

Papaverin. Geometrical and Electronic Structure. Acidic Force.

Abstracts

The first quantum-chemical calculation of the molecule papaverine by the methods AB INITIO/6-311G** and DFT-PBE0/6-311G** has been performed with geometry optimization of all parameters by the standard gradient method. The optimized geometric and electronic structure of this compound has been obtained. Its acid strength ($pK_a \approx 30$ for AB INITIO/6-311G** and $pK_a \approx 30$ for DFT-PBE0/6-311 G**) has been theoretically evaluated. We have established that the molecule of hexoprenaline relates to the class of very weak acids ($pK_a > 14$).

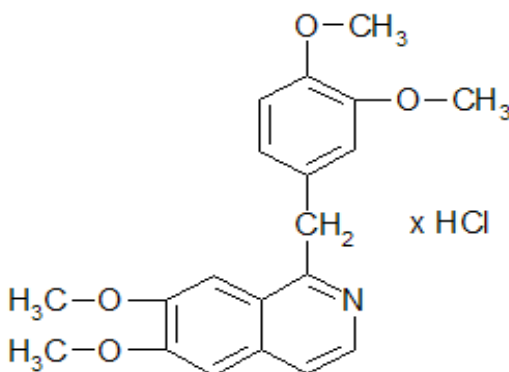
Keywords: quantum chemical calculation, AB INITIO/6-311G**, DFT-PBE0/6-311 G**, papaverine, acidic force

Medical-biological properties and application of papaverine.

Papaverine (Nobel Prize, Robinson, 1947) applies to group miotropic – spasmolytic preparations. They take off spasm from smooth musculature of inner organs and wall of blood-vessels [1-3]. Pharmacological action of papaverine is connected with suppression of phosphodiesterase ferment (PhDF). This leads to accumulate cyclic mononucleotides in cell (CM). Accumulation of CM brake combination of myosin with another protein – actin. This lead to actin- myosin compound defiant shortening of muscle fibres. It is most active influence on smooth musculature of stomach, bowels, bile-duct, uric way. The aim of this work is quantum chemical calculation of the molecule papaverine by the methods AB INITIO/6-311G** and DFT-PBE0/6-311G** with optimization of all parameters by the standard gradient method built-in in PC GAMESS [5] in approach the insolated molecule in gas phase, and the theoretic estimation of the acid strength.

Peculiarity of chemical structure for papaverine.

Molecule of papaverine represent 6,7-dimethoxy-1-(3,4- dimethoxy) iso-chinoline hydrochloride and UV-spectrum [4] lead to Fig.1:



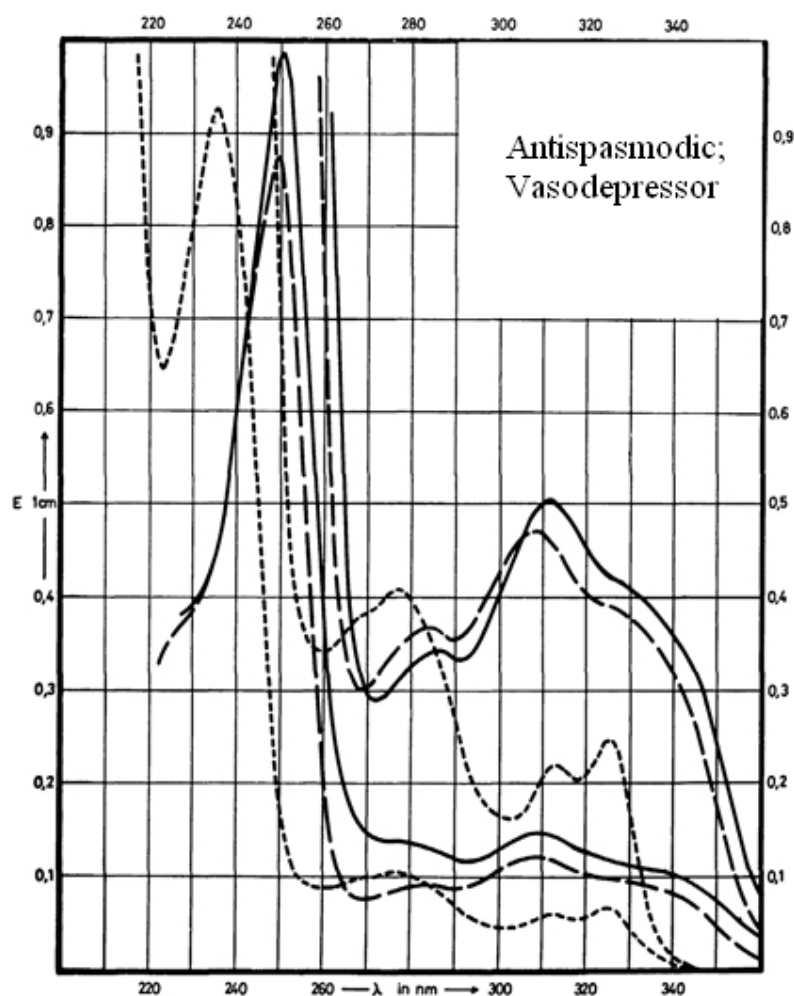


Fig.1.UV-spectrum papaverine (condition of obtaining in table1)

From Fig.1 and table1 can see position and intensity of maximum absorption in UV-spectrum define pH- surroundings. Quantity of papaverine hydrochloride define by titration of salt in alcoholic solution by alkali in presence of phenolphthalein (1 ml. 0.1 N solution KOH correspond to 0.03759 g.)

Table1. Parameters of UV-spectrum (methanol, 0.1M HCl, 0.1M NaOH).

Solution	Methanol	0.1M HCl	0.1M NaOH
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Max.absorption	311 nm 250 nm	308 nm 284 nm 249 nm	326 nm 277 nm 236 nm
$E_{1\%}^{1cm}$	244 1910	228 178 1700	117 196 1800

ϵ	9170 71800	8570 6690 63900	4400 7370 67670
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In alkaline environment show H-acidity of papaverine because of methylene group arrange between aromatic ring. Therefore max. absorption observe for structure obtained in alkaline environment and interest to define HC-acidity in gas phase.

Therefore, it was used quantum chemical methods AB INITIO/6-311G** and DFT-PBE0/6-311 G** with optimizationed geometry.

Result of calculations

Optimum for geometrical and electronic Structures, general and electronic energy papaverine molecule received quantum chemical methods AB INITIO/6-311G** and DFT-PBE0/6-311 G** with optimum Geometry (Table 2,3). pKa for calculation used method [6,7]:

$$pKa=49.04-134.61q_{\max}^{H^+} \text{ (for AB INITIO/6-311G**, } pKa=30)$$

$$pKa=51.048-150.078q_{\max}^{H^+} \text{ (for DFT-PBE0/6-311g**, } pKa=27)$$

где $q_{\max}^{H^+} = +0,14$ (for AB INITIO/6-311G**) и $q_{\max}^{H^+} = +0,16$ (for DFT-PBE0/6-311g**)

Conclusion

So, for the first time carry out quantum chemical methods AB INITIO/6-311G** and DFT-PBE0/6-311g** calculation of papaverine molcul and define pKa=30 (for AB INITIO/6-311G**) and pKa=27 (for DFT-PBE0/6-311g**), which is in fairly good agreement with the calculations performed in the work [9]. It is established that molecule of papaverin is weak acid ($pKa>14$). Ultimately, a similar research on the electronic level can contribute to the development of more effective nanotechnology of search of new antispasmodics.

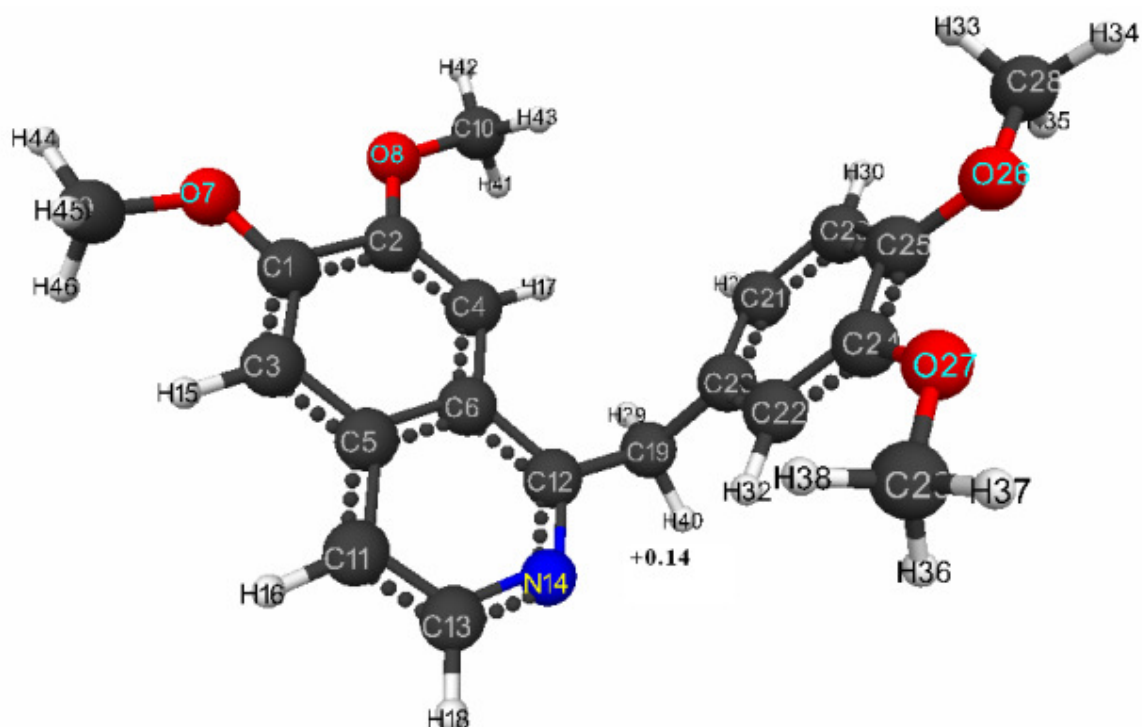


Fig.2. Geometric and electronic structure of molecule papaverine
 $(E_0 = -2949707 \text{ kJ/mol}, E_{\text{rel}} = -8587523 \text{ kJ/mol})$
AB INITIO/6-311G**

Table 2
Bond, Valence angle, Grade, Charges on atoms of molecule papaverine, AB
INITIO/6-311G.**

Bond	R,A	Valence angle	Grade	Atom	Charges
C(2)-C(1)	1.44	C(5)-C(3)-C(1)	121	C(1)	+0.28
C(3)-C(1)	1.35	C(6)-C(4)-C(2)	121	C(2)	+0.25
C(3)-C(5)	1.42	C(2)-C(1)-C(3)	120	C(3)	-0.13
C(4)-C(2)	1.35	C(11)-C(5)-C(3)	122	C(4)	-0.09
C(4)-C(6)	1.43	C(6)-C(5)-C(3)	120	C(5)	+0.08
C(5)-C(11)	1.41	C(1)-C(2)-C(4)	120	C(6)	-0.17
C(6)-C(5)	1.40	C(5)-C(6)-C(4)	119	O(7)	-0.43
O(7)-C(1)	1.33	O(8)-C(2)-C(4)	126	O(8)	-0.44
O(8)-C(2)	1.34	C(12)-C(6)-C(4)	123	C(9)	-0.04
C(9)-O(7)	1.40	C(13)-C(11)-C(5)	119	C(10)	-0.05
C(10)-O(8)	1.40	C(11)-C(5)-C(6)	118	C(11)	-0.21
C(11)-C(13)	1.35	C(2)-C(1)-O(7)	115	C(12)	+0.18
C(12)-C(6)	1.43	C(1)-C(2)-O(8)	115	C(13)	+0.12
C(13)-N(14)	1.35	C(1)-O(7)-C(9)	120	N(14)	-0.43
N(14)-C(12)	1.30	C(2)-O(8)-C(10)	119	H(15)	+0.10
H(15)-C(3)	1.07	N(14)-C(13)-C(11)	124	H(16)	+0.08
H(16)-C(11)	1.07	C(5)-C(6)-C(12)	118	H(17)	+0.13
H(17)-C(4)	1.07	C(12)-N(14)-C(13)	119	H(18)	+0.10

H(18)-C(13)	1.08	C(6)-C(12)-N(14)	122	C(19)	-0.12
C(19)-C(12)	1.52	C(19)-C(12)-N(14)	116	C(20)	-0.15
C(20)-C(19)	1.52	C(1)-C(3)-H(15)	121	C(21)	-0.10
C(21)-C(20)	1.37	C(5)-C(3)-H(15)	118	C(22)	-0.09
C(22)-C(20)	1.40	C(13)-C(11)-H(16)	121	C(23)	-0.14
C(23)-C(21)	1.40	C(2)-C(4)-H(17)	120	C(24)	+0.26
C(24)-C(22)	1.37	C(6)-C(4)-H(17)	119	C(25)	+0.24
C(24)-C(25)	1.41	N(14)-C(13)-H(18)	115	O(26)	-0.44
C(25)-C(23)	1.37	C(6)-C(12)-C(19)	122	O(27)	-0.44
O(26)-C(25)	1.35	C(12)-C(19)-C(20)	114	C(28)	-0.04
O(27)-C(24)	1.34	C(19)-C(20)-C(21)	122	C(29)	-0.04
C(28)-O(26)	1.40	C(22)-C(20)-C(21)	118	H(30)	+0.10
C(29)-O(27)	1.40	C(19)-C(20)-C(22)	120	H(31)	+0.08
H(30)-C(23)	1.07	C(25)-C(24)-C(22)	120	H(32)	+0.13
H(31)-C(21)	1.08	C(20)-C(21)-C(23)	121	H(33)	+0.08
H(32)-C(22)	1.07	C(20)-C(22)-C(24)	121	H(34)	+0.11
H(33)-C(28)	1.09	C(23)-C(25)-C(24)	119	H(35)	+0.09
H(34)-C(28)	1.08	O(26)-C(25)-C(24)	116	H(36)	+0.09
H(35)-C(28)	1.09	C(21)-C(23)-C(25)	121	H(37)	+0.11
H(36)-C(29)	1.09	C(23)-C(25)-O(26)	125	H(38)	+0.09
H(37)-C(29)	1.08	C(22)-C(24)-O(27)	125	H(39)	+0.11
H(38)-C(29)	1.09	C(25)-C(24)-O(27)	116	H(40)	+0.14
H(39)-C(19)	1.08	C(25)-O(26)-C(28)	119	H(41)	+0.09
H(40)-C(19)	1.08	C(24)-O(27)-C(29)	120	H(42)	+0.12
H(41)-C(10)	1.09	C(21)-C(23)-H(30)	119	H(43)	+0.10
H(42)-C(10)	1.08	C(20)-C(21)-H(31)	120	H(44)	+0.12
H(43)-C(10)	1.09	C(20)-C(22)-H(32)	118	H(45)	+0.09
H(44)-C(9)	1.08	O(26)-C(28)-H(33)	112	H(46)	+0.09
H(45)-C(9)	1.09	O(26)-C(28)-H(34)	106		
H(46)-C(9)	1.09	O(26)-C(28)-H(35)	112		
		O(27)-C(29)-H(36)	112		
		O(27)-C(29)-H(37)	106		
		O(27)-C(29)-H(38)	111		
		C(12)-C(19)-H(39)	110		
		C(12)-C(19)-H(40)	106		
		O(8)-C(10)-H(41)	111		
		O(8)-C(10)-H(42)	106		
		O(8)-C(10)-H(43)	111		
		O(7)-C(9)-H(44)	106		
		O(7)-C(9)-H(45)	111		
		O(7)-C(9)-H(46)	111		

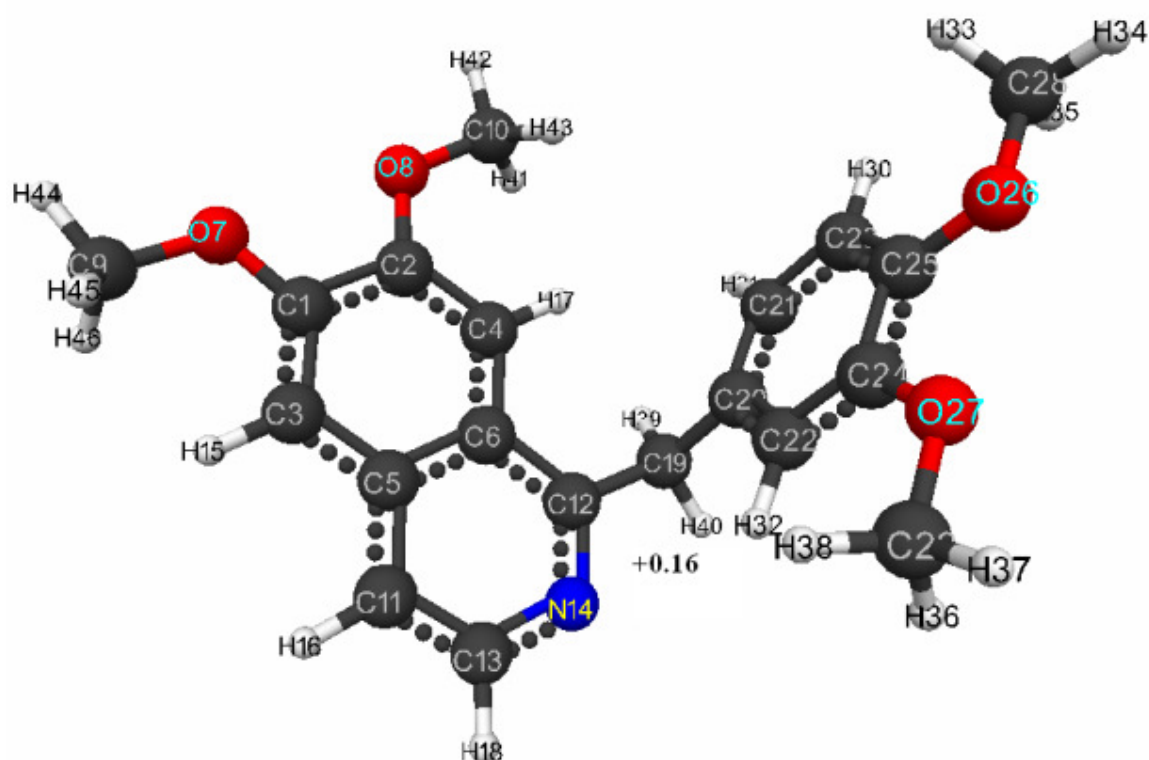


Fig.3 Geometric and electronic structure of molecule papaverine
($E_0 = -2964573$ kJ/mol, $E_{311} = -8621217$ kJ/mol) DFT-PBE0/6-311g**.

Table 3
Bond, Valence angle, Grade, Charges, on atoms of molecule papaverine DFT-PBE0/6-311g**

Bond	R,A	Valence angle	Grade	Atom	Charges
C(2)-C(1)	1.43	C(5)-C(3)-C(1)	121	C(1)	+0.19
C(3)-C(1)	1.37	C(6)-C(4)-C(2)	121	C(2)	+0.16
C(3)-C(5)	1.42	C(2)-C(1)-C(3)	120	C(3)	-0.10
C(4)-C(2)	1.37	C(11)-C(5)-C(3)	123	C(4)	-0.06
C(4)-C(6)	1.42	C(6)-C(5)-C(3)	119	C(5)	+0.06
C(5)-C(11)	1.41	C(1)-C(2)-C(4)	120	C(6)	-0.14
C(6)-C(5)	1.42	C(5)-C(6)-C(4)	119	O(7)	-0.33
O(7)-C(1)	1.34	O(8)-C(2)-C(4)	125	O(8)	-0.33
O(8)-C(2)	1.35	C(12)-C(6)-C(4)	123	C(9)	-0.19
C(9)-O(7)	1.41	C(13)-C(11)-C(5)	119	C(10)	-0.19
C(10)-O(8)	1.41	C(11)-C(5)-C(6)	118	C(11)	-0.18
C(11)-C(13)	1.37	C(2)-C(1)-O(7)	115	C(12)	+0.12
C(12)-C(6)	1.42	C(1)-C(2)-O(8)	115	C(13)	+0.07
C(13)-N(14)	1.35	C(1)-O(7)-C(9)	118	N(14)	-0.37
N(14)-C(12)	1.32	C(2)-O(8)-C(10)	117	H(15)	+0.11
H(15)-C(3)	1.08	N(14)-C(13)-C(11)	124	H(16)	+0.09
H(16)-C(11)	1.09	C(5)-C(6)-C(12)	118	H(17)	+0.14

H(17)-C(4)	1.08	C(12)-N(14)-C(13)	119	H(18)	+0.11
H(18)-C(13)	1.09	C(6)-C(12)-N(14)	123	C(19)	-0.23
C(19)-C(12)	1.51	C(19)-C(12)-N(14)	116	C(20)	-0.16
C(20)-C(19)	1.51	C(1)-C(3)-H(15)	121	C(21)	-0.09
C(21)-C(20)	1.38	C(5)-C(3)-H(15)	118	C(22)	-0.05
C(22)-C(20)	1.40	C(13)-C(11)-H(16)	121	C(23)	-0.15
C(23)-C(21)	1.40	C(2)-C(4)-H(17)	120	C(24)	+0.18
C(24)-C(22)	1.38	C(6)-C(4)-H(17)	119	C(25)	+0.18
C(24)-C(25)	1.41	N(14)-C(13)-H(18)	115	O(26)	-0.34
C(25)-C(23)	1.38	C(6)-C(12)-C(19)	121	O(27)	-0.34
O(26)-C(25)	1.35	C(12)-C(19)-C(20)	114	C(28)	-0.18
O(27)-C(24)	1.35	C(19)-C(20)-C(21)	122	C(29)	-0.19
C(28)-O(26)	1.41	C(22)-C(20)-C(21)	119	H(30)	+0.11
C(29)-O(27)	1.41	C(19)-C(20)-C(22)	120	H(31)	+0.08
H(30)-C(23)	1.08	C(25)-C(24)-C(22)	120	H(32)	+0.13
H(31)-C(21)	1.09	C(20)-C(21)-C(23)	121	H(33)	+0.12
H(32)-C(22)	1.08	C(20)-C(22)-C(24)	121	H(34)	+0.14
H(33)-C(28)	1.10	C(23)-C(25)-C(24)	119	H(35)	+0.12
H(34)-C(28)	1.09	O(26)-C(25)-C(24)	116	H(36)	+0.13
H(35)-C(28)	1.10	C(21)-C(23)-C(25)	121	H(37)	+0.14
H(36)-C(29)	1.10	C(23)-C(25)-O(26)	125	H(38)	+0.13
H(37)-C(29)	1.09	C(22)-C(24)-O(27)	125	H(39)	+0.14
H(38)-C(29)	1.10	C(25)-C(24)-O(27)	115	H(40)	+0.16
H(39)-C(19)	1.10	C(25)-O(26)-C(28)	117	H(41)	+0.12
H(40)-C(19)	1.09	C(24)-O(27)-C(29)	117	H(42)	+0.14
H(41)-C(10)	1.10	C(21)-C(23)-H(30)	119	H(43)	+0.14
H(42)-C(10)	1.09	C(20)-C(21)-H(31)	120	H(44)	+0.15
H(43)-C(10)	1.10	C(20)-C(22)-H(32)	118	H(45)	+0.13
H(44)-C(9)	1.09	O(26)-C(28)-H(33)	112	H(46)	+0.13
H(45)-C(9)	1.10	O(26)-C(28)-H(34)	106		
H(46)-C(9)	1.10	O(26)-C(28)-H(35)	112		
		O(27)-C(29)-H(36)	112		
		O(27)-C(29)-H(37)	106		
		O(27)-C(29)-H(38)	112		
		C(12)-C(19)-H(39)	110		
		C(12)-C(19)-H(40)	106		
		O(8)-C(10)-H(41)	111		
		O(8)-C(10)-H(42)	106		
		O(8)-C(10)-H(43)	111		
		O(7)-C(9)-H(44)	106		
		O(7)-C(9)-H(45)	111		
		O(7)-C(9)-H(46)	111		

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