A THEORETICAL APPROACH TO THE MOLECULAR INTERACTION BETWEEN CHOLESTEROL AND 2-PYRIDINE ALDOXIME METHYL CHLORIDE (2 - PAM)

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abstract: Starting from the associative properties of cholesterol evidenced by our group in different solvents by IR/FTIR spectroscopy we evaluate the molecular interaction between cholesterol and pralidoxime, an antinoxious drug. The first approach of this interaction is realised using molecular mechanics (MM^+) and semiempirical quantum mechanics (AM1) methods. For complex: cholesterol – 2PAM the calculated energy of interaction is negative, which indicate the stability of complex. The order of magnitude shows the possibility of hydrogen bonding formation and the calculated length of this bond is acceptable.

key words: cholesterol, 2-PAM, molecular interaction, AM1, MM^+ .

Introduction

The cholesterol is the most abundant steroid in human body, being a component of red plasma end brain nerve cells [1]. Its benefic or malefic role in metabolism associated with the change of membrane permeability is much debated in literature [2]. The associative properties of cholesterol have been studied by the variable temperature spectroscopy in different solvents [3]. On other hand 2-PAM is known as an antidote to cholinesterase inhibitors, or to organophosphate chemicals [1]. We are interested in the nature of interaction between cholesterol and this medicine (Fig. 1) which represents a cholinesterase activator [5]. The molecular modelling represents theoretical approach to attend this objective in the most efficient mode.

In recent literature [6] interaction of pralidoxime with cholesterol is in the frame of described *ab initio* method with Gaussian 98 program. Head of formation and most probable energetic conformation of the complex cholesterol – 2-PAM are determined. The 2-PAM presents 2 conformers EE and EZ separated by a rotation of 180^0 along with bond N=C.

From the examination of calculated by [6] global atomic charges results that in the complex cholesterol – 2-PAM the six atom members A cycle with oxygen atom from hydroxyl group of the cholesterol molecule is the most important in hydrogen bond establishing interaction.

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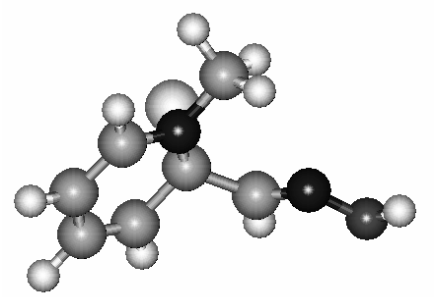

Fig. 1 *The structure of 2 –PAM optimised by AM1 method*

We studied FTIR spectra of complex cholesterol: 2-PAM [7]. This points out that cholesterol can acts an important role in transport of bonded molecule 2-PAM at that site where intoxication with organophosphate components is developed. From comparison of the spectra of pure cholesterol (I), 2-PAM (II), both Merk products p.a., and its equimolecular ratio mixture (III) (all obtained by KBr pellets technique on 400/600 series Jasco FTIR spectrometer) [7] results the formation of hydrogen bonding complex between cholesterol and 2-PAM.

For this reason in this paper we try to use MM+ and AM1 as simplest modelling methods to describe this molecular interaction and to predict some energetic and geometrical properties of the formed complex.

Experimental

Calculation details

We performed MM+ and AM1 calculations in the frame of HYPERCHEM PROGRAM release 6.01 for Windows 2000 HYPERCUBE Inc., using a Pentium IV computer CPU 2.8 Hz, 512MB RAM.

In molecular mechanics has used the force field MM+; the electrostatic term has calculated by approximation of the bond dipole. For the optimisation we used the Polack Ribiere Algorithm with a RMS gradient of 0.001 kcal/mole.

In the quantum mechanics AM1 method we used RHF approximation *in vacuo*. For optimisation we used algorithm Polack Ribiere with a RMS gradient of 001 kcal/mole.

Results and Discussion

The structure of minimal energy of the cholesterol obtained by AM1optimization is shown in Fig. 2.

The cholesterol structure optimised by AM1 method. Some molecular properties of cholesterol calculated by MM+ and AM1 methods are presented comparatively in Table 1.

The same type of data for 2-PAM is shown in Table 2.

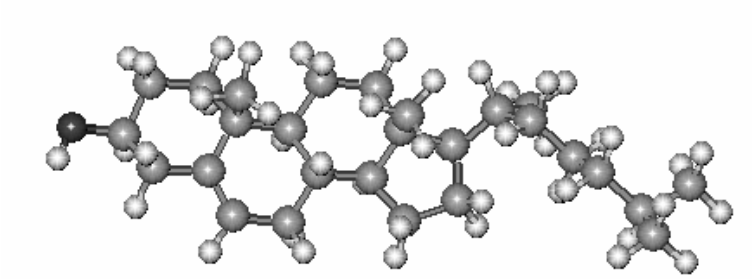

Fig. 2. *The cholesterol structure optimised by AM1 method.*

Table 1. Molecular properties of cholesterol calculated by MM+ and AM1 methods

no.	Properties	MM+ values	AM1 values
1	Grid surface ($Å^2$)	679.45	666.80
2	Aprox surface ($Å^2$)	615.36	600.38
3	Volume (A^3)	1236.27	1217.34
4	Hidratation energy (kcal/mol)	0.10	-0.09
5	Log P	7.17	7.17
6	Refractivity ($Å^3$)	120.62	120.62
7	Polarizability ($Å^3$)	47.67	47.67
8	Molecular weight (uam)	386.66	386.66
9	Dipole moment (D)	-	1.515

Table 2. Molecular properties of 2 –PAM calculated by MM+ and AM1 methods

no.	Properties	MM+ values	AM1 values
1	Grid surface($Å^2$)	358.48	341.13
2	Aprox surface ($Å^2$)	344.03	325.02
3	Volume ($Å^3$)	545.71	518.26
4	Log P	2.37	2.37
5	Refractivity ($Å^3$)	46.20	46.20
6	Polarizability ($Å^3$)	17.73	17.73
7	Molecular weight (uam)	172.61	172.61
8	Dipole moment (D)	–	2.551

Surely it is possible many comparisons about the values of molecular properties calculated by the both methods, but we accord a special attention to significance of the calculated properties for the partner in complex molecules. The surface accessible to solvent and molecular volume is higher for cholesterol.

Further, from examination of these data results the more polar character of 2-PAM demonstrated firstly by the higher value of dipole moment (2.551 D) in comparison with that of cholesterol (1.513D). The higher value of log P (7.17) for cholesterol in comparison with that of 2 PAM (2.37) indicates his pronounced hydrophobic character associated with

a very good solubility in lipid membranes, while the 2-PAM is able to solve in both lipid and aqueous phases.

The structure of complex cholesterol 2-PAM optimised by AM1 method is presented in Fig. 3.

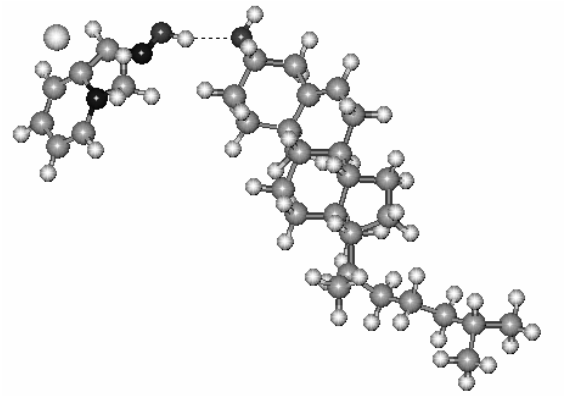

Fig. 3 *The structure of cholesterol –2PAM complex optimised by AM1 method*

From this figure results that in the complex the O-atom of hydroxyl group of cholesterol attract the H of aldoxime group from 2-PAM.

Enthalpy of association cholesterol : 2-PAM was calculated starting from general formula:

$$\Delta H_{assoc} = H_{complex} - (H_{cholest} - H_{2\text{-}PAM}) \quad (1)$$

and is appreciated at –3.32 kcal/mole, which correspond as magnitude order to a weak hydrogen bond.

In the Table 3 are given total energy and its component for the three molecular species: cholesterol, 2-PAM, complex. In the last column of this table are calculated interaction energy and its components after the same formula as precedent enthalpic term.

We can observe that energy of interaction is negative which shows the stability of the formed complex. The magnitude order corresponds to casual hydrogen bonding interaction.

The higher contribution to interaction energy corresponds to van der Waals interaction and to electrostatic term. In this mod the present results are in accord whit our experimental data [7] and complect the conclusion obtained by [6] using more elaborated calculations.

Table 3. Total energy and its components for cholesterol, 2 PAM and complex

Energy components	Energy (kcal/mol)			
	Cholesterol	2-PAM	Complex	$E_{interaction}$
E_{total}	50.65	14.53	60.18	-5.00
$E_{def\ of\ bond}$	3.75	0.71	4.41	-0.05
$E_{def\ of\ ungles.}$	11.65	6.06	17.70	-0.01
$E_{torsiun}$	19.24	-2.69	16.56	0.01
$E_{van\ der\ Waals}$	15.04	9.94	20.78	-4.20
$E_{form.\ ungles\ and\ bond}$	0.79	0.35	1.13	-0.01
$E_{electrostatic}$	0.18	0.15	-.40	-0.07

Conclusion

Interaction between cholesterol and the methyl pyridinium 2- aldoxime chloride an cholinesterase activator, was studied by MM+ and AM1 methods.

Some calculated molecular properties (as solvent accessible surface, molecular volume dipole moment, log P, etc.) of the partner molecules in complex are in accord with observed behaviour.

The calculated values of enthalpy and energy of interaction in complex are in accord whit formation of hydrogen bonding stable complex.

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