Asian Journal of Chemistry; Vol. 29, No. 7 (2017), 1405-1412

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20363

Comparative Studies of Chromen Derivatives by Using Numerical Methods

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Received: 20 October 2016; *Accepted*: 18 February 2017; *Published online*: 13 May 2017; AJC-18362

This study consists to develop program of molecular dynamics and to setup a method for calculations combined with *ab initio* (DFT and HF) to undertake theoretical investigations on products 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin. Studies were undertaken through a use of molecular program of dynamics for various both isothermal-isobaric NPT and canonical NVT of these products. It is showed that the classical approach gives good performances by means of simulation by molecular dynamics. Density functional theory calculations, B3LYP/6-31G, was performed for the determination of geometrical structure and vibrational assignment for the three systems. Full discussion of the framework vibrational modes was done using as criteria the study of the distorted geometric structures generated for each one of the vibrational modes in the low energy region. As results of this research we have obtained and characterized a novel 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin, 7-hydroxy-4-methyl coumarin and we deduced the most probable structure using the experimental data of the infrared spectrum in conjunction with the theoretical DFT procedures. The calculated DFT spectra in the high and low energy regions agree well with the observed ones. The 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin were characterized by elemental analysis, IR, ^{1}H NMR and mass spectrometry. It is hoped that this model with a intermolecular reaction could be an effective starting material for studying the properties of complex system in polar solvent and apolaire.

Keywords: Coumarin, Chromen, Biological activity, Molecular dynamics.

INTRODUCTION

The prediction of thermodynamic properties of toxic system is still an issue of interest in simulation. The literature shows that these systems are widely investigated in both experimental and theoretical ways [1,2]. Theoretically new simulations with path-integral formalism have been conducted to obtain thermodynamic properties and the quantum radial functions involving Feynmann-Hibbs potentials were used for toxic liquid [3]. Present work based on the appraisal of the statistical uncertainties of computed data compared to the experimental or theoretical data when available, it is 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin, 7-hydroxy-4-methyl coumarin. The use of the coumarin derivatives had great success in the organic synthesis. This approach takes on a very particular interest in the fields of antibacterial, antifungal, pest-destroying and antitumor [4,5]. Currently, the coumarinic reasons are used in the field of biotechnologies (fluorescent probes) [6] and likely to have very varied biological effects. The molecule 7-hydroxy-4-methylcoumarine is thus used like ligand fluorescent [7] and starting product for the insecticidal preparation of derivative of hymerocromone [8].

Coumarin present is in many perfumes and one finds the skeleton of coumarin in certain drugs such as the warfarin which is an anticoagulant. Several methods of synthesis are employed for the preparation of coumarins. We find in the literature the following reactions: Perkin [9], Pechmann [10], Knovennagel [11], Reformatsky [12] and Wittig [13]. The simplest cyclic coumarin is obtained mainly by the reaction of Pechmann. The latter consists of three stages: Reaction of cross esterification, followed by an intra-molecular reaction of hydroxy alkylation and ends in a reaction of dehydration. As the reaction is catalyzed, the acids most employed are of Brønsted. Coumarins are benzopyran derivatives. Naturally occurring coumarins have been isolated from over 800 species of plants and microorganisms [14] and many of these natural products exhibit useful drug like activity [15,16]. Moreover, coumarins are a group of compounds that play important roles as food constituents, antioxidants, stabilizers and immunomodulatory substances, as fluorescent markers for use in analyses, in stains and in clinical use [17,18]. Innovative frameworks are needed to integrate these data rich and diverse new for a systematic investigation of the determinants of the toxicity test, including chemical, biological and genetic factors.

The work on 4-hydroxy-chromen-2-one as antimicrobial agents has been cited by Maladenovic *et al.* [19]. We have studied the different properties of some coumarin systems by molecular dynamics by Mesli *et al.* [20,21] as well as work of Mahboub *et al.* [22]. The study of 5,7-dihydroxy-4-methyl coumarin are reported by molecular dynamic and Langevin method simulation. The goal of this set of themes and to put the agreement enters the experimental and theoretical results. The goal of this set of themes and to put the agreement enters the experimental and theoretical results for that, we have to carry out calculate theoretical Gaussian and ^{1}H NMR of 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin. The choice was on the study of the evolution of these molecules au course of time. Simulation has was operated in a unit which keeps the pressure, the temperature fixes for both isothermal-isobaric in addition by maintaining the temperature and volume constants for both canonical. The temperature was maintained constant thanks to the thermostat of Andersen who couples speeds of the atoms with a bath external with a constant of relieving of 0.1 ps. For this purpose our major interest of is compared our results got by molecular dynamics (DM) and estimated NMR has those obtained by red infra and experimental NMR.

In this study, we compared the results of the various thermodynamic and structural properties of the 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin obtained by molecular dynamics. A system simulated with balance is used to measure the structural properties. These last allow the description of the structure based on the functions of radial distribution G (R). The choice of the model of potential of reference L-J and the method of molecular dynamics led both to precise results. Moreover one algorithmic implementation of molecular dynamics was developed which has enables to evaluate the properties of coumarin and these derivatives with precision. It is noted that the study of the thermodynamic properties using simulation by molecular dynamics is a method of choice and conduit to results quite precise and close to the experiment. In order to supplement this set of themes. We considered to be useful to validate our results theoretical and spectroscopic got by the calculation of the displacement of the proton. For this purpose our major interest is to put the point on the reliability of the technique at knowing the agreement of various calculated properties. Knowing, the respective activities, we wish to check by this study the relation structure activity for this kind of reasons. The results obtained are compared with those in the literature, particularly with Mesli *et al.* [20,21].

Present results close to the experimental demonstrate the reliability of the numerical model and the potential accuracy of the model chosen. We compared various thermodynamic properties for two units NVT and NPT for the system 7-hydroxy-4-methylcoumarine, 5,7-dihydroxy-4-méthylcoumarine and 4-hydroxy chromene-2-one. The importance, in the use of simulation, is to acquire a comprehension of fundamental physics simulation is based on certain macroscopic phenomena or the comparison with the theoretical predictions. Mesli *et al.* [20,21] endeavour to establish a link between the macroscopic properties and the intermolecular forces and thus, the potential of interaction used is realistic and the behaviour of the model is close to the real physical system. However, the potential of interaction is only one arrangement (empirical, no empirical or semi empirical) in order to produce certain physical properties. In the choice of the functions of potential, it is a question of assigning the physical properties of the intermolecular interactions to the movements of the particles, this is why the measured quantities are sensitive to this function. However, the results of simulation must be in agreement with the experimental data.

Statistical accuracy of calculated data are carried out and compared to available data, either experimentally or theoretically.

EXPERIMENTAL

Numerical model: Molecular dynamic calculations were performed on a sample of size N = 256 molecules of masse m. The system of interest is 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin in different thermodynamic state points SP(ρ,T) quoted in former work [21]. Each point is characterized by the density (g; cm^3) of the system and temperature T(K). In the following calculation, the system consists of 256 molecules in the molecular dynamics box. We have described the numbers of close molecules obtained by integration to the FDR and determined the properties of 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin. Only molecules of pure compound are considered in the spherical intermolecular interaction. Long range correction are also applied. The integration scheme uses a constant time step algorithm $Dt = 5.10^{-15}$ S. Molecular dynamics simulation techniques are widely used in experimental procedures such as X-ray crystallography and NMR structure determination. Adverse human effects depend on the nature of product, the amount absorbed, the pathway in the body and sensitivity of individuals. Molecular dynamics is a useful technique to study the kinetics and thermodynamics properties of proteins and other bimolecular. This method savers indispensable for any study, our work on the system coumarin was to develop by this method which leads to the best results compared with the theoretical results. Then in order to compare their chemical shifts we have carried out calculate NMR of the proton on the three systems 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methylcoumarin and 7-hydroxy-4-methylcoumarin. This technique was also useful in the quantitative determination of the species absorbance set the molecular structure. Moreover, to obtain information on the environment (natural of the close neighbours) around the central molecule. This method of analysis is used as well in structural analysis as in quantitative analysis. The meeting of a device performing and a computer can lead to exceptional results. A good agreement is obtained with B3LYP/6-31G. In the same way for the NMR, which became essential tools and incomparable.

The configurations which reproduced the peaks of radial distribution functions obtained by molecular dynamics have been considered (Fig. 1). These configurations were drawn using the ACD/ChemSketch. For the spherical interaction, we have considered 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin in position such that these molecules for all the sites are taken in spherical approximation. The molecule i and j of example 4-hydroxy-chromen-2-one are in contact. The distance r1 between the molecule i and the molecule j (with two molecule are in spherical contact) reaches its maximum. This situation corresponds to the peak in g(r)ij. The highest separation is happening when the three molecules i, j and k of example 4-hydroxy-chromen-2-one are in contact (configurations 1-A 1-B and 1-C in Fig. 1). This separation is self-sufficient from the orientation of molecule i and j in space. The configurations responsible of the peaks in Fig. 1 are shown in the representations 2-A, 2-B and 3-A, 3-B and for 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin. From these results, we confirm that the prediction of discontinuities and the top help for explained the unusual form in the function of correlation for our model of potential and that the top which occurs in G (R) is transformed for the model of Lennard-Jones more realistic into small peak at long life.

RESULTS AND DISCUSSION

Structural properties: The periodic conditions around limps cubic power station with the truncation of the minimum image were implemented in calculations. The corrections with long ranges were included. The initial configuration of a solid of structure cubic to face centered (CFC) for the positions of the molecules. Initial speeds are assigned to each molecule according to a law of distribution of Maxwell-Boltzmann. The equilibrium cycle develops over one period of 50 ps. The phase of production of the data extends over one period of 50 ps going as far as 250 ps to increase the precision on the collective functions of autocorrelation. Although the results which we got take account of the corrections with long ranges, we considered to be necessary to calculate the fluctuations on the thermodynamic properties during the 50 ps after the balance of simulation. These results of the digital simulation made it possible to determine the parameters affecting the structure of coumarin and these derivatives and their stabilities in the course of time. Among these parameters, we can quote the number of the close relation, the energy of configuration, as well as the structure. An optimization thus comparative study simulation experiment was presented. Analysis of curves were obtained [22]. We have calculated the numbers of close molecules obtained by integration to the FDR, as well as the position of different maximum and minima for all the two points deferred in Table-1 for coumarin and its derivatives. The number of close relation is given by:

$$n(R) = 4\pi\rho\int_{0}^{R} r^2\, g(r)dr \qquad (1)$$

For a unit NVT, the interaction between center-center the molecules during simulation gives the maximum positions of close molecules per contribution to the central molecule. Present results by molecular dynamic give the first equal maximum at 1.33 for molecule $C_{10}H_8O_3$, a maximum peak of 1.55 for molecule $C_9H_6O_3$ is finally R max for the molecule $C_{10}H_8O_4$ equal at 1.40. These results justify the reliability of the choice of potential (good parameter setting) as well as the

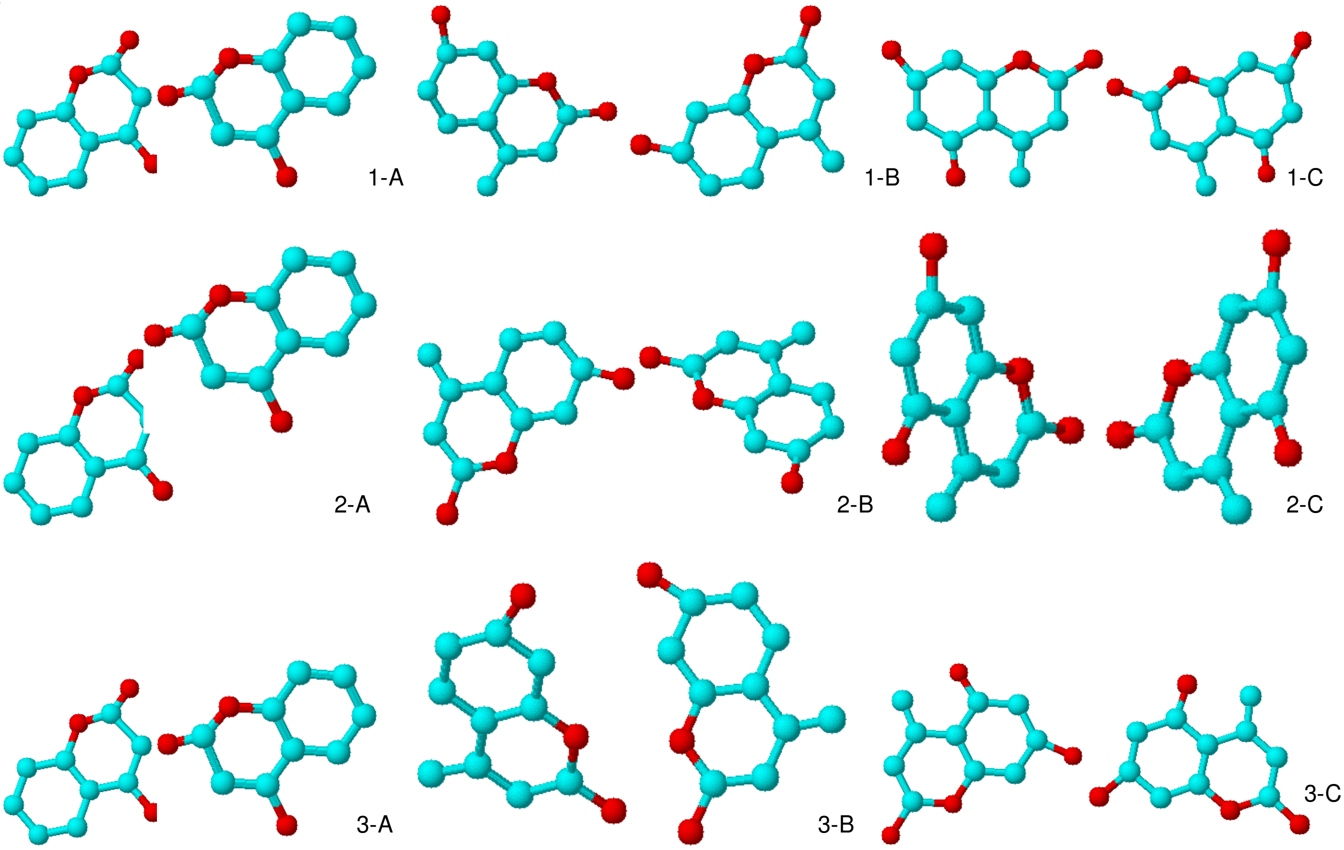
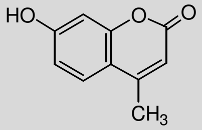
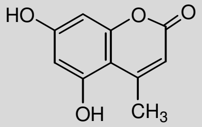
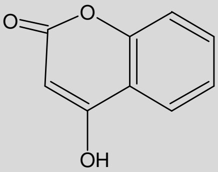


Fig. 1. Main pair interaction of two molecules in spherical approximation: A) 4-hydroxy-chromen-2-one, B) 5,7-dihydroxy-4-methyl coumarin and C) 7-hydroxy-4-methyl coumarin

TABLE-1
POSITION OF PEAKS AND THE NUMBER OF NEIGHBOURS AND THE RANGE IN NVT AND NPT UNIT OF 4-HYDROXY-CHROMEN-2-ONE ($C_9H_6O_3$), 5,7-DIHYDROXY-4-METHYL COUMARIN ($C_{10}H_8O_4$), 7-HYDROXY-4-METHYL COUMARIN ($C_{10}H_8O_3$)

Compound	m.f.	Ensemble	RMAX1	NMAX1	Area
	$C_{10}H_8O_3$	NPT NVT	1.33 1.31	42.06 42.06	9.53 9.53
	$C_{10}H_8O_4$	NPT NVT	1.40 1.45	38.45 38.45	8.42 8.42
	$C_9H_6O_3$	NPT NVT	1.55 1.45	55.02 53.00	12.55 10.55

good choice of the algorithm to model this type of the system. Analysis of the curves quoted in the reveals us the following results. Trisubstituted coumarin gives a strong peak. This last confirms the existence of two attractive effects (OH) and an effect donor (CH_3). This peak falls thus with the number of substituents. The disubstituted molecule gives a peak to 0.55 s and not substituted coumarin gives a peak minima to 0.5 s, on the other hand the chromen gives a peak strong that of to the existence of an attractive grouping (OH) in third close position with the double connection carbon-oxygen. We find the same results on the level of the biological activity. Thus the disubstituted isomer is more active than trisubstituted isomer. Position of peaks and the number of neighbours are given in Fig. 2.

Thermodynamic properties: Using an approach by digital simulation of molecular dynamics, we studied the evolution of the various thermodynamic properties in the course of time, for two units NVT and NPT [20]. The thermodynamic properties (P*, U*, H*) are calculated in reduced units from the related references [23,24]. All the results are given in Table-2.

It is noticed that the evolution of energy changes according to the increase in the temperature. In addition, the increase in energies is important for the trisubstituted derivative, which confirms the stability of this molecule substituted with respect to others two coumarin derivatives. We also noted that the internal energy is more significant for system NPT. The same remarks apply for the variation of the enthalpy safe for derivative $C_{10}H_8O_4$ where the situation is reversed. The pressure is irregular and changes according to the change of the temperature. Its value varies and increases with the substitution of the molecule and becomes important for unit NVT.

Using the molecular dynamics simulation approach, we have studied the thermodynamic properties of 4-hydroxy-chromen-2-one, 5,7-dihydroxy-4-methyl coumarin and 7-hydroxy-4-methyl coumarin in NVT and NPT ensemble. Energy interns is the total energy of the system. It corresponds the sum of the potential energy U and the kinetic energy of translation and rotation that can be utilized by the following form.

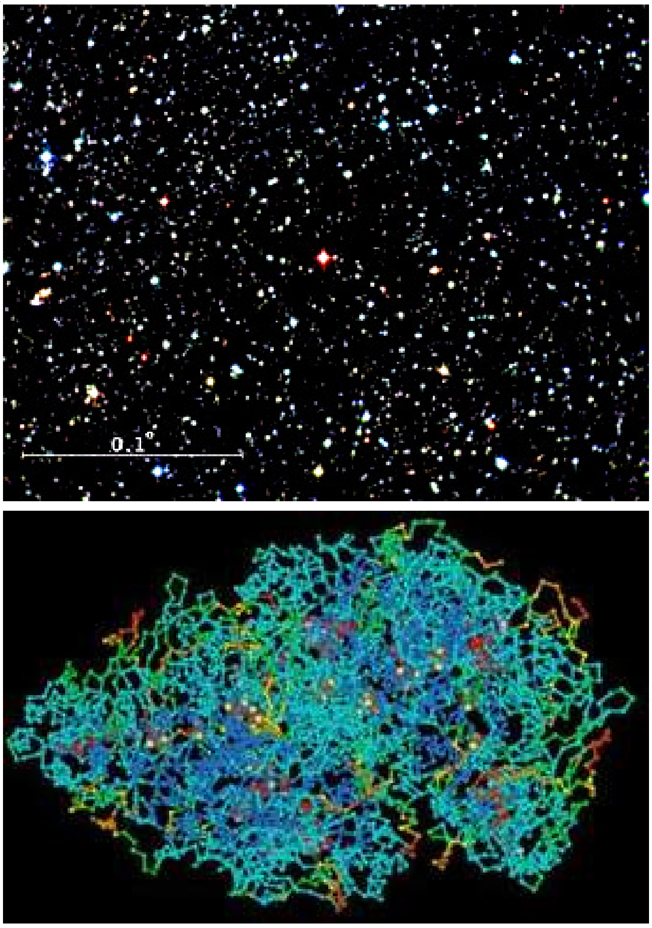


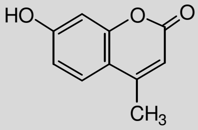
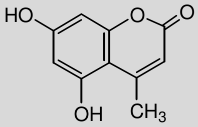
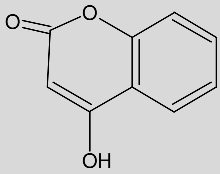
Fig. 2. Geometry of pair interaction of two molecules in spherical approximation of chromen system

$$ET = (EKT + EKR) + U \tag{2}$$

$$EKT = \frac{1}{N}\sum\left[\sum\left(m_i \frac{v_i^2}{2}\right)\right] \tag{3}$$

$$EKR = \frac{1}{N}\sum\left[\sum\left(I \frac{w_i^2}{2}\right)\right] \tag{4}$$

TABLE-2
THERMODYNAMIC PROPERTIES CALCULATED IN REDUCED UNITS FOR NVT AND NPT.
ENTHALPY H* = H/Nε, PRESSURE P* = P σ^{-3}/ε AND ENERGY OF CONFIGURATION U* = U/Nε

Ensemble	Molecular dynamics	H*	P *	U *
NVT		-0.0178 ± 0.0001 -0.3560 ± 0.1356 -8.225 ± 0.34500	0.4256 ± 1.5845 0.2536 ± 1.2360 0.122 ± 0.12500	-0.0687 ± 0.00726 -0.2546 ± 0.12560 -9.125 ± 0.057000
NPT		-0.0562 ± 0.0256 -0.2458 ± 0.0524 -8.005 ± 0.24500	0.3256 ± 1.52365 0.1560 ± 1.12450 0.2110 ± 0.12200	-0.0452 ± 0.1236 -0.1986 ± 0.1522 -9.012 ± 0.05700
NPT		-0.0487 ± 0.0140 -0.2047 ± 0.0500 -7.1255 ± 0.2012	0.2016 ± 1.50450 0.1074 ± 1.12050 0.2520 ± 0.15250	-0.0307 ± 0.1254 -0.1562 ± 0.12100 -9.5202 ± 0.0241

$$U = \frac{1}{N}\sum\left[\sum\sum\left(U\left(r_{ij}\right)\right)\right] \tag{5}$$

$$ET = \frac{1}{N}\sum\left[\sum\frac{m_i v_i^2}{2}+\sum I\frac{w_i^2}{2}+\sum\sum\left(U\left(r_{ij}\right)\right)\right] \tag{6}$$

where m is the mass of particle i, v_i is the speed, I is inertia moment and w_i angular speed.

It was necessary to calculate the total energy, because it allows checking the accuracy of the algorithm and especially testing the evolution of the system in equilibrium [25].

The evolution of the intern energy and Hamiltonien system in time for the three systems were evaluated. We can concluded that the thermostat settings are kept constant over time. Thermostat system is balanced for both movements in time. Fluctuations on the intern energy and Hamiltonien at equilibrium are low energy oscillates around a constant value (Figs. 3 and 4).

It is noticed that the energy interns for the derivatives of the chromen is preserved and fluctuates around a fixed value and after having reached its state of balance starting from a CFC structure. Thus the chart of the internal energy of the system according to the iteration count remain similar for same the points U = 0.0453 in reduced unit in both NPT. This energy is much more important within the framework where the molecule is substituted in $C_{10}H_8O_4$. The value of internal energy decreases according to nature of the groupings substituted ($C_{10}H_8O_3$) is less outstanding by contribution has $C_9H_6O_3$. Thus, more the drifts of the chromen are substituted, more the molecules are less stable and their energies are important (Fig. 4).

The pressure tends to be stabilized for the three compounds in the course of time (Fig. 5).

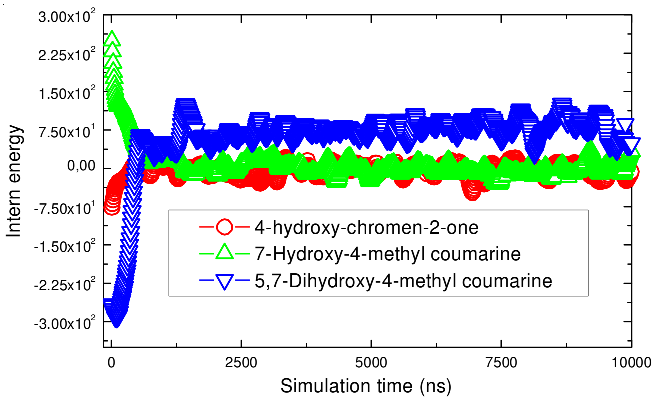


Fig. 3. Evolution of the intern energy in NVT unit

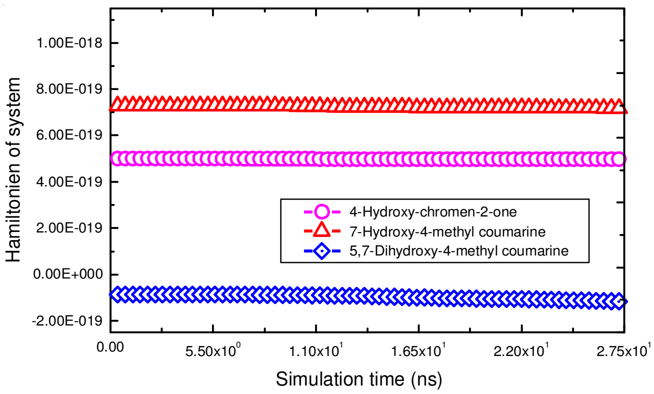


Fig. 4. Evolution of Hamiltonien in NVT unit

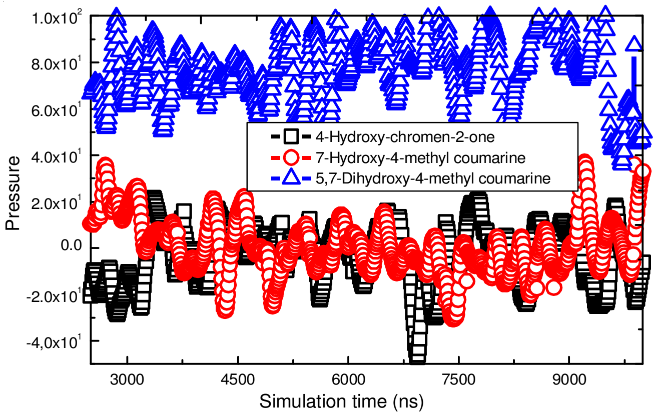


Fig. 5. Evolution of the pressure in NVT unit

The pressure is calculated by the theorem of virial coefficients from the following equation:

$$P = \frac{1}{3V}\left(2E_c - \Psi\right) \qquad (7)$$

$$\Psi = \frac{1}{N}\sum\left[\sum\sum\left(r\frac{\partial}{\partial r_{ij}}U\left(r_{ij}\right)\right)\right] \qquad (8)$$

$$P = \frac{2}{3V}E_c - \frac{1}{3VN}\sum\left[\sum\sum\left(r\frac{\partial}{\partial r_{ij}}U\left(r_{ij}\right)\right)\right] \qquad (9)$$

Ψ: the virial is simply the product of the force of interaction by the ray of interaction and V is the total volume.

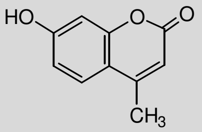
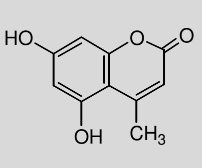
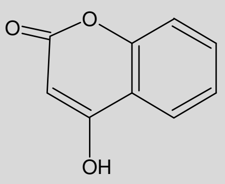
The pressure is irregular and changes according to the temperature for simple coumarin. For substituted isomers, the pressure is stabilized in the course of time. The pressure in molecular dynamics can be computed from the kinetic energy and the viriel. The pressure is kept constant at the court of our simulation. Thus, the thermostatage proposed initially is validated and Lax-Wendroff algorithm is well suited (adapted).

Comparison between calculations of simulation and spectroscopic analyses: The chemical shifts of the proton of chromen and their substituted derivatives are compared with the other experimental work and presented in Table-3.

Table-3 showed that the δ values obtained a clear reduction for isomer more substituted except for the protons methyls. This last is a bulky group, located near a group rich in electron (OH) and attractive, which exerts an effect of weak shielding. Thus, the value increased towards the weak fields (from 2.41 to 2.50 ppm). In addition, the H_6 protons and H_8 are seen modified. For the 7-hydroxy-4-methylcoumarin ($C_{10}H_8O_3$), H_6 undergoes the effect of the current of the cycle and the anisotropy, which increase its chemical shift. In case of 5,7-dihydroxy-4-methyl-coumarin ($C_{10}H_8O_4$), H_6 is subjected to the two electronic effects of orbital nonflexible of oxygens of the -OH groups; H_8 is only under the effect of the current of cycle. For H_6, that results in a steric effect, which decreases its displacement. On the other hand in the case of 4-hydroxy-chromen-2-one $C_9H_6O_3$, the values obtained of δ reveal an increase for isomer less substituted. As displacement ∇, it is noticed that the difference most important are those obtained for the methyl group. This is due to the interactions which take account of the spherical form and the volume of this group. The presence of a form enol in balance with ketone gives negatives and more important for H_3 (-0.33) of the 5,7-dihydroxy-4-methylcoumarin.

Our results by B3LYP/6.311G** (to calculate) obtained for the calculation of the frequencies of substituted coumarins, very similar to those obtained par FT-IR are substituted [20]. These results are given in Table-4.

TABLE-3
CHEMICAL SHIFTS OF THE PROTON OF SUBSTITUTED COUMARINS

Composed	^{1}H NMR (δ ppm) (experimental)	^{1}H NMR (δ ppm) (estimated)*	Δ (ppm)
	A 300 MHz (DMSO-d_6) δ: 10.56 [s, 1H, OH]; 7.59 [d, 1H, 8.6 Hz, H5]; 6.80 [dd, 1H, 8.6 Hz, H6]; 6.70 [d, 1H, 8.6 Hz, H8]; 6.12 [s, 1H, H3]; 2.36 [s, 3H, CH$_3$][124].	7.46 [1H, H5]; 6.69 [1H, H6]; 6.67 [1H, H8]; 6.23 [1H, H3]; 1.71 [3H, CH$_3$].	+0.13 +0.11 +0.03 **-0.11** +0.65
	A 400 MHz (Acetone-d_6) δ: 9.50 [s, 1H, OH]; 7.59 [d, 1H, 8.6 Hz, H5]; 6.84 [dd, 1H, 8.6 Hz, 2.3 Hz, H6]; 6.72 [d, 1H, 2.3 Hz, H8]; 6.06 [s, 1H, H3]; 2.41 [s, 3H, CH$_3$][125].	7.46 [1H, H5]; 6.69 [1H, H6]; 6.67 [1H, H8]; 6.23 [1H, H3]; 1.71 [3H, CH$_3$].	+0.13 +0.15 +0.05 **-0.17** +0.70
	A 200 MHz (DMSO-d_6) δ: 10.5 [s, 1H, OH, H7]; 10.3 [s, 1H, OH, H5]; 6.30 [s, 1H, H8]; 6.20 [s, 1H, H6]; 5.90 [s, 1H, H3]; 2.50 [s, 3H, CH$_3$][121].	6.23 [1H, H8]; 6.16 [1H, H6]; 6.23 [1H, H3]; 1.71 [3H, CH$_3$].	+0.07 +0.04 **-0.33** +0.79
	A 200 MHz (CD3OD-d_6) δ: 12.6 [s, 1H, OH]; 7.84 [d, 1H, 6.9 Hz, H5]; 7.66 [d, 1H, 6.9 Hz, H2]; 7.40 [d, 1H, 6.9 Hz, H4]; 7.37 [t, 1H, H3]; 5.64 [s, 1H, H$_7$].	7.46 [1H, H5]; 7.48 [1H, H2]; 6.87 [1H, H4]; 6.57 [1H, H3]; 5.50 [1H, H7].	+0.38 +0.18 **+0.53** +0.8 +0.14
	A 300 MHz (DMSO-d_6) δ: 12.40 [s, 1H, OH]; 7.68 [d, 1H, 7.2 Hz, H5]; 7.53-7.48 [m, 1H, 7.2 Hz, H6]; 7.24-7.18 [m, 2H, 7.2 Hz]; 5.45 [s, 1H, H3];	7.53 [1H, H5]; 7.15 [1H, H6]; 5.55 [1H, H3].	+0.15 +0.35 +1.66

*Computed values by CS ChemDraw software; Δ (ppm) = δ (^{1}H experimental) - δ (^{1}H estimated).

It is found that trisubstituted coumarin gives a strong aptitude. The latter confirms the existence of two attractive effects (–OH) and an effect donor (–CH_3) (Fig. 6). This peak falls thus with the interaction of the pairs of first near close and second near close and also the number grouping to substitute. The disubstituted molecule gives an average aptitude and not substituted coumarin on the other hand gives an amplitude minimum the chromen gives a broad surface that of to the existence of an attractive grouping (–OH) in third close position to the double connection carbon-oxygen. We find the same results on the level of the biological activity. Thus the disubstituted isomer for the even interaction is more active than isomer trisubstituted.

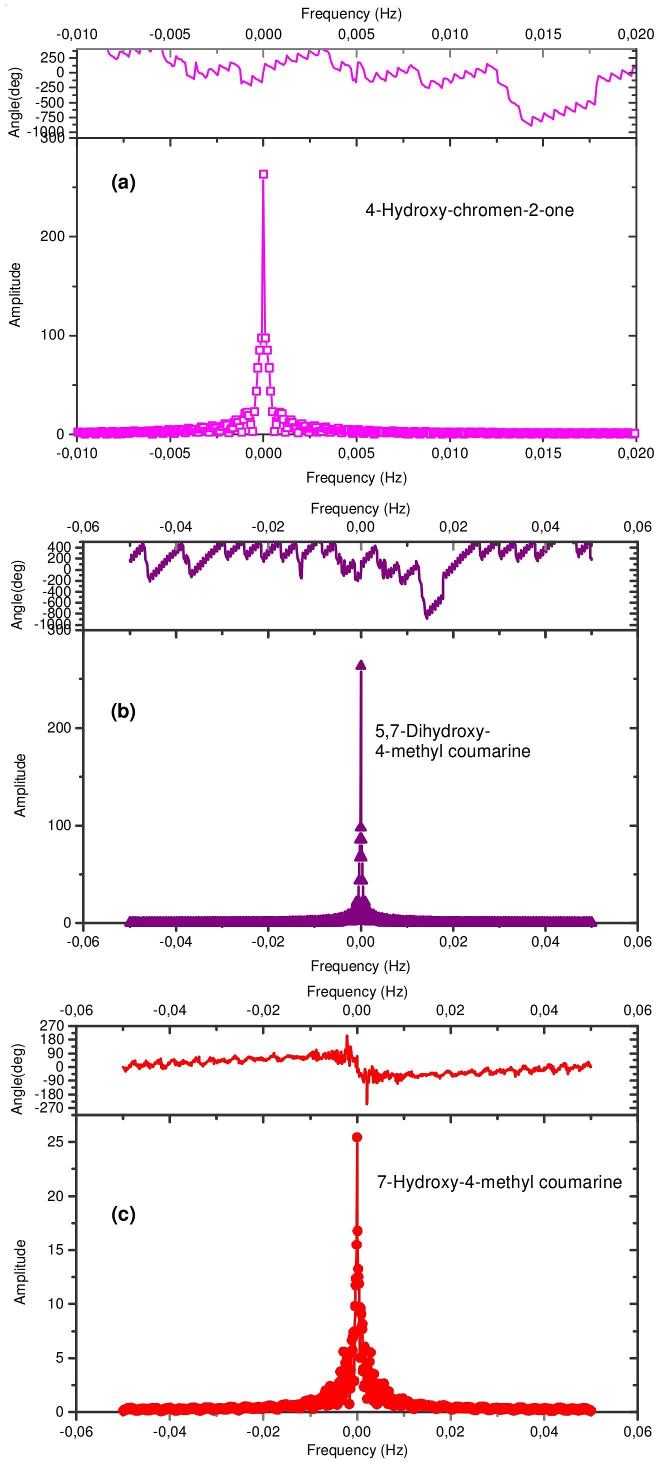


Fig. 6. Frequency of pair interaction of two molecules in spherical approximation of (a) 4-hydroxy-chromen-2-one, (b) 5-7-dihydroxy-4-methyl coumarin and (c) 7-hydroxy-4-methyl coumarin

Conclusion

The choice of the model of potential of reference L-J in spherical interaction and the power of the method of molecular dynamics led both to precise results. The use of the software enables us to evaluate the properties of coumarin and its derivatives. For that, an algorithmic implementation was developed to undertake investigations of various points (T,ρ) of coumarin and its derivatives. The study of the thermodynamic properties in a simulation by molecular dynamics for a unit NPT better and is led to results quite precise and close to the experiment. We can widen our comprehension under investigation reaction of du the mixture between coumarins and/or coumarin in a suitable solvent. The technique of molecular dynamics confirms the stability of the systems; More the molecule is to substitute by an attractive effect plus them unstable that this is translated by the existences of the peaks strong on the level of the radial distribution, this phenomenon decreases by effect donor. We find the same results on the level of the biological activity. Thus the disubstituted isomer is more active than trisubstituted isomer. Our results compare favourably with both experiment and more sophisticated theoretical approaches that incorporate quantum effects. It is concluded that present results by density functional theory calculations, B3LYP/6-31G, was performed for the determination of geometrical structure for the toxic product gives precise results and approaches very well and similar to those obtained par FT-IR. This work presents the opportunity to obtain chemical shifts of the proton of substituted coumarins with high accuracy, which allows the elucidation of process chemicals in the toxic liquid state. This displacement (D) reveal a clear reduction for isomer more substituted and the attractile effect exerts an effect of weak more important shielding. It is hoped that this model with a intermolecular reaction could be an effective starting material for studying the properties of complex system in polar solvent as well as non-polar solvent.

ACKNOWLEDGEMENTS

The authors thank National Agency for the Development of University Research (ANDRU) in Algeria for its financial support.

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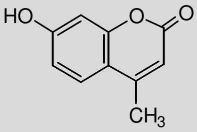
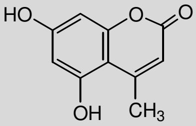
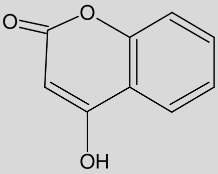
TABLE-4
IR FREQUENCIES OF SUBSTITUTED COUMARINS

Composed	Exp-IR (ν, cm^{-1}) (with KBr)	Calculated (ν, cm^{-1}) (B3LYP/6-311G**)	∇ (cm^{-1})
 	3013 (Ar-H) str.	3125 (Ar-H)	-112
	2858 (CH_3) str.	2768 (CH_3)	+90
	1679 (C=O) str.	1670 (C=O);	+09
	1068 (C-O) bend[124].	1015 (C-O)	+53
	3119 (Ar-H) str.	3042 (Ar-H),	+77
	3500 (OH) str.	3450 (OH),	+50
	2816 (CH_3) str.	2789 (CH_3),	+27
	1670 (C=O) str.	1670 (C=O),	00
	1075 (C-O) bend[125].	1175 (C-O)	+100
 	3159 (O-H) str.	3245 (O-H),	-86
	1670 (C=O) str[121].	1546 (C=O)	+124
 	2750 (Ar-H) str.	2855 (Ar-H)	-105
	3100 (OH) str.	3050 (OH)	+50
	1600 (C=O) str.	1600 (C=O);	00
	1300 (C-O) bend[123]	1350 (C-O)	-50

∇ (cm^{-1}) = Exp-IR (cm^{-1})-Calculated (ν, cm^{-1}); *Computed values by CS ChemDraw software

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