Theoretical studies on nanostructure of 2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde

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The polarized continuum model (PCM) model has been used to optimize 2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde (safranal) in aqueous phase, methanol and carbon tetra chloride at B3LYP/6-31G** level of theory and the solvent effect has been studied. The principle of maximum hardness has been tested by calculating chemical hardness and chemical potential at B3LYP/6-31G** level of theory to predict the order of stability of the structure in solutions. The maximum IR intensity is related to the C4=C5 stretching vibrations. Also, the vibrational free energy, heat capacity, entropy, thermal energy and zero point vibrational energy obtained from the calculated frequencies and these are compared in different media.

Key words: Polarized continuum model (PCM), functional theory methods (DFT), solvent, IR, safranal.

INTRODUCTION

The biological activity of saffron as a natural preventing substance in anticancer research is in development (Mollaamina et al., 2011; Mollaamin et al., 2010; Abe and Saito, 2000; Soeda et al., 2001; Monajjemi et al., 2009; Abdullaev et al., 2002; Abdullaev et al., 2003; Rivero´n-Negrete et al., 2002). Saffron is the world's most expensive spice and apart from its traditional value as food additive recent studies indicate its potential as an anti-cancer agent.

The value of saffron (dried stigmas of Crocus sativus L.) is determined by the existence of three main secondary metabolites: crocin and its derivatives which are responsible for color; picrocrocin, responsible for taste; and safranal responsible for odor. The amount of these compounds in dried stigma tissues is the most important indicator of quality of this spice.

Safranal, a pleasantly odoriferous component of saffron develops during the process of drying by hydrolysis of the bitter substance picrocrocin, which is present in the fresh stigmata. The Greeks considered saffron as a sensual perfume. It was strewn in Greek halls, courts, theatres and in Roman baths. In Rome the streets were sprinkled with saffron when Nero entered the city. In the Middle East saffron is used to prepare an oil-based perfume called ‘Zaafraan Attar’, which is a mixture of saffron and sandalwood.

An alcoholic tincture of saffron is sometimes used as a fragrance ingredient particularly in oriental-type perfumes. Saffron is used as a perfume ingredient in many famous perfume brands. The spices is also employed in some types of incense. Nowadays the use of saffron in the cosmetic industry is increasing owing to its active substances and to the trend to use natural products in cosmetic formulations (Basker and Negbi, 1983; Safinter, 1999; www. Babysaffron.com/gis. html).

Safranal is the main component of the essential oil and is responsible for the characteristic saffron aroma, which is obtained from picrocrocin and 4-hydroxy-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde (HTCC) during the saffron drying process (Iborra et al., 1992; Raina et al., 1996; Himeno and Sano, 1987; Lozanoa et al., 2000). As this compound is not present in the fresh stigma, its concentration in saffron depends strongly on both the drying and storage conditions.

Safranal, the principal substance responsible for the aroma of saffron, has the molecular formula C10H14O, which corresponds to 2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde (Gonzalo et al., 1996).
In the present study, functional theory methods (DFT) have been used to optimize the exchange functional (B3) (Monajjemi et al., 2010) combined with gradient corrected correlation functional of Lee–Yang–Parr (LYP) and BLYP of DFT methods have been employed to optimize the molecules by implementing the 6-31G, 6-31G*, 6-31G basis sets. We found 6-31G** is the best basis set.

The labeling of atoms in 2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde is given in Figure 1. The optimized geometrical parameters (bond length, order and angle) in gas phase are listed in Table 1. The dipole of a molecule induced a dipole in the medium, and the electric field of the solvent dipole in turn interacts with the molecular dipole, leading to a overall stabilization (Monajjemi et al., 2011).

Comparing the values calculated at the B3LYP/6-31G** level with the result at the HF/6-31G** level , we found that the C=C bond length increases by more than 0.021Å, the C=O bond length increases 0.031Å, while changes in the C4–C11, C6–C7, C6–C10 bond lengths are less than 0.006Å. From previous studies it is known that the DFT methods can achieve greater accuracy than the Hartree–Fock theory (Foresman and Frisch, 1996; Wiest et al., 1994).

Solvent effects are important in molecular thermodynamic properties, including zero-point vibrational energy (ZPVE), enthalpy, free energy and total energy. 

ZPVE is needed for theoretical studies of thermochemistry. The ZPVE in the gas phase is -464.478082 kcal/mol. Comparatively, this parameter in CCl4, methanol and in water, decreases 0.0001, 0.0001 and 0.0002 kcal/mol, respectively. Sum of electronic and thermal Free Energies of the gas phase is -464.52672 kcal/mol. For the CCl4, methanol and water, this parameter decreases 0.0002, 0.0007 and 0.0008 kcal/mol, respectively.

The total energy in the gas phase is 464.70621 kcal/mol. In comparison with the gas phase, the total energies in the CCl4, methanol and water become much lower, decrease 0.00018, 0.011 and 0.0062 kcal/mol, respectively. Hence, the molecule in solvent is more stable than the neutral. In addition, the corresponding dipole moments increase in going from the gas phase to solutions, 0.44 (CCl4), 1.69 (methanol) and 1.75 (water) Debye, respectively. Therefore, the molecular polarity in medium is little stronger than that in the neutral.

The DFT calculated frequencies in the solvents were obtained using the PCM model at the B3LYP/6-31G** level. The calculated frequencies and their intensities are given in Table 3. The safranal (Figure 1) belongs to C1 point group and 69 normal mode vibrational frequencies. The optimized geometrical parameters (bond length, order and angle) in gas phase are listed in Table 1. The dipole of a molecule induced a dipole in the medium, and the electric field of the solvent dipole in turn interacts with the molecular dipole, leading to a overall stabilization (Monajjemi et al., 2011).

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The DFT calculated frequencies in the solvents were obtained using the PCM model at the B3LYP/6-31G** level. The calculated frequencies and their intensities are given in Table 3. The safranal (Figure 1) belongs to C1 point group and 69 normal mode vibrational frequencies. The shifts of frequencies and changes of IR intensities from the gas phase to medium are listed in Table 2. On going from the gas phase to solutions, shifts of frequencies are nearly same in Carbon tetra chloride and gas phase. In the methanol and water, there is small frequency shifts for v1, u4- u11, u14, u17- u30, u32- u35, u37- u40, u44, u53, u54, u56- u64, u66 and u67. For instance, significant changes of IR intensities are observed in u36, v55, u65, u68 and u69. Where, u36 is Methyl antisymmetric stretching and C–H stretching vibration has the largest changes in intensities (up to 97 km.mol⁻¹ in the CCl4). Spectrums that have the highest
Table 1. Optimized geometry for Safranal in gas phase.

| Coordinate a | B3LYP | 6-31G** | BLYP | HF |
|--------------|-------|---------|------|----|
|               | Length/ Angle | order | Length/ Angle | order | Length/ Angle | order |
| C(1)-C(2)    | 1.499  | 1      | 1.508  | 1      | 1.501  | 1      |
| C(1)-C(6)    | 1.549  | 1      | 1.562  | 1      | 1.541  | 1      |
| C(1)-H(12)   | 1.097  | 1      | 1.104  | 1      | 1.086  | 1      |
| C(1)-H(13)   | 1.103  | 1      | 1.111  | 1      | 1.091  | 1      |
| C(2)-C(3)    | 1.343  | 1      | 1.355  | 1      | 1.322  | 1      |
| C(2)-H(14)   | 1.087  | 1      | 1.094  | 1      | 1.077  | 1      |
| C(3)-C(4)    | 1.464  | 1      | 1.468  | 1      | 1.478  | 1      |
| C(3)-H(15)   | 1.087  | 1      | 1.094  | 1      | 1.076  | 1      |
| C(4)-C(5)    | 1.371  | 1      | 1.387  | 1      | 1.342  | 1      |
| C(4)-C(11)   | 1.509  | 1      | 1.519  | 1      | 1.509  | 1      |
| C(5)-C(6)    | 1.545  | 1      | 1.558  | 1      | 1.541  | 1      |
| C(5)-C(8)    | 1.470  | 1      | 1.477  | 1      | 1.484  | 1      |
| C(6)-C(7)    | 1.547  | 1      | 1.560  | 1      | 1.541  | 1      |
| C(6)-C(10)   | 1.546  | 1      | 1.558  | 1      | 1.542  | 1      |
| C(7)-H(16)   | 1.094  | 1      | 1.101  | 1      | 1.084  | 1      |
| C(7)-H(17)   | 1.097  | 1      | 1.104  | 1      | 1.087  | 1      |
| C(7)-H(18)   | 1.095  | 1      | 1.102  | 1      | 1.086  | 1      |
| C(8)-O(9)    | 1.226  | 1      | 1.241  | 1      | 1.195  | 1      |
| C(8)-H(19)   | 1.109  | 1      | 1.118  | 1      | 1.094  | 1      |
| C(10)-H(20)  | 1.093  | 1      | 1.100  | 1      | 1.084  | 1      |
| C(10)-H(21)  | 1.096  | 1      | 1.103  | 1      | 1.086  | 1      |
| C(10)-H(22)  | 1.095  | 1      | 1.102  | 1      | 1.086  | 1      |
| C(11)-H(23)  | 1.095  | 1      | 1.102  | 1      | 1.087  | 1      |
| C(11)-H(24)  | 1.094  | 1      | 1.101  | 1      | 1.086  | 1      |
| C(11)-H(25)  | 1.093  | 1      | 1.100  | 1      | 1.076  | 1      |
| C(2)-C(1)-C(6) | 113.464 |     | 113.615 |     | 113.224 |     |
| C(2)-C(1)-H(12) | 110.791 |     | 110.825 |     | 110.503 |     |
| C(2)-C(1)-H(13) | 108.090 |     | 108.057 |     | 108.042 |     |
| C(2)-C(1)-H(12) | 109.057 |     | 109.075 |     | 109.132 |     |
| C(2)-C(1)-H(13) | 109.392 |     | 109.387 |     | 109.441 |     |
| H(12)-C(1)-H(13) | 105.751 |     | 105.559 |     | 106.255 |     |
| C(1)-C(2)-C(3) | 120.217 |     | 120.211 |     | 120.385 |     |
| C(1)-C(2)-H(14) | 119.108 |     | 119.094 |     | 118.897 |     |
| C(2)-C(2)-H(14) | 120.584 |     | 120.590 |     | 120.662 |     |
| C(2)-C(3)-C(4) | 121.807 |     | 122.025 |     | 121.563 |     |
| C(2)-C(3)-H(15) | 120.587 |     | 120.453 |     | 120.835 |     |
| C(4)-C(3)-H(15) | 117.562 |     | 117.476 |     | 117.574 |     |
| C(3)-C(4)-C(5) | 119.589 |     | 119.726 |     | 119.505 |     |
| C(3)-C(4)-C(11) | 116.319 |     | 116.396 |     | 114.362 |     |
| C(5)-C(4)-C(11) | 124.089 |     | 123.874 |     | 126.127 |     |
| C(4)-C(5)-C(6) | 120.626 |     | 120.424 |     | 121.146 |     |
| C(4)-C(5)-C(8) | 120.885 |     | 121.030 |     | 121.824 |     |
| C(6)-C(5)-C(8) | 118.088 |     | 118.136 |     | 116.702 |     |
| C(1)-C(6)-C(5) | 109.863 |     | 110.027 |     | 109.656 |     |
| C(1)-C(6)-C(7) | 109.793 |     | 109.738 |     | 109.912 |     |
| C(1)-C(6)-C(10) | 106.863 |     | 106.833 |     | 106.846 |     |
| C(5)-C(6)-C(7) | 108.418 |     | 108.277 |     | 109.186 |     |
| C(5)-C(6)-C(10) | 112.897 |     | 112.961 |     | 112.147 |     |
| C(7)-C(6)-C(10) | 108.978 |     | 108.975 |     | 109.058 |     |
Table 1. Contd

| Bond                  | Carbon tetrachloride | Methanol | Water |
|-----------------------|----------------------|----------|-------|
| C(6)-C(7)-H(16)      | 111.174              | 111.244  | 111.158 |
| C(6)-C(7)-H(17)      | 110.704              | 110.675  | 110.709 |
| C(6)-C(7)-H(18)      | 110.847              | 110.852  | 111.116 |
| H(16)-C(7)-H(17)     | 111.244              | 110.715  | 110.876 |
| H(16)-C(7)-H(18)     | 110.793              | 110.711  | 110.591 |
| C(5)-C(8)-O(9)       | 126.349              | 126.482  | 126.553 |
| C(6)-C(10)-H(20)     | 112.888              | 112.865  | 112.869 |
| C(6)-C(10)-H(21)     | 109.494              | 109.515  | 109.669 |
| C(6)-C(10)-H(22)     | 111.408              | 111.403  | 111.284 |
| H(20)-C(10)-H(21)    | 106.931              | 106.990  | 106.896 |
| C(4)-C(11)-H(23)     | 110.983              | 111.063  | 110.439 |
| C(4)-C(11)-H(24)     | 110.476              | 110.542  | 110.409 |
| C(4)-C(11)-H(25)     | 111.857              | 111.845  | 113.385 |
| H(23)-C(11)-H(24)    | 108.495              | 108.495  | 107.122 |
| H(23)-C(11)-H(25)    | 109.640              | 109.542  | 109.409 |
| H(24)-C(11)-H(25)    | 110.640              | 110.750  | 109.564 |

Table 2. The calculated frequencies and their intensities.

| No. | Gas phase | Carbon tetrachloride | Methanol | Water |
|-----|-----------|----------------------|----------|-------|
|     | freq. a  | Int.(IR)             | freq. a  | Δb    | Int.(IR) |
|-----|----------|----------------------|----------|-------|----------|
| u1  | 65.624   | 1.1                  | 65.444   | -0.18 | 0.79     |
| u2  | 95.871   | 1.2                  | 97.876   | 1.915 | 1.47     | 115.51  | 19.64  | 1.06 |
| u3  | 132.644  | 0.26                 | 131.084  | -1.56 | 0.26     | 134.63  | 1.986  | 0.29 |
| u4  | 164.694  | 2.46                 | 166.978  | 2.285 | 2.19     | 172.345 | 7.651  | 1.96 |
| u5  | 214.397  | 5.24                 | 214.783  | 0.386 | 5.71     | 222.516 | 8.119  | 6.95 |
| u6  | 235.491  | 1.14                 | 237.104  | 1.613 | 1.08     | 243.927 | 8.436  | 1.21 |
| u7  | 279.282  | 2.02                 | 281.063  | 1.781 | 2.19     | 286.52  | 7.238  | 2.35 |
| u8  | 295.395  | 1.31                 | 297.094  | 1.699 | 0.94     | 305.973 | 10.578 | 0.15 |
| u9  | 308.009  | 0.58                 | 309.146  | 1.137 | 0.68     | 313.013 | 5.004  | 0.97 |
| u10 | 326.487  | 1.59                 | 327.04   | 0.553 | 1.52     | 328.507 | 2.02   | 1.64 |
| u11 | 335.72   | 0.52                 | 337.056  | 1.336 | 0.57     | 341.665 | 5.945  | 0.36 |
| u12 | 366.734  | 0.55                 | 366.478  | -0.256 | 0.59   | 369.362 | 2.628  | 0.49 |
| u13 | 407.357  | 2.06                 | 408.295  | 0.938 | 2.22     | 409.135 | 1.778  | 2.4 |
| u14 | 442.409  | 1.05                 | 443.214  | 0.805 | 0.95     | 445.789 | 3.38   | 0.91 |
| u15 | 480.504  | 2.65                 | 480.862  | 0.358 | 2.6     | 482.288 | 1.784  | 2.46 |
| u16 | 502.216  | 6.83                 | 502.589  | 0.373 | 6.79     | 504.088 | 1.872  | 6.76 |
| u17 | 566.954  | 0.59                 | 568.861  | 1.907 | 0.7      | 569.482 | 2.528  | 0.79 |
| u18 | 629.99   | 5.27                 | 630.539  | 0.549 | 5.19     | 634.203 | 4.213  | 4.99 |
| u19 | 685.296  | 20.58                | 687.104  | 1.808 | 20.56    | 689.378 | 4.082  | 20.18 |
| u20 | 751.262  | 22.28                | 751.958  | 0.696 | 22.39    | 756.394 | 5.132  | 22.52 |
| u21 | 807.533  | 6.94                 | 810.497  | 2.964 | 6.63     | 813.151 | 5.618  | 5.8 |
| u22 | 846.773  | 4.19                 | 848.924  | 2.151 | 3.96     | 850.511 | 3.738  | 4.21 |
| u23 | 908.918  | 1.36                 | 910.952  | 2.034 | 1.38     | 912.55  | 3.632  | 1.23 |
| u24 | 931.819  | 2.76                 | 934.51   | 2.691 | 2.43     | 935.658 | 3.839  | 2.34 |
| u25 | 947.801  | 0.26                 | 949.737  | 1.936 | 0.25     | 952.333 | 4.532  | 0.26 |

Monajjemi et al. 3027
intensity of IR are u 53, u 55 and u 56; where maximum IR intensity is in u 53 (in water: freq=1575.22 cm\(^{-1}\) and intensity=203.859 km mol\(^{-1}\)).

It is related to the C4=C5 stretching vibrations. This frequency difference between water and gas phase is to -7.22. IR spectrum intensity increases with increasing dielectric constant from gas toward the water. u 55 (in water: freq=1721.05 cm\(^{-1}\) and IR intensity=148.52 km.mol\(^{-1}\)) is related to the mixed modes of C8=O9 and C4=C5 stretching vibrations. u 56 (in water: freq=2941.09
The calculated IR spectra in gas phase and solutions. (a) Gas phase (b) Water (c) Methanol (d) Carbon tetra Chloride.

| Temp. (K) | Carbontetra chloride | Methanol | Water |
|----------|----------------------|----------|-------|
|          | Cv \(^a\) S \(^b\) E(Thermal) \(^c\) | Cv \(^a\) S \(^b\) E(Thermal) \(^c\) | Cv \(^a\) S \(^b\) E(Thermal) \(^c\) |
| 293.05   | 43.056 101.460 142.403 | 42.882 100.520 142.327 | 42.866 100.548 142.350 |
| 298.15   | 43.735 102.251 142.627 | 43.564 101.308 142.550 | 43.547 101.335 142.573 |
| 303.15   | 44.375 102.994 142.841 | 44.206 102.048 142.763 | 44.189 102.075 142.786 |
| 308.15   | 45.034 103.758 143.064 | 44.868 102.809 142.985 | 44.851 102.836 143.008 |
| 310.15   | 45.298 104.063 143.154 | 45.132 103.113 143.075 | 45.115 103.140 143.098 |
| 313.15   | 45.693 104.521 143.291 | 45.529 103.569 143.211 | 45.512 103.596 143.234 |

(a) cal.mol\(^{-1}\)K\(^{-1}\) (b) cal.mol\(^{-1}\)K\(^{-1}\) (c) kcal.mol\(^{-1}\)

cm\(^{-1}\) and IR intensity=120.42 km.mol\(^{-1}\)) is related to the C8-H19 stretching vibrations. The calculated IR spectra in gas phase and solutions in Figures 2 and 3 show the IR spectrum intensity diagram according to dielectric constant in \(\varepsilon\) 53.

On the basis of vibrational analyses and statistical thermodynamics, the standard thermodynamic functions: heat capacity (Cv), entropy (S) and thermal energy (E) were obtained and listed in Table 3. As observed from Figure 3 and Figure 4, all the values of Cv, S and E increase with the increase of temperature from 290.15 to 313.15, which is attributed to the enhancement of the molecular vibration while the temperature increases. The chemical hardness (\(\eta\)) and chemical potential (\(\mu\)) are important tools to study the relative stabilities of a molecule. The chemical hardness parameter received much attention after the invention of Pearson’s maximum hardness principle (Pearson, 1973), which states that the minimum energy structure has the maximum chemical hardness. The chemical hardness and chemical potentials of safranal are calculated at B3LYP/6-31G** level of theory for both gaseous and solution phases. The maximum hardness principle (MHP) is able to predict the most stable structure. As you see in Table 4 the calculated chemical hardness values in solution phase are more or less similar to that of gas phase and indicate that there is no considerable change in molecular orbital energies of the structure in SCRF calculations.

**Conclusion**

Density-functional calculations were performed to determine electric and thermo chemical properties of safranal (the main component of the essential oil and is responsible for the characteristic saffron aroma). On going from the gas phase to solutions and, the solvent reaction field has general weak influence on the skeletal
Figure 3. IR spectrum intensity versus dielectric constant from gas toward the water in u53.

Figure 4. $C_v$, $S$, and $E$ versus $T$ for the title compound.

Table 4. $\eta$, $\chi$, $S$, $\omega$ in gas phase and CCl$_4$, MeOH and H$_2$O.

| Medium                | $\eta$ | $\chi$  | $S$     | $\omega$ |
|-----------------------|--------|---------|---------|----------|
| Phase Gas             | 0.0769 | -0.0769 | 6.5019  | 0.0383   |
| Tetrachloride carbon  | 0.0763 | -0.0763 | 6.5530  | 0.0380   |
| Methanol              | 0.0746 | -0.0746 | 6.7024  | 0.0368   |
| Water                 | 0.0745 | -0.07455| 6.7069  | 0.0368   |
bond angles, dipole moment, and thermodynamics properties of the molecule. The frequencies using the PCM model at the B3LYP/6-31G** level were calculated. The infrared spectrum of the molecule is weak influenced by the solvent reaction field. u36 is Methyl antisymmetric stretching and C–H stretching vibration has the largest changes in intensities (up to 97 km.mol\(^{-1}\) in the CCl\(_4\)). Spectrums that have the highest intensity of IR are 53, 55 and 56. All the values of Cv, S and E increase with the increase of temperature from 290.15 to 313.15. The calculated chemical hardness values in solution phase are more or less similar to that of gas phase and indicate that there is no considerable change in molecular orbital energies of the structure in SCRF calculations.

REFERENCES

Abdullaev FI, Rivero˜n-Negrete L, Caballero-Ortega H, Manuel Hernandez J, Pe´rez-Lo´pez I, Pereda-Miranda R, Espinosa-Aguirre JJ (2003). Use of in vitro assays to assess the potential antigenotoxic and cytotoxic effects of saffron (Crocus sativus L.), Toxicol. In Vitro, 17: 731-736.

Abdullaev FJ, Caballero-Ortega H, Rivero ‘n-Negrete L, Pereda-Miranda R, Rivera-Luna R, Manuel Herna’ndez J, Pe´rez-Lo’pez I, Espinosa-Aguirre JJ (2002). In vitro evaluation of the chemopreventive potential of saffron., Rev. InVest. Clin., 54: 430- 436.

Abe K, Saito H (2000). Effects of saffron extract and its constituent crocin on learning behaviour and long-term potentiation. Phytother. Res., 14: 149-152.

Basker D, Negbi M (1983). Uses of Saffron, Econ. Bot., 37: 228–236.

Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dauprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (2001.) GAUSSIAN98, Revision A.11.2, Gaussian, Inc., Pittsburgh, PA, 2001.

Himeno H, Sano K (1987). Synthesis of Crocin, Picrocrocin and Saframal by Saffron Stigma-like Structures Proliferated in vitro, Agric. Biol. Chem., 51: 2395-2400.

Ibhair JL, Castellar I, Car名誉n M, Manjo‘n A (1992). TLC Preparative Purification of Picrocrocin, HTCC and Crocin from Saffron. J. Food Sci., 57: 714-716.

Lozanoa P, Delgadob D, Go‘mez D, Rubiob M, Iborra JL (2000). A non-destructive method to determine the safranal content of saffron (Crocus sativus L.) by supercritical carbon dioxide extraction combined with high-performance liquid chromatography and gas chromatography, J. Biochem. Biophys. Methods, 43: 367-378.

Mollaamin F, Layaili I, Ilkhani AR, Monajjemi M (2010). Nanomolecular simulation of the voltage–gated potassium channel protein by gyration radius study. Afr. J. Microbiol. Res., 4: 2795-2803.

Mollaamina F, Varmaghani Z, Monajjemi M (2011). Dielectric effect on thermodynamic properties in vinblastine by DFT/Onsager modeling, Phy. Chem. Liq., 49: 318-336.

Monajjemi M, Honarpavar B, Nasseri SM, Khaledian M (2009). NMR and NMR study of hydrogen bonding interactions in anhydrous and monohydrated guanine cluster model: A computational study Journal of Structural Chemistry, J. Struct. Chem., 50: 67-77.

Monajjemi M, Razavian MH, Mollaamin F, Naderi N, Honarpavar B (2008). A Theoretical thermochemical study of solute-solvent dielectric effects in the displacement of codon-anticodon base pairs, J.Russian Phys.Chem.A., 82: 113-121.

Pearson RG (1973). Hard and Soft Acids and Bases, Dowden (Hutchinson & Ross), Stroudsburg, PA.

Raina BL, Agarwal SG, Bhatia AK, Gaur GS (1996). Changes in Pigments and Volatiles of Saffron (Crocus sativusL) During Processing and Storage. J. Sci. Food Agric., 71: 27-32.

Rivero‘n-Negrete L, Caballero-Salazar S, Ordez-Tellez M, G, Abdullaev F (2002). The combination of natural and synthetic agents a new pharmacological approach in cancer chemoprevention. Proc. West Pharmacol., 45: 74-75.

Soeda S, Ochiai T, Paopong L, Tanaka H, Shoyama Y, Shimeno H (2001). Crocin suppresses tumor necrosis factor-?-induced cell death of neuronally differentiated PC-12 cells, Life Sci., 69: 2887-2898.

Wiest O, Black KA, Houk KN (1994). Density Functional Theory Isotope Effects and Activation Energies for the Cope and Claisen Rearrangements, J. Am. Chem. Soc., 116: 10336–10337.