(1H)-one and 6-bromoquinoxalin-2(1H)-one molecule with *n* (*n* = 1, 2, 3, 4, and 5) water molecules for various values of the angle α located at level of the intracyclic nitrogen atom.

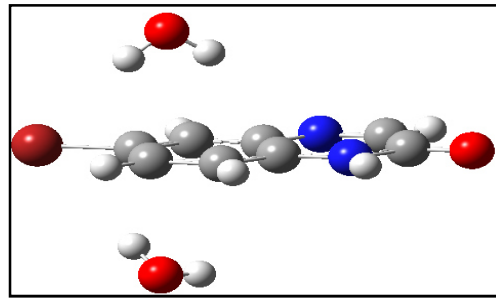
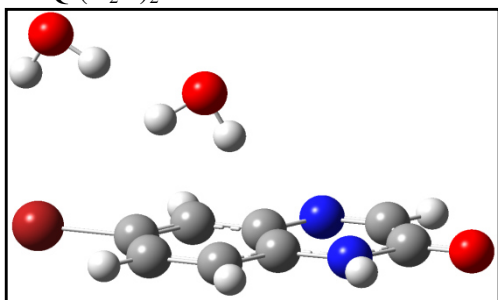
Q-(H₂O)₂



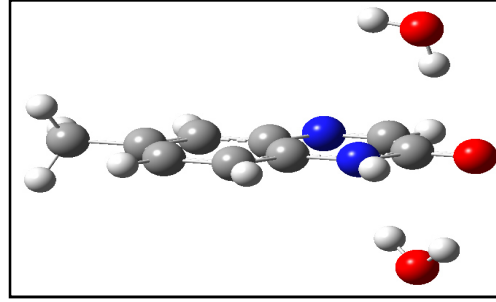
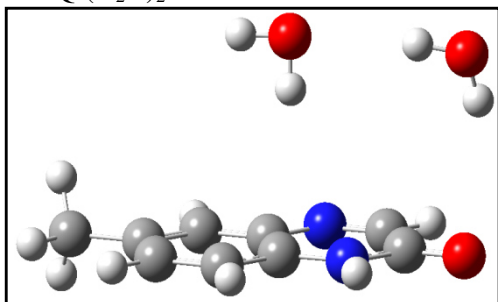
6-CQ-(H₂O)₂



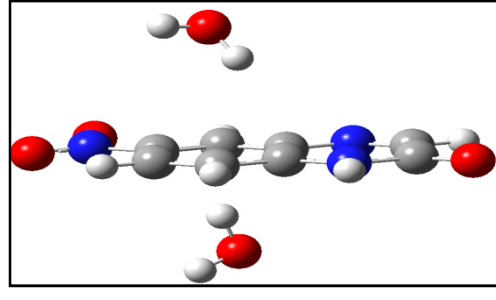
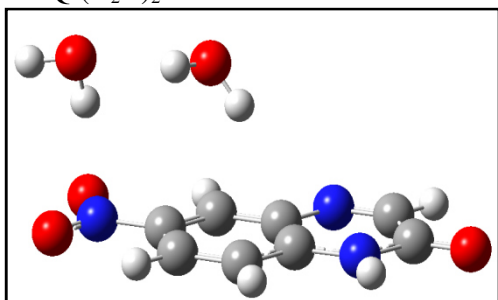
6-BQ-(H₂O)₂



6-MQ-(H₂O)₂



6-NQ-(H₂O)₂



(a)

(b)

Figure 3: Two forms (a) and (b) of quinoxalin-2(1H)-one and its derivatives on interaction with two water molecules.

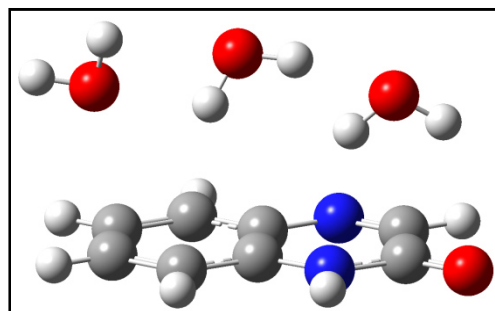


Figure 4: The most stable conformation of complexes Q-(H₂O)_n

Table.2: Total interaction energy (E_t) (in Kcal/mol) of complexes (1-1) to (1-5) according to the angle α (in degree) of 6-chloroquinoxalin-2(1H)-one.

$\alpha(^{\circ})$	116	117	118	119	120,192	121	122	123
1-1	-5,332	-5,328	-5,327	-5,330	-5,325	-5,325	-5,323	-5,316
1-2	-14,507	-14,528	-14,544	-14,558	-14,569	-14,583	-14,602	-14,615
1-3	-26,663	-26,705	-26,686	-26,774	-26,714	-26,641	-26,615	-26,598
1-4	-42,244	-42,396	-42,490	-43,692	-43,476	-42,445	-42,422	-42,145
1-5	-44,974	-45,375	-46,463	-49,386	-47,129	-46,047	-46,026	-45,073

Table.3: Total interaction energy (E_t) (in Kcal/mol) of complexes (1-1) to (1-5) according to the angle α (in degree) of 6-bromoquinoxalin-2(1H)-one.

$\alpha(^{\circ})$	116	117	118	119	120,181	121	122	123
1-1	-5,506	-5,502	-5,501	-5,504	-5,499	-5,499	-5,497	-5,490
1-2	-14,681	-14,702	-14,718	-14,732	-14,743	-14,757	-14,776	-14,789
1-3	-26,837	-26,879	-26,860	-26,948	-26,888	-26,815	-26,789	-26,772
1-4	-42,418	-42,57	-42,664	-43,866	-43,650	-42,619	-42,596	-42,319
1-5	-45,148	-45,549	-46,637	-49,56	-47,303	-46,221	-46,200	-45,247

Analysis of Table 2 and 3 shows that the interactions induced by one and two water molecules are insufficient to support a well defined conformation, and that the complex 1-3 having the angle 120° has an interaction energy which is favored as much than the complex 1-3 having angles 117°, 118° and 119°. These four supermolecules are thus statistically equiprobable and have the most stable energy. The interaction induced by three water molecules on the 6-CQ and 6-BQ molecule is insufficient to support a well defined conformation.

The values of this table indicate that at the time of interaction of the 6-CQ and 6-BQ molecule with four water molecules the most stable conformations energetically are those which correspond to the complexes where $\alpha = 119^{\circ}$ and 120° . Therefore, the interaction induced by a fourth water molecule is also insufficient to support a quite precise conformation. One is interested primarily in conformations in which the interaction between the water molecules is maximum. The data in Table 2 and 3 shows that when the 6-CQ and 6-BQ molecule interacts with five water molecules, the most stable conformation corresponds to an angle α of 119° (Fig. 5). The energy brought by the fifth water molecule compared with complex 1-4 is approximately -5.7 kcal/mol.

3.4. Intermolecular interaction 6-methylquinoxalin-2(1H)-one-water/ 6-nitroquinoxalin-2(1H)-one-water

Experimentally, the single-crystal structure of 6-méthylquinoxalin-2(1H)-one (C₉H₈N₂O) was determined at room temperature. The compound is monoclinique, $P2_1/c$ with $Z = 4$, the molecule is none symmetrical. The unit-cell dimensions are $a = 4.506 \text{ \AA}$, $b = 7.568 \text{ \AA}$, $c = 23.289 \text{ \AA}$, $V = 785.9 \text{ \AA}^3$ and $d = 1.354 \text{ g.cm}^{-3}$. Other, the single-crystal structure of 6-nitroquinoxalin-2(1H)-one (C₈H₅N₃O₃) was determined at room temperature. The compound is monoclinique, $P2_1/n$ with $Z = 4$, the molecule is none symmetrical. The unit-cell dimensions are $a=4.856(2) \text{ \AA}$, $b = 12.438(3) \text{ \AA}$, $c = 13.019(10) \text{ \AA}$, $\beta = 93.09(2)^{\circ}$, $V = 785.2(4) \text{ \AA}^3$ and $d = 1.617 \text{ g.cm}^{-3}$.

The total interaction energy minima (E_t) obtained for different values of the angle α varying from 116° with 123° in steps of 1° , are listed in the Table 4 and 5.

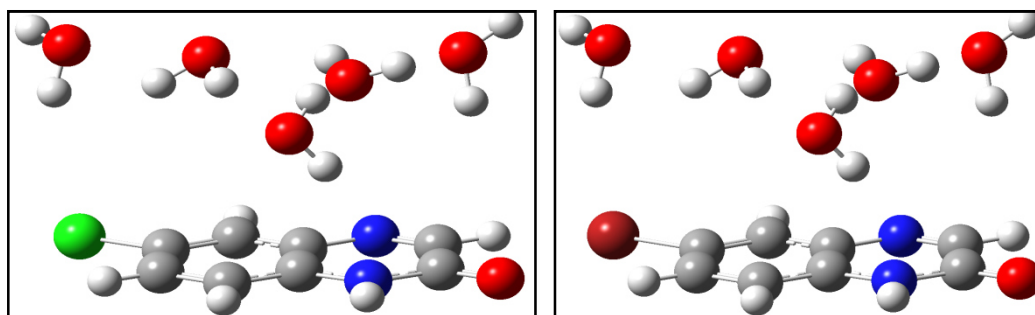


Figure 5: The most stable conformation of complexes 6-CQ-(H₂O)_n and 6-BQ-(H₂O)_n

Table.4: Total interaction energy (E_i) (in Kcal/mol) of complexes (1-1) to (1-6) according to the angle α (in degree) of 6-methylquinoxalin-2(1H)-one.

α (°)	116	117	118	119	120,267	121	122	123
1-1	-13,020	-13,034	-13,047	-13,060	-13,074	-13,086	-13,099	-13,112
1-2	-13,655	-13,671	-13,684	-13,697	-13,711	-13,723	-13,736	-13,751
1-3	-30,435	-30,026	-30,778	-31,043	-31,064	-30,077	-30,081	-30,093
1-4	-36,440	-38,284	-40,421	-41,328	-40,563	-37,614	-33,325	-32,432
1-5	-48,711	-46,055	-56,709	-55,976	-53,637	-49,571	-49,609	-50,061
1-6	-54,990	-56,870	-59,363	-51,383	-52,300	-51,667	-50,303	-50,470

Table.5: Total interaction energy (E_i) (in Kcal/mol) of complexes (1-1) to (1-6) according to the angle α (in degree) of 6-nitroquinoxalin-2(1H)-one.

α (°)	116	117	118	119	120,293	121	122	123
1-1	-13,194	-13,208	-13,221	-13,234	-13,248	-13,260	-13,273	-13,286
1-2	-13,829	-13,845	-13,858	-13,871	-13,885	-13,897	-13,910	-13,925
1-3	-30,609	-30,200	-30,952	-31,217	-31,238	-30,251	-30,255	-30,267
1-4	-36,614	-38,458	-40,595	-41,502	-40,737	-37,788	-33,499	-32,606
1-5	-48,885	-46,229	-56,883	-56,150	-53,811	-49,745	-49,783	-50,235
1-6	-55,164	-57,044	-59,537	-51,557	-52,474	-51,841	-50,477	-50,644

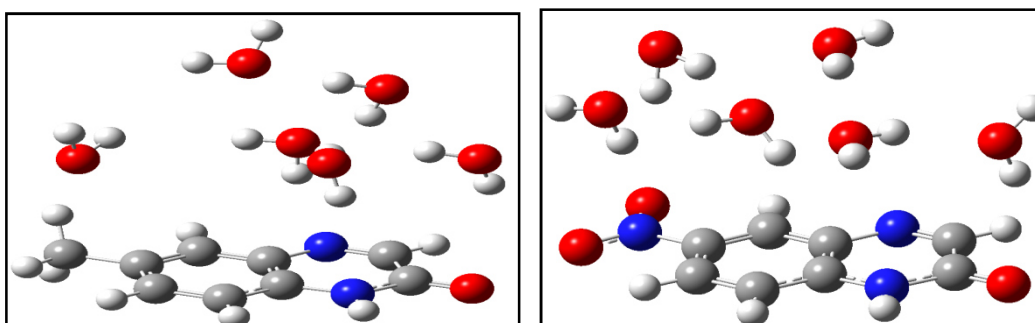


Figure 6: The most stable conformation of complexes 6-MQ-(H₂O)_n and 6-NQ-(H₂O)_n

This tables shows that interactions induced by one or two water molecules are insufficient to support well defined conformation, and that at the time of interaction of the molecule with three and four water molecules, the most stable conformation energies are those which correspond to the complexes for which the angle $\alpha = 118^\circ$, 119° et 120° . This table also indicates that when the 6-MQ and 6-NQ molecule interacts with five water molecules the most stable conformation energies are those corresponding to the angles $\alpha = 118^\circ$ and 119° . The interaction induced by five water molecules does not support a quite precise conformation. The most stable conformation energies correspond to the angle $\alpha = 118^\circ$ (Fig. 6) and this is for the supermolecule complex with six water molecules. Therefore, the increase in the interaction energy of the water molecules between them further stabilizes the supermolecule.

Conclusion

We performed calculations of intermolecular interaction by use of AMYR formalism to simulate the effect of the surrounding medium and to locate the most active site. Indeed, for the quinoxalin-2(1H)-one molecule we found that the π systems of the two rings are involved in interaction with the water molecule. Calculation of the intermolecular interaction envisages also the possibility of interaction by hydrogen bonding and a conformational change when this bond interacts with molecules of the solvent (water) ready to be complexed with the aqueous solution molecule; for the molecules 6-CQ, 6-BQ, 6-MQ and 6-NQ only the hexagonal ring constitutes the interaction zone.

For quinoxalin-2(1H)-one, the interaction energy calculation for complex 1–3 for different values of the angle α indicates that the supermolecules relating to angles 120.32° and 121° are almost isoenergetic (-77.754 and -75.689 kcal/mol) and correspond to the most stable conformations. When the 6-CQ and 6-BQ molecule are in interaction with five water molecules, the most stable conformation corresponds to an angle α of 119° with an interaction energy of approximately $-49,386$ and $-49,560$ kcal/mol. For 6-MQ and 6-NQ the results indicate that the most stable conformation energetically corresponds to the angle $\alpha = 118^\circ$ with an energy of $-59,363$ and $-59,537$ kcal/mol and the complex is a supermolecule with six water molecules. Ces résultats est compatible avec celle que nous avons trouvé récent sur les benzodiazépines [23].

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