

Structural and electronic properties of xanthohumol metabolite

Şakir Erkoç^{a,*}, Meltem Yilmazer^b, Figen Erkoç^c

^aDepartment of Physics, Middle East Technical University, 06531 Ankara, Turkey

^bDepartment of Toxicology, Faculty of Pharmacy, Gazi University, 06330 Ankara, Turkey

^cDepartment of Biology Education, Gazi University, 06500 Ankara, Turkey

Received 12 September 2001; accepted 30 November 2001

Abstract

The structural and electronic properties of xanthohumol metabolite (M2) have been investigated theoretically by performing semi-empirical molecular orbital theory at the level of MNDO/3 calculations. The optimized structure and the electronic properties of the isolated molecule are obtained. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Xanthohumol metabolite (M2); Reactive flavonoid; MNDO/3 method

1. Introduction

Flavonoids are a large group of polyphenolic compounds that naturally occur in nature. Over 4000 different flavonoids have been described in plants including fruits, vegetables, nuts, seeds, flowers, and bark [1]. A wide range of biological activities have been established with various natural flavonoids, e.g. antiallergic, antiinflammatory, antiviral, antifungal, antibacterial, antioxidative, antiproliferative, and anticarcinogenic [2]. Also it has been shown that the intake of flavonoids was inversely associated with the risk of coronary heart disease in elderly males [3].

Xanthohumol (XN) is the major prenylated flavonoid of hop plants and has been detected in beer and shown to have some of the biological properties cited earlier with promising cancer-chemopreventive properties [2,4]. It is known

that some flavonoids such as quercetin may go through metabolic activation leading to concentration-dependent cytotoxic effect [5]. The major metabolite of XN produced by liver microsomes from rats, namely 5''-(2'''-hydroxyisopropyl)-dihydrofurano(2'',3'':3',4'(-2',4-dihydroxy-6'-methoxychalcone (M2) may also lead to the similar properties as parent compound, XN. The metabolite has been isolated and identified recently by Yilmazer et al. [1].

Although there is general agreement that flavonoids possess both excellent iron chelating and radical scavenging properties, there is much discussion and contradiction regarding their relative contribution and the structure activity relationships (SAR) on the antioxidant activity. The low solubility of these compounds hampers experimental investigations and necessitates theoretical investigations for the elucidation of biological reactivity [6].

In this study we have investigated the structural and electronic properties of the M2 molecule for the first time theoretically by performing semi-empirical

* Corresponding author. Tel.: +90-312-210-3285; fax: +90-312-210-1281.

E-mail address: erkoc@erkoc.physics.metu.edu.tr (Ş. Erkoç).

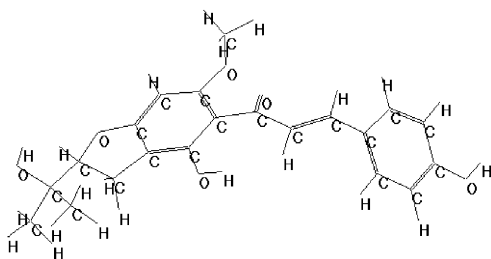


Fig. 1. The optimized structure of the M2, $C_{21}O_6H_{22}$, with atomic labels.

molecular orbital (MO) calculations, because of their biological importance.

2. Method of calculation

In the present study, M2 has been considered theoretically by performing the MNDO/3 type semi-empirical MO calculations. The MNDO/3 semi-empirical method [7] within the restricted Hartree–Fock (RHF) [8] formalisms is sufficient to study the system considered in this work.

Geometry optimization is carried out by using a conjugate gradient method (Polak–Ribiere algorithm [9]), then the electronic structure of the M2 is calculated by applying the semi-empirical MO MNDO/3 method within the RHF level. The SCF convergence is set to $0.01 \text{ kcal mol}^{-1}$ in the calculations. We have performed all the calculations by using the HyperChem-5.1 packet.

In the calculations RHF formalism is applied for the M2 with singlet symmetry. The closed formula for M2 is in the form $C_{21}O_6H_{22}$. The optimized structure with atomic labels of the M2 is shown in Fig. 1.

Table 1
Some molecular information about the M2

Quantity	Value
No. of electrons	142
No. of doubly occupied levels	71
No. of total orbitals	130
Ground state multiplicity	Singlet
Molecular point group	C_1

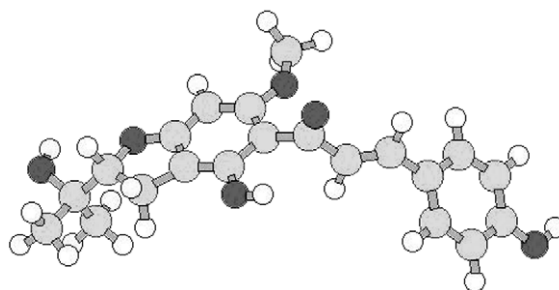


Fig. 2. The ball and stick model structure of the M2.

3. Results and discussion

Some molecular information about the system considered are given in Table 1. The MNDO/3 geometry optimization yields a nonplanar structure as the stable form of the M2. The ball and stick model of the molecule is shown in Fig. 2.

The calculated excess charge on the atoms are shown in Fig. 3. In the M2 some of the carbon atoms have positive excess charge, some of them have negative excess charge; the magnitude of positive charges vary from $+0.018$ to $+0.654$, whereas the magnitude of negative charges vary from -0.005 to -0.448 . All the oxygen atoms have negative excess charge, their magnitude vary from -0.428 to -0.539 . Similar to carbon atoms some of the hydrogen atoms have positive excess charge, some of them have negative excess charge; the magnitude of positive charges vary from 0.004 to 0.259 , whereas the magnitude of negative charges vary from -0.005 to -0.087 . The large charge accumulation takes place on the oxygen atoms.

Calculated energies are given in Table 2. The M2 molecule has a binding energy value of about

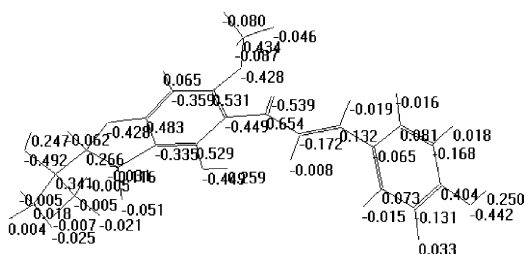


Fig. 3. Excess charge (in units of electron charge) on the atoms of the M2.

Table 2
Energy values (in kcal mol⁻¹) of the M2

Quantity	Value
Total energy	-112,011.31
Binding energy	-5321.90
Isolated atomic energy	-106,689.41
Electronic energy	-796,826.48
Core-core interaction	684,815.18
Heat of formation	-229.61
Zero point energy of vibration	250.15

-5322 kcal mol⁻¹. On the other hand, the heat of formation of the system studied is exothermic and has the value of about -230 kcal mol⁻¹

The MO energy (eigenvalue) spectrum of the

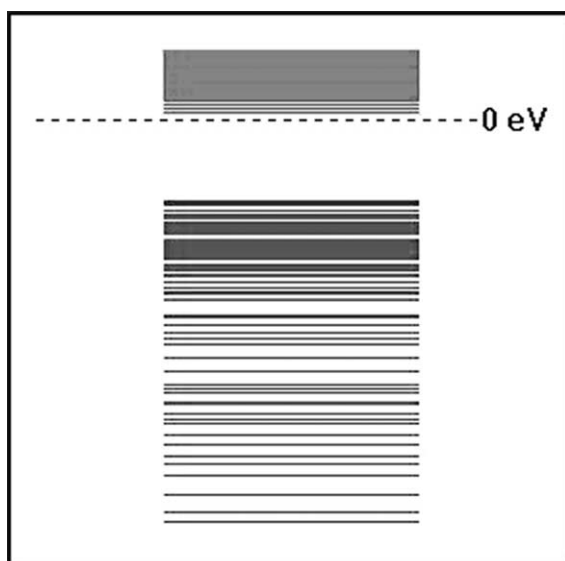


Fig. 4. The MO energy spectrum of the M2.

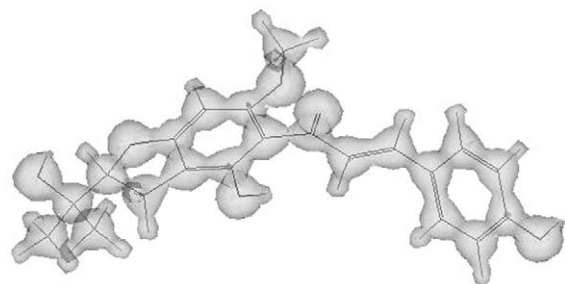


Fig. 5. The total charge density plot in three-dimensions of the M2.

Table 3
HOMO, LUMO, the interfrontier MO energy gap, ΔE , and the MO energies of the lowest and the highest levels (in eV) of the M2. The dipole moment, μ , is in Debyes

Quantity	Value
HOMO	-8.308
LUMO	0.514
ΔE	8.822
Lowest level	-40.156
Highest level	6.625
μ_x	-4.500
μ_y	1.388
μ_z	-1.708
μ	5.010

systems studied are shown in Fig. 4. The highest occupied and the lowest unoccupied MO (HOMO and LUMO, respectively) energies and the interfrontier MO energy gap (LUMO–HOMO energy difference, ΔE) with the lowest and highest level energy values are given in Table 3. The LUMO–HOMO gap of the M2 is about 9 eV.

The calculated dipole moment values of the system

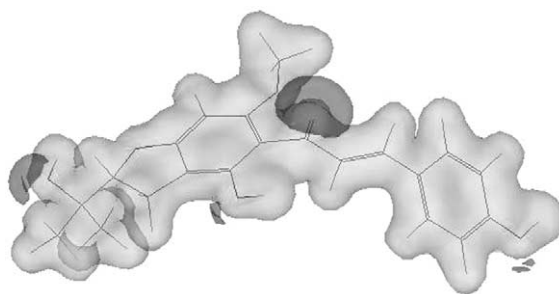


Fig. 6. The electrostatic potential plot in three-dimensions of the M2.

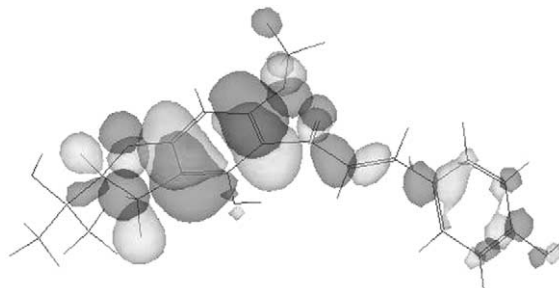


Fig. 7. The HOMO plot in three-dimensions of the M2.

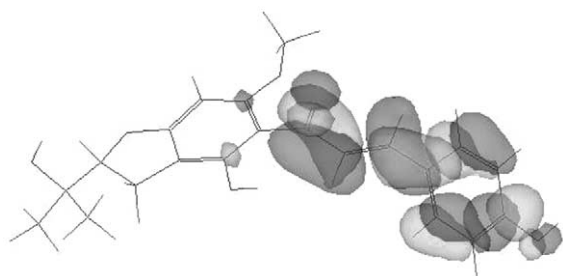


Fig. 8. The LUMO plot in three-dimensions of the M2.

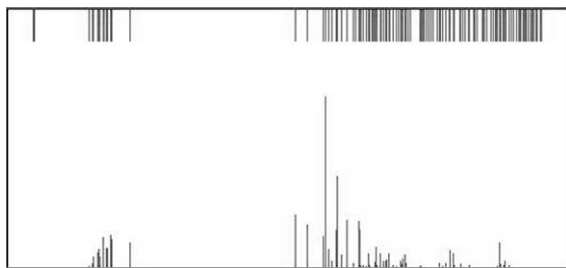


Fig. 9. The vibrational spectrum (normal mode frequencies, vary between 10 and 3961 cm^{-1}), and infrared band intensities (vary between 0 and 587 km mol^{-1}) of the M2.

considered are also given in Table 3. The resultant dipole moment of the M2 molecule is about 5 Debyes. This value of dipole moment may be considered as large for such a molecule. This high dipole moment may make the M2 molecule reactive and attractive for the interaction with other systems, in other words the M2 molecule with larger dipole moment might be very polar in solution and may therefore be more vulnerable and/or interactive.

The three-dimensional total charge density and electrostatic potential plots of the M2 molecule are shown in Figs. 5 and 6, respectively. The three-dimensional plots of HOMO and LUMO of the M2 are shown in Figs. 7 and 8, respectively. According to the HOMO plot it seems that the pentagon ring (furan) and the hexagon ring next to the furan in the M2 molecule are sensitive before excitation, on the other hand, according to the LUMO plot the hexagon

ring at the end of the M2 molecule seems to be more sensitive after excitation. In other words, in the excitation process of the M2 molecule the furan region is more reactive before excitation and the hexagon region (at the end) is more reactive after excitation.

The normal mode frequencies (vibrational frequencies) and the infrared band intensities of the M2 molecule are shown in Fig. 9. The range of the vibrational frequencies vary between 10 and 3961 cm^{-1} . The infrared band intensities vary between 0 and 587 km mol^{-1} . The first three maximum intensities with magnitudes 587.39, 317.14, 183.63 correspond to the frequency values of 1686.39, 1599.78, 1921.72, respectively.

Acknowledgements

The authors (Ş.E. and F.E.) would like to thank Türkipetrol Vakfı for partial support, and (Ş.E.) would like to thank METU for partial support through the project METU-AFP-2001-01-05-05.

References

- [1] M. Yilmazer, J.F. Stevens, M.L. Deinzer, D.R. Buhler, *Drug Metab. Dispos.* 29 (2001) 223.
- [2] J.F. Stevens, C.L. Miranda, D.R. Buhler, M.L. Deinzer, *J. Am. Soc. Brew. Chem.* 56 (1998) 136.
- [3] S.O. Kelly, M.G.L. Hertog, E.J.M. Feskens, D. Kromhout, *Arch. Intern. Med.* 156 (1996) 637.
- [4] M. Yilmazer, J.F. Stevens, D.R. Buhler, *FEBS Lett.* 491 (2001) 252.
- [5] D. Metodiewa, A.K. Jaiswal, N. Cenas, E. Dickancaite, J. Segura-Aguilar, *Free Rad. Biol. Med.* 26 (1999) 107.
- [6] S.A.B.E. van Acker, D. van den Berg, M.N.J.L. Tromp, D.H. Griffioen, W.H. van Bennekom, W.J.F. van der Vijgh, A. Bast, *Free Rad. Biol. Med.* 20 (1996) 331.
- [7] R.C. Bingham, M.J.S. Dewar, D.H. Lo, *J. Am. Chem. Soc.* 97 (1975) 1285.
- [8] C.C.J. Roothaan, *Rev. Mod. Phys.* 23 (1951) 69.
- [9] P. Fletcher, *Practical Methods of Optimization*, Wiley, New York, 1990.