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INVESTIGATION OF MEDIBOROL ON THE BASIS OF DENSITY FUNCTIONAL THEORY

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Keywords: density functional theory, B3LYP/6-31G(d), medioborol, natural orbital communication.

Annotation. Quantum-chemical calculations of the mediborol in the gas phase and in solution by using the density functional with use all-electron basis set 6-31G(d) on GAUSSIAN'03 and TZ2P+ on Amsterdam density functional program. It is shown that the possibility of the mediborol reaction with iron chloride, the analysis of orbital interactions was carried out. It is provided the thermodynamic impossibility of this reaction.

Introduction. In recent years sharply increased the interest in space-hindered phenol (SHP) from the discovery of many aspects of their practical application. One of the most promising low-toxic compounds of this group is a new semi-synthetic antioxidant mediborol (4-methyl-2,6-diizobornil-phenol), which has a pronounced effect on the vascular-platelet hemostasis, neuroprotective (in violation of cerebral circulation) and reticula protective activity and is the basis for the creation of free radical pathologies in neurology and ophthalmology.

The important stage is to study of chemical and physical-chemical properties of mediborol for development of parameters of quality of his substance. Reactive functional groups of mediborol are phenolic hydroxyl and a methyl group.

However, in a number of SHP hydroxyl group, due to its proximity to her bulky substituents, it becomes inactive and does not enter into a specific reaction (with the iron salts, formation of the azo dyes). Therefore, the aim of this work was a quantum-chemical calculation of mediborol molecular structure for the identifying of the reaction ability of this compound.

Mediborol has a white or cream color, microcrystalline powder with a specific odor with T_{mt} 206–208°C, has pronounced lipophilic properties: practically insoluble in water, slightly soluble in lower alcohols, esters soluble in benzene, and readily soluble in halogenated hydrocarbons.

UV spectra of the terpenophenols in the range 220–320 nm are characterized by short-wavelength maximum near 220 nm and a wide absorption at 280 nm.

UV spectrum of the ethanol solution of mediborol has characteristic SHP two absorption bands - in the area of 210–230 and 270–290 nm, with the analytical value has an absorption maximum at a wavelength of 282±2 nm [1, 2].

The IR spectra of the hydroxyl group of SHP band are a narrow signal is shifted to shorter wavelengths in comparison with unsubstituted phenol.

The observed increase in the frequency of vibrations of OH groups, probably deal with the interaction of the electron clouds of hydroxyl and ortho-substituted groups, what is more, hydroxyl group the frequency depends on the size of the substituents.

For para-substituent, with increasing its electronegativity influencing on the polarization of the O-H bond, take place decreases of the frequency hydroxyl group [3].

An important feature is the lack of bands of the aromatic ring in the range 1510–1500 cm^{-1}. Splitting the bands and the intensity ratio of the individual components in the range of characteristic oscillations of the aromatic rings (1600–1450 cm^{-1}) depends on the volume and branching orto radical. Splitting the bands and the intensity ratio of the individual components in the range of characteristic oscillations of the aromatic rings (1600–1450 cm^{-1}) depends on the volume and branching orto radical: with an increase volume of radical in intensity of the band at 1600 cm^{-1} decreases, which is clearly manifested in the IR spectrum of mediborol.

Concerning to the interaction mediborol with iron salts, the experimental results indicate the absence of the possibility of such reaction.

Experimental part

The calculations were performed with using a standard software package *GAUSSIAN'03* [4]. For carry out to theoretical studies was used quantum-chemical method of functional density (DFT, Functional Theory). The calculations performed by the hybrid density functional B3LYP, with the exchange functionality Beke (B3) [5] and correlation functional of Lee, Yang and Couple (LYP) [6]. For all atoms used as a fully electronic basis set 6-31G (d), and the SDD pseudopotential for iron atom. Updates designed molecules have been fully optimized, lack of imaginary frequency oscillation confirmed their stationary character Calculations in ethanol solution carried out with the same methods with using polarized continuum model (PCM) [7]. Energy of the calculated compounds adjusted to reflect a zero vibrational energy (ZPVE) and reduced to standard conditions (298,15 K, 1 atm.) with using thermal corrections to the enthalpy and free energy. The optimized geometry was used for calculations as the total energy of the molecules within the software package ADF'2004 (Amsterdam density functional) in the gas phase and the solution by COSMO method [8]. We used the exchange functionality OPTX [9], combined with a correlation functional PBE [10], using a triple-ζ with considering polarization basis set of Slater orbitals.

Results and its discussion

Fairly well, it is known that the quality of any quantum-chemical calculations is determined by agreement between the experimental and calculated molecular parameters. Analysis of calculated structural parameters of mediborol molecules shows that the bond lengths and angles are quite close to the standard values in organic compounds [11] (Figure 1). The optimization of mediborol geometry by ADF gave similar results for the bond lengths and angles.

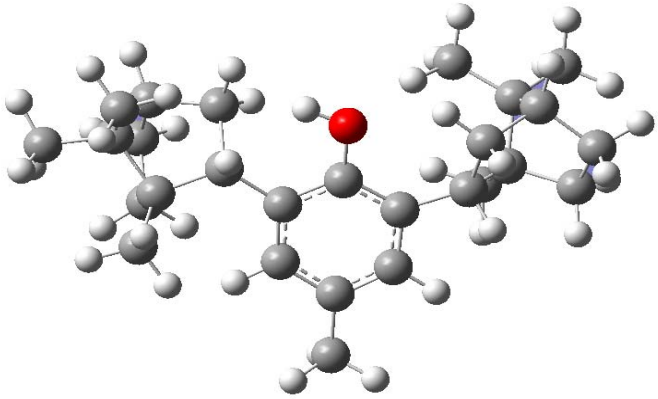


Figure 1 – Optimized structure of the mediborol by B3LYP/6-31G(d)

The calculated and experimental values of the spectra of UV wavelengths (λ), IR spectra (ω) and ^{13}C NMR spectra (δ) in ethanol solution of mediborol allowed obtaining correlation ratio between the experimental and calculated parameters. These equations (1-3) show that the calculations performed allow us to evaluate the spectral parameters with sufficient accuracy.

$$\lambda^{exp.} = 48 + 0.8\,\lambda^{cal} \qquad (r = 0.999;\ s = 1;\ n = 3) \qquad (1)$$

$$\delta^{exp\,13}C = -0{,}23 + 0{,}94\,\delta^{cal\ 13}C \qquad (r = 0.999;\ s = 1.6;\ n = 14) \qquad (2)$$

$$\omega^{exp.} = -8 + 1{,}01\,\omega^{cal.} \qquad (r = 0.999;\ s = 10;\ n = 31) \qquad (3)$$

In these and the following regression equations r – is the correlation coefficient, s – standard deviation, and n – number of compounds included in the correlation. The calculation of the chemical shifts in NMR spectrum is carried out by the method GIAO B3LYP/6-311+G(2d,p) for their visualization.

The obtained correlations of the spectral parameters suggest that the calculated structure of mediborol molecules apparently close enough to the real-life.

In addition, [12] it was shown that among the density functional methods (BLYP, B3LYP, PB86, B3P86, BPW91, B3PW91 and SVWN) B3LYP method most accurately predicts thermodynamic parameters with absolute accuracy of 13 kJ/mol. This indicates that we calculated thermodynamic parameters are sufficiently close to the experimental values. Completed earlier by us thermodynamic calculations of a number of organic reactions by the same method resulted in good agreement between the calculated and experimental values [13].

In order to evaluate the possibility of interaction of mediborol with the iron chloride, we calculated the coordination compound mediborol·$FeCl_2$ by the B3LYP/ SDD (Figure 2). It turned out that exist chemical bond of the iron atom to the oxygen atom of the phenolic group with a length of 1,58Å, which corresponds to the standard values of such bond [14].

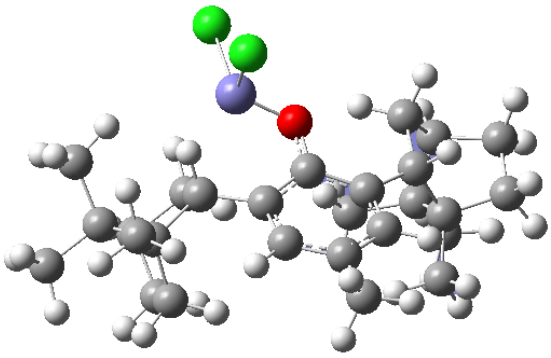
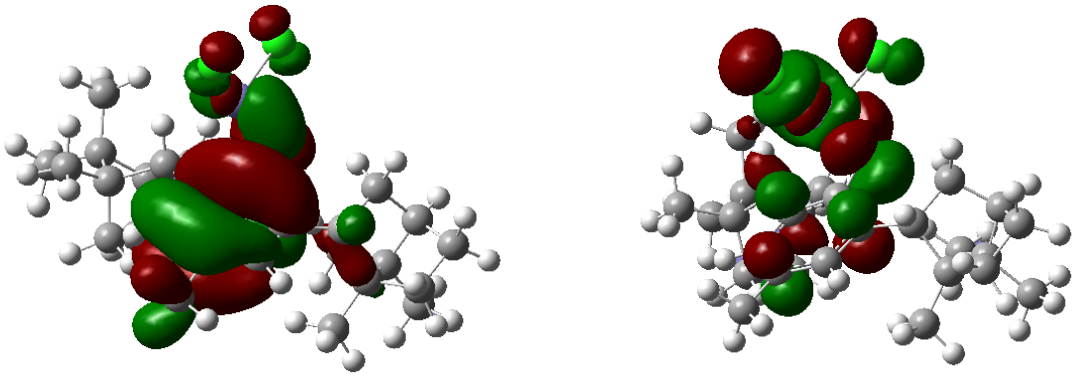


Figure 2. Optimized coordination structure of mediborol·$FeCl_2$ by B3LYP/SDD

This chemical interaction is confirmed by the views of the highest occupied molecular orbital (HOMO) of the complex of the mediborol·$FeCl_2$ (Figure 3a), that includes an aromatic ring and the electrons of Fe-O bonds. The lowest unoccupied molecular orbital (LUMO) consists mainly of $FeCl_2$ by lone electron pairs of iron and chlorine atoms (pic. 3b). This interaction between the HOMO and LUMO is confirmed by the calculation carried out by natural orbitals bond [15].



a b

Figure 3 – Molecular orbitals of borneol·$FeCl_2$: B3MO (a), HCMO (b)

Table 1 – Analysis of the binding in the complex borneol·$FeCl_2$

Bond	Hybridization			The occupancy, e	The interaction between orbitals	E_2, kcal/mol
	%s	%p	%d			
Fe-O	12.9	5.5	81.6	0.981	BD(C-C) → BD*(C-C)	20
LP(Fe)			100	0.990	LP(O) → LP(Fe)*	134
			100	0.988	LP(Cl) → LP(Fe)*	119
			100	0.993	LP(Fe) → LP(Fe-Cl)*	34

This method, in terms of the theory of second-order perturbation, allows estimating the interaction energy between a donor and an acceptor part of the complex with considering bonding orbitals and unshared electron pairs of the atoms.

From table 1 can be seen that, along with a few interactions bonding orbitals of the aromatic ring BD(C-C) with nonbonding orbitals BD*(C-C), there are quite significant for the energy of interaction between the unshared electron pairs of oxygen atoms LP(O) and chlorine LP(Cl) with unbinding lone pairs of iron atom. In addition, the analysis showed that the population of the Fe-O bond and unshared electron pairs of the iron atom is close to unity.

Thus, from the point of view of formation of coordination bonds between mediborol and $FeCl_2$ there are no explicit barriers to this type of interaction and the formation of the azo dye. However, the experimental compound is not formed. To determine the cause of this, we have analyzed the thermodynamic parameters on as the basis of calculations in Gaussian program and the Amsterdam Density Functional. The results are shown in Table 2 in the gas phase and the ethanol solution.

Table 2 – Thermodynamic parameters of mediborol and it's complex

Compound	G (gas), a.e.	G (ethanol), a.e.	E (gas), kcal/mol	E (ethanol), kcal/mol
Mediborol	-1119.629	-1119.611	-9181	-8926
$FeCl_2$	-1042.022	-1042.113	-282	-208
Mediborol·$FeCl_2$	-2160.972	-2160.978	-9362	-9112
ΔG (ΔE), kcal/mol	426	468	101	12

It was found that large positive values of Gibbs free energy (ΔG) and the total energy of the molecules of the calculation method of ADF (ΔE), both in the gas phase and in the ethanol solution do not allow for interaction between the iron chloride and mediborol due to thermodynamic reasons. It is possible that no formation of complex compound caused significant activation energy of this process.

Conclusions. Using the calculation method B3LYP/6-31G(d) provides adequate results in predicting geometrical parameters, IR, UV and NMR spectra of the mediborol. Spend analysis of orbital bonding of investigate structure in terms of the theory of second-order perturbation was carry out. The possibility of spatial interaction between mediborol and ferric chloride was shown. The thermodynamic parameters were calculated and the impossibility of the complex formation was determined.

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ТЫҒЫЗДЫҚ ФУНКЦИОНАЛДЫ ТЕОРИЯСЫ НЕГІЗІНДЕ МЕДИБОРОЛДЫ ЗЕРТТЕУ

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Түйін сөздер: тығыздық функционалының теориясы, B3LYP/6-31G(d), медиоборол, байланыстың табиғи орбитальдары.

Аннотация. Медиборалдың газды фазадағы және ерітіндідегі тығыздықты функционал тәсілімен тығыздықтың Амстердам функционалы бағдарламасында GAUSSIAN'03 және TZ2P+ бағдарламалық пакетінде 6-31G(d) толық электронды базисты жиынтығын қолдана отырып квантты-химиялық есептеулер жүргізілді. Медиборолдың темір хлоридімен реакциясының құрылымдық мүмкіндігі көрсетілді және орбитальдық әрекеттесулерге талдау жасалды. Осы реакцияның жүруінің термоинамикалық мүмкін еместігі көрсетілді.

ИССЛЕДОВАНИЕ МЕДИБОРОЛА НА ОСНОВАНИИ ТЕОРИИ ФУНКЦИОНАЛА ПЛОТНОСТИ

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Ключевые слова: теория функционала плотности, B3LYP/6-31G(d), медиоборол, натуральные орбитали связи.

Аннотация. Проведены квантово-химические расчеты медиборола в газовой фазе и в растворе методом функционала плотности с использованием полноэлектронного базисного набора 6-31G(d) в программном пакете GAUSSIAN'03 и TZ2P+ в программе Амстердамский функционал плотности. Показана структурная возможность реакции медиборола с хлоридом железа, проведен анализ орбитальных взаимодействий. Показана термодинамическая невозможность протекания этой реакции.

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