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Essa, A. H.; Jalbout, A. F.
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Analysis of the structural and electronic properties of 1-(5-Hydroxymethyl - 4 –[5 – (5-oxo-5-piperidin-1-yl-penta-1,3dienyl)-benzo[1,3]dioxol-2-yl] -tetrahydro-furan-2-yl)-5-methyl-1H-pyrimidine-2,4dione molecule

A. H. Essa[1], *A. F. Jalbout*[2*]
[1]*Department of Chemistry, College of Science, University of Basrah, Basrah, IRAQ*
[2]*Instituto de Química, Universidad Nacional Autónoma de México, México D.F.*
** ajalbout@u.arizona.edu*

Abstract: The structural and electronic properties of 1-(5-Hydroxymethyl - 4 –[5 – (5-oxo-5-piperidin- 1 -yl-penta- 1,3 -dienyl)-benzo [1,3] dioxol- 2 -yl]- tetrahydro -furan-2 -yl)-5-methy l-1H-pyrimidine-2,4dione (AHE) molecule have been investigated theoretically by performing density functional theory (DFT), and semi empirical molecular orbital calculations. The geometry of the molecule is optimized at the level of Austin Model 1 (AM1), and the electronic properties and relative energies of the molecules have been calculated by density functional theory in the ground state. The resultant dipole moment of the AHE molecule is about 2.6 and 2.3 Debyes by AM1 and DFT methods respectively, This property of AHE makes it an active molecule with its environment, that is AHE molecule may interacts with its environment strongly in solution.

Keywords: anti-HIV drugs; AHE molecule; Austin Model 1 (AM1).

Introduction

AZT is an anti-HIV drug that reduces the amount of virus in the body. Anti-HIV drugs, such as AZT slow down or prevent damage to the immune system, and reduce the risk of developing AIDS-related illnesses. AZT is one of the nucleoside reverse transcriptase inhibitors (NRTIs).[1] These drugs work by disrupting an HIV protein or enzyme called reverse transcriptase which is involved in the production of new viruses. AZT is an abbreviation for the name azidothymidine. The drug is often referred to by its generic name, zidovudine, which is abbreviated to ZDV.[2] Its chemical name is 3'-azido-3'-deoxythymidine Figure (I), molecular formula is $C_{10}H_{13}N_5O_4$, and the molecular mass 267.24 . AZT was the first drug approved against HIV-1 and is still widely used in combination with other antiretroviral drugs.[3]

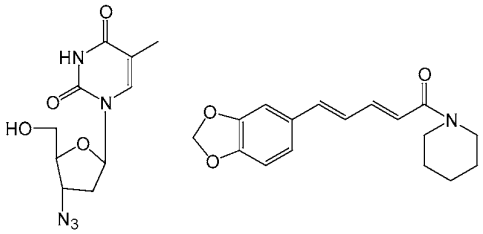
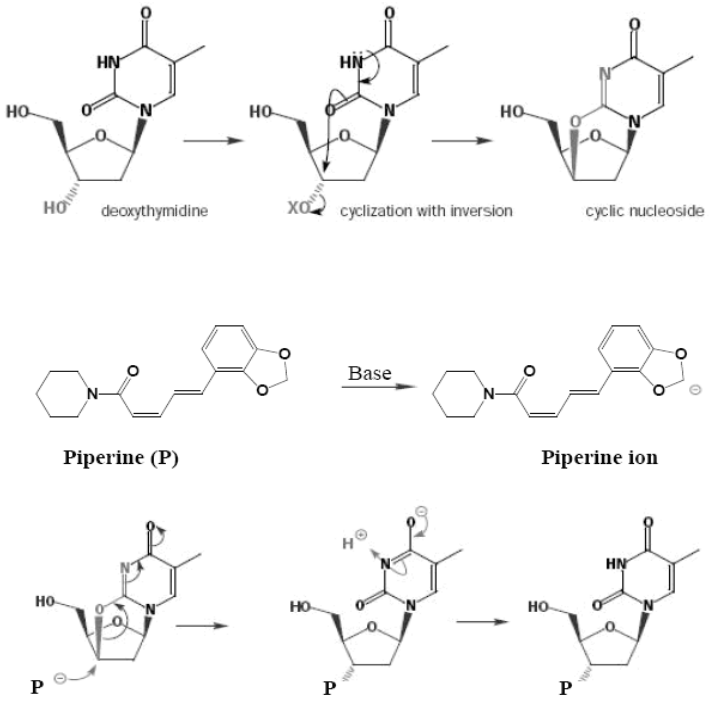


Figure 1. The chemical structure of a : AZT ; b : Piperine.

Common side-effects of AZT include nausea, vomiting, headache, dizziness, fatigue, weakness and muscle pain. Other side-effects occasionally reported from AZT include rashes, severe muscle pain and inflammation, nausea, insomnia, nail discoloration, and kidney disorders. These toxicities are more severe and more common in people with damaged immune systems.[4] Medicines to control nausea and headache can be prescribed before starting AZT. The side-effects of AZT are most likely to occur during the early weeks of treatment. AZT may damage the bone marrow, the substance in the body which produces blood cells. People with more advanced HIV infection are more likely to suffer blood deficiencies such as anemia (low levels of red blood cells) or neutropenia (low levels of neutrophils, a type of white blood cell). In combination with other risk factors for anemia, such as other medications and opportunistic infections, taking AZT may result in more severe side-effects.[5,6] Most of the side effects are caused by the azid group (N_3).[7-10] Therefore, many of researchers are having some spectacular success at the moment (1999) against HIV and AIDS by using a combination of AZT.[11-18] A much more modified nucleoside 1-(5-Hydroxymethyl-4–[5–(5-oxo-5-piperidin-1-yl-penta-1,3-dienyl)–benzo[1, 3]dioxol-2-yl]-tetrahydro-furan-2-yl)-5-methyl-1H-pyrimidine-2,4dione (AHE), which is active against AZT-resistant viruses. This drug is based on AZT but the azide group has been replaced by piperine though it is recognizably similar especially in the stereochemistry.[19] The chemical name of piperine (Figure I) is 1-[(2E, 4E)-5-(1, 3-benzodioxol-5-yl)-1-oxo-2, 4-pentadienyl], and the chemical formula is C_{17} H_{19} N O_3. Piperine can be isolated in good yield from ground black pepper, which is made up of 5-9 % of alkaloids that also include piperidine, piperettine and piperanine and comes from the dried fruit of aschanti.[20] The IUPAC name of the studied molecule is 1-(5-Hydroxymethyl -4–[5–(5-oxo-5-piperidin-1-yl-penta-1,3dienyl)–benzo[1,3]dioxol-2-yl]-tetrahydro-furan-2- yl)- 5 -methyl -1H -pyrimidine-2,4dione (AHE), and its chemical formula is $C_{27}H_{31}N_3O_7$. The chemical structure is shown in Figure 2.



Scheme 1.

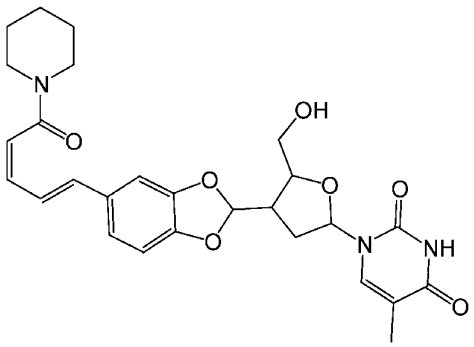


Figure 2. The chemical structure of AHE.

The relative stereochemistry around the ribose ring of the nucleosides in DNA and RNA because the bases can be persuaded to cyclize on to the ring in certain reactions. Treatment of deoxythymidine with reagents that make oxygen atoms into leaving groups leads to cyclization by intramolecular S_N2 reaction. The amide oxygen of the base attacks the 3?-position in the sugar ring. This S_N2 reaction has to happen with inversion, proving that the base and the 3?-OH group are on opposite sides of the ribose ring. The cyclized product is useful too. If it is reacted with piperine ion the ring reopens with inversion in another S_N2 reaction and AHE is formed as shown in scheme I.[21] Because of the biological and medical importance of the AHE molecule I have investigated the structural features and electronic properties theoretically in this work.

Method of calculation

The AHE molecule has been investigated theoretically by performing semi-empirical molecular orbital and density functional theory calculations.

Semi-empirical self-consistent-field molecular orbital (SCF-MO) method at Austin Model 1 (AM1) level,[22] within the restricted Hartree-Fock (RHF).[23] Formalism has been considered to optimize fully the geometry of the AHE molecule in its ground state. Geometry optimization is carried out by using a conjugate gradient method (Polak-Ribiere algorithm),[24] then the electronic structure of the system has been calculated by applying the density functional theory (DFT) method [25] considering B3LYP exchange-correlation functional.[26,27] 3-21G basis set [28] has been chosen in the DFT calculations. The SCF convergency is set to 0.001 kcal/mol and the RMS gradient is set to 0.001 kcal/(A^o mol) in the calculations. We have performed all the calculations by using the HyperChem-7 packet program,[29] running on Windows XP Workstation in Pentium IV PC.

Results and Discussion

Some molecular information about the system considered are given in Table (I) .

Table 1. Some molecular information about the AHE

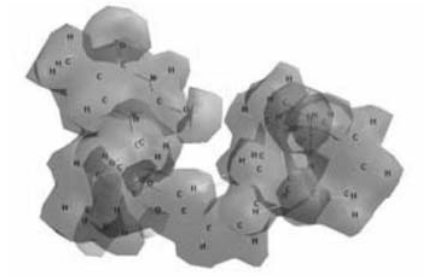
Quantity	Value	
	AM1	DFT
No. of electrons	196	270
No. of doubly occupied levels	98	135
No. of total orbitals	179	216

Quantity Value AM1 DFT No. of electrons 196 270 No. of doubly occupied levels 98 135 No. of total orbitals 179 216 The geometry optimization of AM1 and DFT methods yields a non-planar structure as the stable form with C1 symmetry of the AHE. In the AHE some of the carbon atoms have positive excess charge, some of them have negative excess charge, the magnitude of positive charges vary from + 0.047 to + 0.403 (AM1) and 0.021 to + 0.451 (DFT), whereas the magnitude of negative charges vary from - 0.010 to - 0.235 (AM1) and - 0.001 to - 0.274 (DFT). All the oxygen atoms have negative excess charge, their magnitude vary from – 0.235 to – 0.384 (AM1) and - 0.267 to - 0.378 (DFT). 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 0.076 to 0.226 (AM1) and 0.004 to 0.219 (DFT), where as the magnitude of negative charges vary from - 0.010 to - 0.021 (DFT).

Finally, the nitrogen atoms have negative excess charge, their magnitude vary from – 0.283 to – 0.382 (AM1) and – 0.379 to – 0.441 (DFT). The large charge accumulation takes place on the oxygen and nitrogen atoms. Isosarface of the electrostatic potential (ESP) of molecule is shown in Figure (III). Dark (green) colors indicate negative ESP regions and light (violet) colors indicate positive ESP regions. These figures shown that oxygen and nitrogen atoms have more negative ESP regions in compare with other atoms. This means that oxygen and nitrogen atoms undergo protonation reaction with acidic reagents.[30]

The calculated energies values obtained by different methods (AM1 and DFT) of the system studied as well as the highest occupied and

(a)



(b)

Figure 3. Isosurface of electrostatic potential in the spatial vicinity of AHE. a: AM1 b: DFT.

Table 2. The energy values (in kcal mol^{-1}), the MO energy of HOMO,LUMO levels,æ *E* (in eV), and dipole moment μ (in Debyes) for AHE which is calculated by AM1 and DFT methods.

Quantity	Method	
	AM1	DFT
Total energy	-155448.6	-443286.2
Binding energy	-7045.7	------
Isolated atomic energy	-148402.9	------
Electronic energy	-1444071.3	-2955179
Core-core interaction	1288622.7	------
Heat of formation	-60.58	------
Lowest level	7.203	-594.9
Highest level	-42.76	93.109
HOMO	-8.500	14.669
LUMO	-0.285	15.133
ΔE	8.215	0.464
μ	2.575	2.309
eK, ee and eN Energy	------	-2955178.9

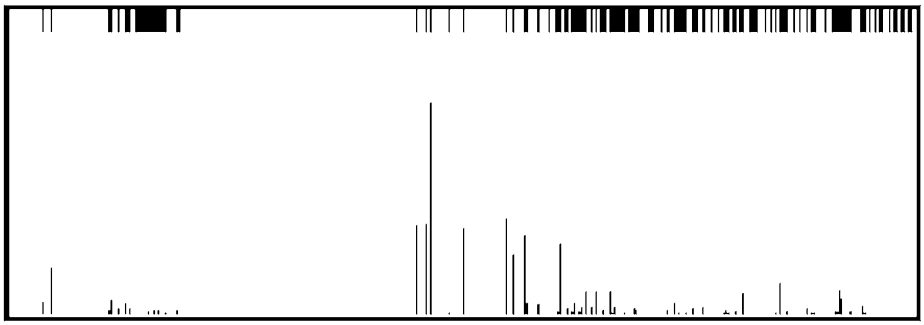


Figure 4. The vibration spectrum of the studied molecules. Normal mode frequencies, varies between 290 and 3520 cm^{-1}, and infraded band intensities vary between 20 and 360 km mol^{-1}.

the lowest unoccupied MO (HOMO and LUMO respectively) energies and the interfrontier MO energy gap (LUMO – HOMO energy difference, æ *E*) with the lowest and highest level energy values are also given in Table (II).

The AHE molecule has a binding energy value of about – 7045.7 kcal mol^{-1} (AM1). On the other hand, the heat of formation of the system studied is exothermic and has the value of about -60.58 kcal mol^{-1}.The LUMO – HOMO gap of the AHE is about 8 eV by AM1 and 1 by DFT methods.

The resultant dipole moment of the AHE molecule is about 2.6 and 2.3 Debyes by AM1 and DFT methods respectively .This value of dipole moment may be considered as large for such a molecule.[31] This high dipole moment may make the AHE molecule reactive and attractive for the interaction with other systems, in other words the AHE molecule with large dipole moment my be very polar (hydrophilic). This property of AHE makes it an active molecule with its environment that is AHE molecule may interacts with its environment strongly in solution.[32]

The infrared spectrum (IR) for the studied molecule calculated according to DFT method is displayed in Figure IV. To best of our knowledge, the experimental spectrum has not been reported in the literature. The range of the vibrational frequencies varies between 290 and 3503 cm^{-1}. The infrared band intensities vary between 20 and 360 km mol^{-1}. The principal peaks are as following: The scaled –OH rocking in the range 299-650 cm^{-1}, several CH_2 rocking in the range 900-1000 cm^{-1}, the asymmetric stretching of C-C-O in the range 1000-1060 cm^{-1}, C-O stretching in the range 1100-1200 cm^{-1}, the O-H and C-H rocking in the range 1300-1425 cm^{-1}, the -CH_3 wagging in 1400-1550 cm^{-1}, the stretching C=O in the range 1650 and 1780 cm^{-1}, the stretching C-H appear in the range 2800-3050 cm^{-1}, stretching of N-H in the range 3300-3390 cm^{-1}, finally the O-H stretching in the range 3450-3390 cm^{-1}. These values could be compared with the peaks obtained for the IR spectra of the parent molecules AZT and Piperine. For example, the 1470 cm^{-1} peak could be related with the experimental 1495 cm^{-1}; the 1513 cm^{-1} peak could be related with the experimental 1450 cm^{-1}; and the 3442 cm^{-1} peak could be related with the experimental 3390 cm^{-1}.

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References

[1] P. L. Boyer, S. G. Sarafianos, E. Arnold, and S. H. Hughes, *Journal of Virology*. 2001 ,*75*, 4832-4836.
[2] J. Lennerstrand,1, K. Hertogs, D. K. Stammers, and B. A. Larder1, *Journal of Virology*, 2001,*75*, 7202-7207.
[3] L. Odriozola, C. Cruchaga, M.Andréola, V. Dollé, C. H. Nguyen, L. Tarrago-Litvak, A. Pérez-Mediavilla, and J. J. Martínez-Irujo. *J. Biol. Chem*. 2003, *43*, 42710-42714.
[4] P. Herdewijn, E. De Clercq, Dideoxynucleoside analogues as inhibitors of HIV replication, In Design of Anti-Aids Drugs, E. De Clercq, Ed.: Elsevier Science, Amsterdam (1990), pp. 141-171.
[5] B.A. Larder, S.D. Kemp , and P.R.Harrigan , *Science*. 1995, *269* , 696-702.
[6] A.S. Ray, A. Basavapathruni, and K.S. Anderson. *J.Biol Chem*. 2002, *277*, 40479- 40485.
[7] M. Maillard J. C Florent,. M. LemaitreF.Begassat, A. Bugnicourt, C. Ferrieux, C. Rombi, E.D. Pacaud, D.E. Thierry, A. Zerial, C.Monneret, and D.S.Grierson. *Bioorg. Med. Chem. Lett.* 1992, *2*, 1469-1474.
[8] Y. Kitade,.A. Suzuki, K. Hirota, Y. Maki, H. Nakane, K. Ono, M. Baba, S. Shigeta, *Chem. Pharm. Bull.*1992, *40*, 920-924.
[9] Y. Sato, K. Utsumi, T. Maruyama, T. Kimura, I. Yamamoto, D.D. Richman, *Chem. Pharm. Bull*. 1994, *42*, 595- 598.
[10] I. Yamamoto, T. Kimura, Y. Tateoka, K. Watanabe, I. K.Ho, *J. Med. Chem.*1987, *30* 2227-2231.
[11] D. R. Adams, C. Perez,. M. Maillard,. J.C. Florent,. M. Evers,. Y. He´nin, S. Litvak, L. Litvak, C. Monneret, and D. S. Grierson. *J. Med. Chem.*1997, *40*, 1550-1558.
[12] P. Vlieghe,. T. Clerc,. C. Pannecouque,. M. Witvrouw, E. De Clercq, J. P. Salles, and J.L. Kraus, *J. Med. Chem.*2001,*44*, 3014-3021
[13] S. Chang, W. George ,W. Griesgraber, P. J. Southern,. and C.R. Wagner, *J. Med. Chem.*2001, *44*,, 223-231.
[14] A. Rosowsky, H. Fu, N. Pai, J. Mellors, D. D. Richman, and K. Y. Hostetler.
*J. Med. Chem.*1997,*40*, 2482-2490.
[15] L.Wang, K. W. Morin, R. Kumar, M. Cheraghali, K. G. Todd, G. B. Baker, E. E. Knaus, and L. I. Wiebe, *J. Med. Chem.* 1996, *39*, 826-833.
[16] V. E. Marquez, A. Ezzitouni, P. Russ, M. A. Siddiqui, H. Ford, R. J. Feldman, H. Mitsuya, C. George, and J. J. Barchi, *J. Am. Chem. Soc.*1998,*120*, 2780-2789
[17] A. Lavie, M. Konrad, R. Brundiers, R. S. Goody, I. Schlichting, and J. Reinstein, *Biochemistry*, 1998, *37*, 3677-3686.
[18] D. Arion, N. Kaushik, S. McCormick, G. Borkow, and M. A. Parniak, *Biochemistry*, 1998, *37*,15908-15917.
[19] W.W. Epstein, D.F. Netz, and J.L.Seidel, *J. Chem. Ed.* 1993,*70*, 598-603.
[20] R. Ikan, Natural products, A Laboratory Guide, 2nd ed.; Academic Press: New York, (1991), pp. 55-60.
[21] A. Faraj, M. Maillard, M. Lemaˆtre, S. Letellier, F. Frappier, J. Florent, D.S. Grierson, C. Monneret, A. Zerial, *J. Med. Chem*. 1992, *27*,141-148.

[22] M.J.S.Dewar, E.G.Zoebisch, E.F.Healy, and J.J.P.Stewart, *J. Ame. Chem.Soc*. 1985,*107*, 3902-3907.
[23] C.C.J. Roothaan , *Rev .Mod .Phys*.1951, *23*, 69-75.
[24] P.Fletcher, Practical Methods of Optimization, Wiley, New York, (1990), pp.144-150.
[25] W.Kohn, L.J.Sham, *Phys. Rev*. 1965, *140*, A1133.
[26] A.D.Becke, *J.Chem. Phys*.1993, *98* , 5648-5762.
[27] C.Lee, W. Yang, R.G.Parr, *Phys. Rev.* 1988, *785*,B37.
[28] R.Krishnan, J.S.Kinkley, R. Seeger, J.A.Pople, *J. Chem. Phys*.1980, *72*, 650-655.
[29]] Hyperchem TM release 7.52. Windows Molecular Modeling System,Hypercube,Inc. and Autodesk, Inc. Developed by Hypercube, Inc.
[30] A.J. Hameed , J. Mole. Struct . THEOCHEM, 2005,*728*, 43-47.
[31] S. Erkoc, M.Yilmazer, and F. Erkoc, J. Mole. Struct . THEOCHEM, 2002,*583*, 169-205.
[32] S. Erkoc, and F. Erkoc, J. Mole. Struct . THEOCHEM, 2005, *719*, 1-5.