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**QUANTUM-CHEMICAL CALCULATION OF ANTIVIRAL
DEXAMETHASONE MEDICATION BY MNDO, AB INITIO AND DFT
METHODS**

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Abstract: For the first time, the calculation of the antiviral dexamethasone medication was performed using the classical quantum-chemical methods MNDO, DFT and AB INITIO. Its acidic strength is theoretically estimated ($pK_a = 12-14$). It was found that this medication belongs to the class of weak acids ($9 < pK_a < 14$). It has been hypothesized that the effectiveness of dexamethasone is determined by its acidic strength.

Keywords: dexamethasone, acid strength, quantum-chemical calculation, AB INITIO method, DFT method, pK_a is a universal indicator of acidity.

Introduction

A study carried out in Oxford proved that dexamethasone (8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2-dihydro-xiacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,-16-oxyhydrocyclopenta[a]phenanthrene-3-, ($C_{22}H_{29}FO_5$) as an anti-inflammatory medication that reduces the risk of death of COVID-19 in those patients, who plugged to lung ventilator, by 35%, and among patients who received oxygen, by 20% [1]. For this reason, dexamethasone is currently being actively studied as a potential treatment for coronavirus infection COVID-19. Therefore, it is obvious that the problem of studying and increasing the effectiveness of this medication is very relevant. One of the ways to increase its effectiveness is to solve the issue of regulating its acidic strength and determining its maximum efficiency/selectivity of action in various biochemical reactions.

Therefore, the purpose of this report is a theoretical assessment of acidic strength of dexamethasone. To pursuing this objective, a quantum-chemical calculation of its optimal geometric and electronic structure (pKa) was carried out, as well as obtaining various quantum-chemical parameters characterizing this medication (E_0 is the total energy of $C_{22}H_{29}FO_5$ molecule, E_{el} - its total electron energy, q_A - distribution of atomic electron density, and, in particular, $q_{max}^{H^+}$ - distribution of maximum atomic hydrogen charges). The results obtained can be used in other studies, for example, when studying the mechanisms of various reactions in which dexamethasone can participate.

Methodical part

For quantum-chemical calculation of studied dexamethasone [3] three methods were chosen: MNDO, AB INITIO/6-311G* and DFT-PBEO/6-311G**, the advantages and disadvantages of which are described in sufficient detail, for example, in monographs [4, 5]. The calculations were carried out within the molecular model in the gas phase using the program [6, 7, 8] similarly to [9-11]. The total charge of the molecular system of dexamethasone in all models is zero, since the calculation was performed in the ground state. Therefore, $M = 1$ (M - multiplicity), since $M = 2S + 1$, therefore, the total type is zero, since in the ground state all electrons are paired.

Calculation results

Optimized geometric and electronic structure of dexamethasone molecule is shown in Fig. 1 (AB INITIO method), in Fig. 2 (DFT method), and Fig. 3 (MNDO method). The quantum-chemical parameters (E_0 , E_{el} , $q_{max}^{H^+}$) and pKa of studied compound are presented in Table 1. For model of dexamethasone obtained by AB INITIO method, the optimized bond lengths between carbon atoms

in the ring are within the range 1.32-1.59 Å, for C-O- - within the range 1.19 -1.40 Å, for C-H- - within the range 1.07- 1.09 Å, for HO- - are equal 0.94 Å, and for FC- - are equal 1.39 Å.

Optimized values of bond angles (in degrees) are obtained, respectively, as follows: C(5)-C(6)-C(1)- 122, C(1)-C(2)-C(3)-123, C(10)-C(4)-C(3)-108, C(2)-C(3)-C(4)-123, C(14)-C(10)-C(4)-116, C(7)-C(3)-C(4)-116, C(9)-C(10)-C(4)-112, C(3)-C(4)-C(5)-111, C(10)-C(4)-C(5)-112, C(23)-C(4)-C(5)-105, C(4)-C(5)-C(6)-125, C(2)-C(1)-C(6)-115, C(2)-C(3)-C(7)-121, C(3)-C(7)-C(8)-109, C(10)-C(9)-C(8)-112, C(7)-C(8)-C(9)-111, C(14)-C(10)-C(9)-109, C(13)-C(14)-C(10)-113, O(22)-C(14)-C(10)-113, C(8)-C(9)-C(11)-111, C(10)-C(9)-C(11)-115, C(17)-C(12)-C(11)- 104, C(9)-C(11)-C(12)- 114, C(16)-C(17)-C(12)- 105, C(15)-C(11)-C(12)-104, C(18)-C(17)-C(12)- 111, O(26)-C(17)-C(12)- 111, C(11)-C(12)-C(13)- 108, C(17)-C(12)-C(13)- 109, C(37)-C(12)-C(13)-109, C(12)-C(13)-C(14)- 115, C(9)-C(11)-C(15)- 118, C(11)-C(15)-C(16)- 104, C(15)-C(16)-C(17)- 106, C(20)-C(16)-C(17)- 114, C(16)-C(17)-C(18)- 112, O(26)-C(17)-C(18)- 107, C(17)-C(18)-C(19)- 123, O(21)-C(18)-C(19)- 118, C(15)-C(16)-C(20)- 114, C(17)-C(18)-O(21)- 120, C(13)-C(14)-O(22)- 108, C(3)-C(4)-C(23)- 109, C(10)-C(4)-C(23)- 111, C(14)-C(10)-F(24)- 106, C(18)-C(19)-O(25)- 111, C(16)-C(17)-O(26)-111, C(2)-C(1)-O(27)- 122, C(1)-C(2)-H(28)- 115, C(4)-C(5)-H(29)- 116, C(5)-C(6)-H(30)-122, C(1)-C(6)-H(30)- 117, C(3)-C(7)-H(31)- 110, C(3)-C(7)-H(32)- 110, C(7)-C(8)-H(33)- 110, C(7)-C(8)-H(34)- 109, C(8)-C(9)-H(35)- 107, C(10)-C(9)-H(35)- 105, C(9)-C(11)-H(36)- 105, C(11)-C(12)-C(37)- 113, C(17)-C(12)-C(37)- 113, C(12)-C(13)-H(38)- 110, C(12)-C(13)-H(39)- 110, C(13)-C(14)-H(40)- 110, C(11)-C(15)-H(41)- 113, C(11)-C(15)-H(42)- 111, C(15)-C(16)-H(43)-106, C(18)-C(19)-H(44)-112, C(18)-C(19)-H(45)-106, C(16)-C(20)-H(46)-111, C(16)-C(20)-H(47)-112, C(16)-C(20)-H(48)-110, C(14)-O(22)-H(49)-109, C(4)-C(23)-H(50)-113, C(4)-C(23)-H(51)-111, C(4)-C(23)-H(52)-109, C(19)-O(25)-H(53)-108, C(17)-O(26)-H(54)-109, C(12)-C(37)-H(55)-111, C(12)-C(37)-H(56)-112, C(12)-C(37)-H(57)-113. Atomic charges: C(1)- (+0.387), C(2)- (-0.137), C(3)- (-0.034), C(4)-(-0.319), C(5)- (+0.018), C(6)- (-0.159), C(7)- (-0.092), C(8)- (-0.129), C(9)- (-0.188), C(10)- (+0.30), C(11)- (-0.12), C(12)- (-0.428), C(13)- (-0.044), C(14)- (+0.203), C(15)- (-0.086), C(16)- (-0.245), C(17)- (+0.248), C(18)- (+0.283), C(19)- (+0.14), C(20)- (-0.146), O(21)- (-0.471), O(22)- (-0.492), C(23)- (-0.179), F(24)- (-0.427), O(25)- (-0.466), O(26)- (-0.514), O(27)- (-0.447), H(28)- (+0.099), H(29)- (+0.151), H(30)- (+0.111), H(31)- (+0.114), H(32)- (+0.113), H(33)- (+0.103), H(34)- (+0.126), H(35)- (+0.12), H(36)- (+0.107), C(37)-(-0.164), H(38)- (+0.124), H(39)- (+0.12), H(40)- (+0.112), H(41)- (+0.108), H(42)- (+0.132), H(43)- (+0.103), H(44)- (+0.114), H(45)- (+0.11), H(46)- (+0.107), H(47)- (+0.087), H(48)- (+0.088), H(49)- (+0.258), H(50)- (+0.097), H(51)- (+0.116), H(52)- (+0.122), H(53)- (+0.268), **H(54) -(+0.276)**, H(55)- (+0.119), H(56)- (+0.093), H(57)- (+0.105) (see Fig.1).

For model of dexamethasone obtained by DFT method, the optimized bond lengths between carbon atoms in the ring are within the range of 1.33-1.59 Å, for C-O- - within the range of 1.22-1.41 Å, for C-H- - within the range of 1.08-1.10 Å, for HO- - within the range of 0.96-0.97 Å, and for FC – are equal 1.41 Å. C(5)-C(6)-C(1)- 122, C(1)-C(2)-C(3)-124, C(10)-C(4)-C(3)-107, C(2)-C(3)-C(4)-123, C(14)-C(10)-C(4)-116, C(7)-C(3)-C(4)-116, C(9)-C(10)-C(4)-112, C(3)-C(4)-C(5)-112, C(10)-C(4)-C(5)-111, C(23)-C(4)-C(5)-106, C(4)-C(5)-C(6)-124, C(2)-C(1)-C(6)-115, C(2)-C(3)-C(7)-121, C(3)-C(7)-C(8)-109, C(10)-C(9)-C(8)-112, C(7)-C(8)-C(9)-111, C(14)-C(10)-C(9)-110, C(13)-C(14)-C(10)-112, O(22)-C(14)-C(10)-112, C(8)-C(9)-C(11)-111, C(10)-C(9)-C(11)-115, C(17)-C(12)-C(11)-104, C(9)-C(11)-C(12)-114, C(16)-C(17)-C(12)-105, C(15)-C(11)-C(12)-104, C(18)-C(17)-C(12)-110, O(26)-C(17)-C(12)-111, C(11)-C(12)-C(13)-108, C(17)-C(12)-C(13)-108, C(37)-C(12)-C(13)-110, C(12)-C(13)-C(14)-115, C(9)-C(11)-C(15)-117, C(11)-C(15)-C(16)-105, C(15)-C(16)-C(17)-106, C(20)-C(16)-C(17)-114, C(16)-C(17)-C(18)-112, O(26)-C(17)-C(18)-107, C(17)-C(18)-C(19)-123, O(21)-C(18)-C(19)-118, C(15)-C(16)-C(20)-114, C(17)-C(18)-O(21)-119, C(13)-C(14)-O(22)-108, C(3)-C(4)-C(23)-110, C(10)-C(4)-C(23)-111, C(14)-C(10)-F(24)-105, C(18)-C(19)-O(25)-111, C(16)-C(17)-O(26)-112, C(2)-C(1)-O(27)-122, C(1)-C(2)-H(28)-116, C(4)-C(5)-H(29)-115, C(5)-C(6)-H(30)-122, C(1)-C(6)-H(30)-116, C(3)-C(7)-H(31)-110, C(3)-C(7)-H(32)- 110, C(7)-C(8)-H(33)- 110, C(7)-C(8)-H(34)-109, C(8)-C(9)-H(35)-107, C(10)-C(9)-H(35)-105, C(9)-C(11)-H(36)-105, C(11)-C(12)-C(37)-114, C(17)-C(12)-C(37)-113, C(12)-C(13)-H(38)- 110, C(12)-C(13)-H(39)- 110, C(13)-C(14)-H(40)- 110, C(11)-C(15)-H(41)-113, C(11)-C(15)-H(42)-111, C(15)-C(16)-H(43)-107, C(18)-C(19)-H(44)-112, C(18)-C(19)-H(45)-106, C(16)-C(20)-H(46)-111, C(16)-C(20)-H(47)-112, C(16)-C(20)-H(48)-110, C(14)-O(22)-H(49)-107, C(4)-C(23)-H(50)-113, C(4)-C(23)-H(51)-111, C(4)-C(23)-H(52)-109, C(19)-O(25)-H(53)-105, C(17)-O(26)-H(54)-106, C(12)-C(37)-H(55)-110, C(12)-C(37)-H(56)-112, C(12)-C(37)-H(57)-113. Atomic charges: C(1)- (+0.246), C(2)- (-0.102), C(3)- (+0.011), C(4)- (-0.36), C(5)- (+0.012), C(6)- (-0.133), C(7)- (-0.184), C(8)- (-0.186), C(9)- (-0.206), C(10)- (+0.20), C(11)- (-0.151), C(12)- (-0.423), C(13)-(-0.098), C(14)- (+0.079), C(15)- (-0.15), C(16)- (-0.264), C(17)- (+0.142), C(18)- (+0.195), C(19)- (+0.019), C(20)- (-0.255), O(21)- (-0.375), O(22)- (-0.393), C(23)- (-0.268), F(24)- (-0.322), O(25)- (-0.392), O(26)- (-0.40), O(27)- (-0.355), H(28)- (+0.101), H(29)- (+0.152), H(30)- (+0.114), H(31)- (+0.145), H(32)- (+0.139), H(33)- (+0.133), H(34)- (+0.156), H(35)- (+0.157), H(36)- (+0.138), C(37)- (-0.244), H(38)- (+0.156), H(39)- (+0.146), H(40)- (+0.142), H(41)- (+0.139), H(42)- +0.154, H(43)- (+0.137), H(44)- (+0.149), H(45)- (+0.144), H(46)- (+0.135), H(47)- (+0.123), H(48)- (+0.122), H(49)- (+0.248), H(50)-(+0.127), H(51)- (+0.143), H(52)- (+0.153), H(53)- (+0.250), **H(54) –(+0.250)**, H(55)- (+0.145), H(56)- (+0.122), H(57)- (+0.132) (see Fig. 2).

For model of dexamethasone obtained by MNDO method, the optimized bond lengths between carbon atoms in the ring are within the range of 1.35-1.61 Å, for C-O- within 1.23-1.40 Å, for C-H- within the range of 1.09-1.12 Å, for H-O- are equal 0.95 Å, and for F-C- are equal 1.36 Å.

Optimized values of bond angles (in degrees) are obtained, respectively, as follows: C(5)-C(6)-C(1)- 122, C(1)-C(2)-C(3)-124, C(2)-C(3)-C(4)-123, C(7)-C(3)-C(4)-117, C(3)-C(4)-C(5)-110, C(23)-C(4)-C(5)-104, C(4)-C(5)-C(6)-126, C(2)-C(1)-C(6)-115, C(2)-C(3)-C(7)-120, C(3)-C(7)-C(8)-112, C(7)-C(8)-C(9)-113, C(14)-C(10)-C(9)-107, C(8)-C(9)-C(10)-113, C(13)-C(14)-C(10)-114, C(11)-C(9)-C(10)-117, O(22)-C(14)-C(10)-113, C(8)-C(9)-C(11)-112, C(9)-C(11)-C(12)- 116, C(15)-C(11)-C(12)-106, C(11)-C(12)-C(13)-109, C(37)-C(12)-C(13)-109, C(12)-C(13)-C(14)-117, C(9)-C(11)-C(15)-118, C(11)-C(15)-C(16)-108, C(15)-C(16)-C(17)-107, C(20)-C(16)-C(17)-118, C(16)-C(17)-C(18)-112, O(26)-C(17)-C(18)-107, C(17)-C(18)-C(19)-123, O(21)-C(18)-C(19)-119, C(15)-C(16)-C(20)-113, C(17)-C(18)-O(21)-118, C(13)-C(14)-O(22)-110, C(3)-C(4)-C(23)-109, C(9)-C(10)-F(24)-111, C(14)-C(10)-F(24)-108, C(18)-C(19)-O(25)-114, C(16)-C(17)-O(26)-107, C(2)-C(1)-O(27)-122, C(1)-C(2)-H(28)-115, C(4)-C(5)-H(29)-116, C(5)-C(6)-H(30)-121, C(1)-C(6)-H(30)-117, C(3)-C(7)-H(31)-110, C(3)-C(7)-H(32)-111, C(7)-C(8)-H(33)-108, C(7)-C(8)-H(34)-109, C(8)-C(9)-H(35)-105, C(9)-C(11)-H(36)-103, C(11)-C(12)-C(37)-112, C(12)-C(13)-H(38)-109, C(12)-C(13)-H(39)-110, C(13)-C(14)-H(40)-108, C(11)-C(15)-H(41)-110, C(11)-C(15)-H(42)-112, C(15)-C(16)-H(43)-107, C(18)-C(19)-H(44)-110, C(18)-C(19)-H(45)-108, C(16)-C(20)-H(46)-113, C(16)-C(20)-H(47)-111, C(16)-C(20)-H(48)-110, C(14)-O(22)-H(49)-114, C(4)-C(23)-H(50)- 114, C(4)-C(23)-H(51)-112, C(4)-C(23)-H(52)-110, C(19)-O(25)-H(53)-113, C(17)-O(26)-H(54)-114, C(12)-C(37)-H(55)-112, C(12)-C(37)-H(56)-112, C(12)-C(37)-H(57)-113. Atomic charges: C(1)- (+0.286), C(2)- (-0.102), C(3)- (-0.077), C(4)- (-0.007), C(5)- (-0.033), C(6)- (-0.131), C(7)- (+0.027), C(8)- (-0.001), C(9)- (-0.039), C(10)- (+0.169), C(11)- (-0.018), C(12)- (-0.088), C(13)- (-0.015), C(14)- (+0.116), C(15)- (-0.001), C(16)- (-0.035), C(17)- (+0.115), C(18)- (+0.154), C(19)- (+0.146), C(20)- (+0.057), O(21)- (-0.275), O(22)- (-0.317), C(23)- (+0.047), F(24)- (-0.235), O(25)- (-0.304), O(26)- (-0.311), O(27)- (-0.286), H(28)- (+0.078), H(29)- (+0.076), H(30)- (+0.082), H(31)- (+0.015), H(32)- (+0.018), H(33)- (+0.011), H(34)- (+0.024), H(35)- (+0.016), H(36)- (+0.009), C(37)- (+0.039), H(38)- (+0.021), H(39)- (+0.028), H(40)- (+0.041), H(41)- (+0.012), H(42)- (+0.032), H(43)- (+0.01), H(44)- (-0.002), H(45)- (+0.051), H(46)- (+0.007), H(47)- (+0.008), H(48)- (-0.009), H(49)- (+0.195), H(50)- (-0.002), H(51)- (+0.007), H(52)- (+0.007), H(53)- (+0.187), **H(54)** - (+0.199), H(55)- (+0.009), H(56)- (+0.001), H(57)- (-0.009) (see Fig.3).

According to formula $pK_a = 49.04-134.61 q_{\max}^{H^+}$ [10] - for AB INITIO/6-311G** method, (where $q_{\max}^{H^+} = +0, 276$), $pK_a = 51.048-150.078 q_{\max}^{H^+}$ [11] - for DFT-PBE0/6-311G** method

(where $q_{\max}^{\text{H}^+} = +0, 25$), and $\text{pKa} = 42.11-147.18 q_{\max}^{\text{H}^+}$ [12] - for MNDO method (where $q_{\max}^{\text{H}^+} = +0, 199$) () were found that $\text{pKa} = 12, 13, 14$, respectively.

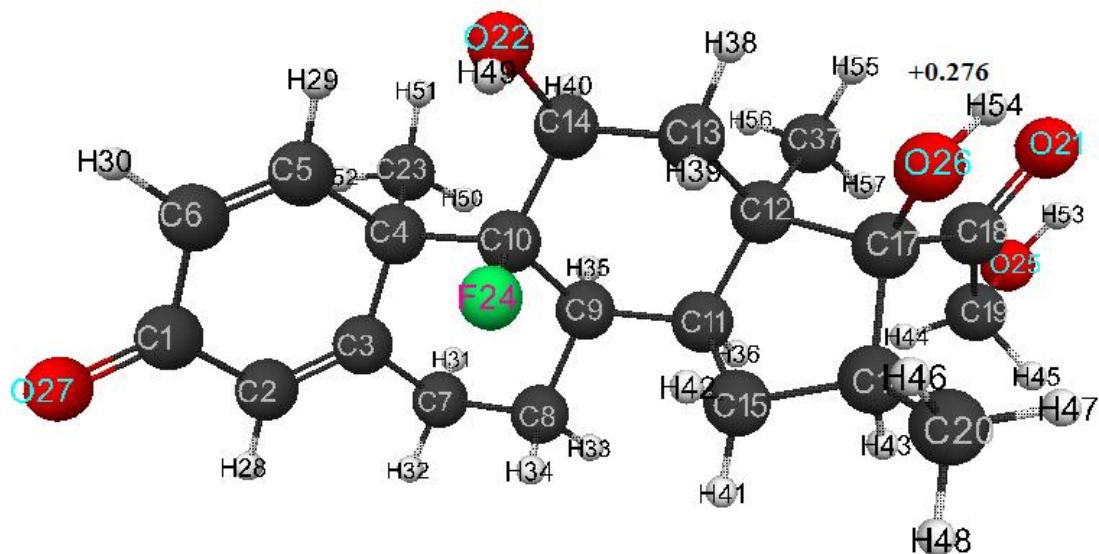


Figure 1. Geometric and electronic structure of dexamethasone molecule obtained by AB INITIO method.

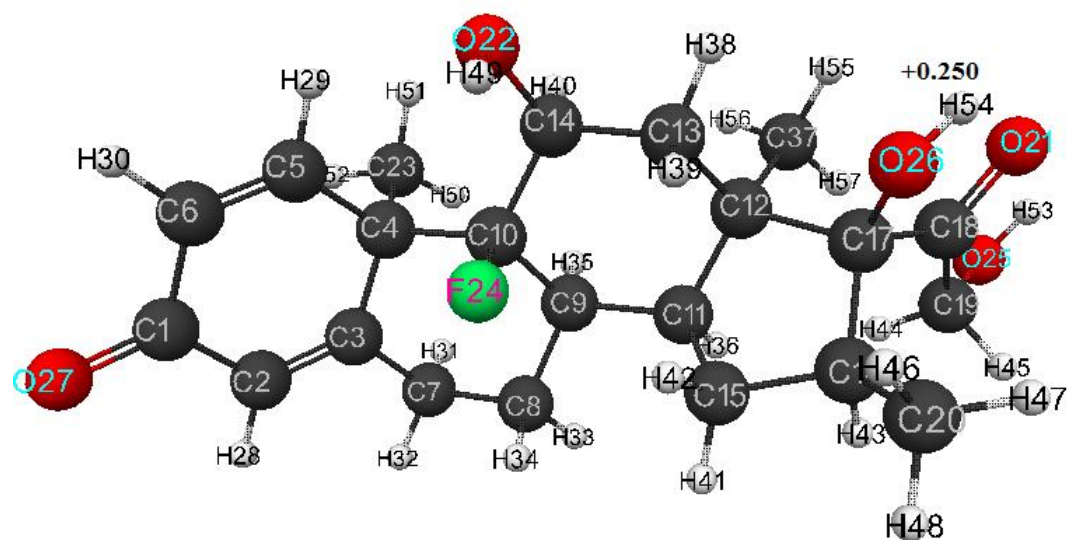


Figure 2. Geometric and electronic structure of dexamethasone molecule, obtained by DFT method.

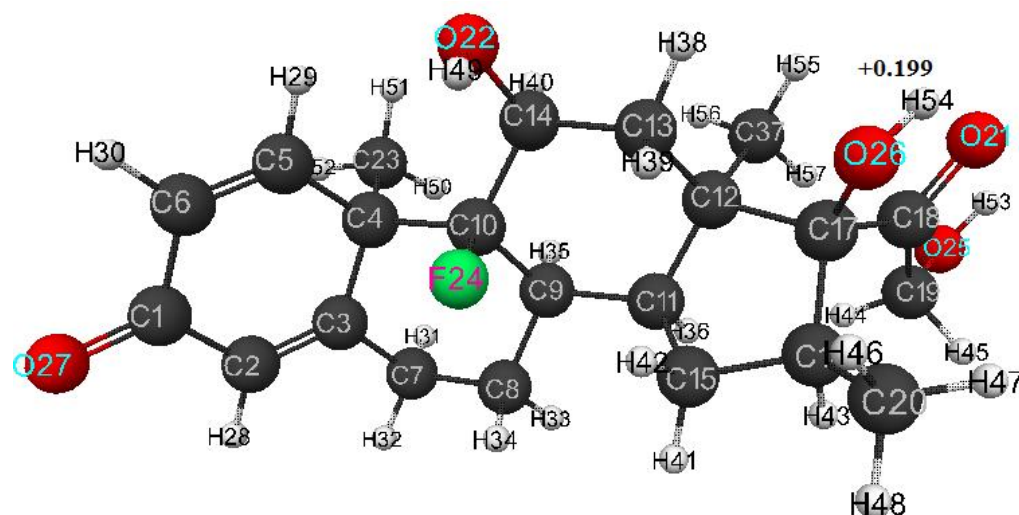


Figure 3. Geometric and electronic structure of dexamethasone molecule, obtained by MNDO method.

Table 1. Quantum-chemical parameters (E_0 , E_{el} , $q_{max}^{H^+}$) and pKa of dexamethasone studied.

Preparation	Method	E_0 , kJ/mol	E_{el} , kJ/mol	$q_{max}^{H^+}$	pKa
Dexamethasone	AB INITIO	-3475589	-11311734	+0, 276	12
	DFT	-3492820	-11356356	+0, 25	14
	MNDO	-512487	-4309672	+0, 199	13

Thus, the optimized atomic-molecular structures of the studied medication (dexamethasone) were obtained by DFT, AB INITIO and MNDO methods. The quantum-chemical parameters (E_0 , E_{el} , $q_{max}^{H^+}$) and distribution of atomic electron density (which is in full compliance with the law of charge conservation), etc., were calculated. It was proved that studied compound belongs to the class of weak acids ($9 < pK_a < 14$). It is obvious that proposed hypothesis – i.e. dependence of dexamethasone effectiveness on its acidic strength - requires experimental verification.

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