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Quantum-Chemical Study of Alkyloxybenzenes Hydrophobicity

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Abstract—Equilibrium states of alkyloxybenzenes (1-methyl-3,5-dioxybenzene C_1-AOB, 1-butyl-3,5-dioxybenzene C_4-AOB, and 1-hexyl-3,5-dioxybenzene C_6-AOB) and their complexes with water (H_2O–C_n-AOB, n = 1, 3, or 6) have been optimized by means of the DFT/ROB3LYP method. For various conformations, intermolecular energy profiles, and thermodynamic parameters of C_n-AOB interaction with water have been calculated. The dissociation energy of the alkyloxybenzenes–water complexes has been calculated in the frame of the DFT/6-31G(2p,2d) method, and the alkyloxybenzenes hydrophobicity has been estimated.

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It is known that reduction of water content in the cells below a certain level causes irreversible changes, or even stops the biological processes. Efficiency of a molecule interaction with water is determined by its hydrophobicity. However, there is no universal criterion for hydrophobicity estimation. Commonly, the water properties change in the presence of the studied molecule, the hydrophobic interaction energy, or the hydration shell thickness are taken as a measure of hydrophobicity. Other characteristics to describe hydrophobicity may be partial molar volume or heat capacity [1]. In [2] the hydration shell size was determined by taking the solution compressibility equal either to zero or to that of ice. In [3] more precise “molecular probe” method was applied. In some papers [1, 3] the hydration shell of the biopolymer bearing polar, hydrophobic, or charged groups was described in terms of sum of the changes in water properties in the vicinity of the considered atomic groups. Newer methods of determination of the energy of hydrophobic interaction presumed estimation of the free energy, enthalpy, and entropy changes upon transfer of the considered molecule from water into a nonpolar organic solvent. For the linear hydrocarbons, it was demonstrated that those changes were enhanced with increasing length of the hydrocarbon chain [4]. For calculating the overall hydrophobicity of the amino acid residues of *Bacillus intermedius* ribonuclease and of ribonuclease A, the change in the free energy during transfer from ethanol into water (with respect to the amino acid side group) was used as a measure of hydrophobicity [5]. It is commonly assumed that the hydrophobic bonding is due to the change in the solvent properties whose structure suffers disorganization [6]. Konovalenko et al. [7] attempted to quantify the dependence of hydrophobicity on the absolute entropy, and determined that the dependence was cubic for the series of substituted adamantanes.

Another commonly accepted hydrophobicity measure of a compound is its partition coefficient between water and organic solvent. A standard pair used for such estimation is water and octanol-1 [8].

Alkyloxybenzenes belong to a class of d_1-factors, anabiosis auto inducing agents. In human organism, ingesta is a source of alkyloxybenzenes, or they may be synthesized by some specimens of microbial community. Alkyloxybenzenes are known to influence the cell membrane state, causing its structural changes, including pores and channels formation. The nature of membrane-alkyloxybenzene interaction is determined by the alkyloxybenzene hydrophobicity.

This work aimed at evaluation of the alkyloxybenzenes C_1-AOB, C_4-AOB, and C_6-AOB hydrophobicity, and the estimation of the stability of their complexes with water. To accomplish this, it was necessary to determine the equilibrium geometry of the alkyloxybenzenes and of different conformations of their aquatic complexes, and to calculate the intermolecular (D_e) and thermodynamic (ΔS_{298}, ΔH_{298}, ΔG_{298}) potentials of the interaction of water with

C_1-AOB, C_4-AOB, and C_6-AOB by means of quantum-chemical methods. To the best of our knowledge, such quantum-chemical calculations have not been reported before.

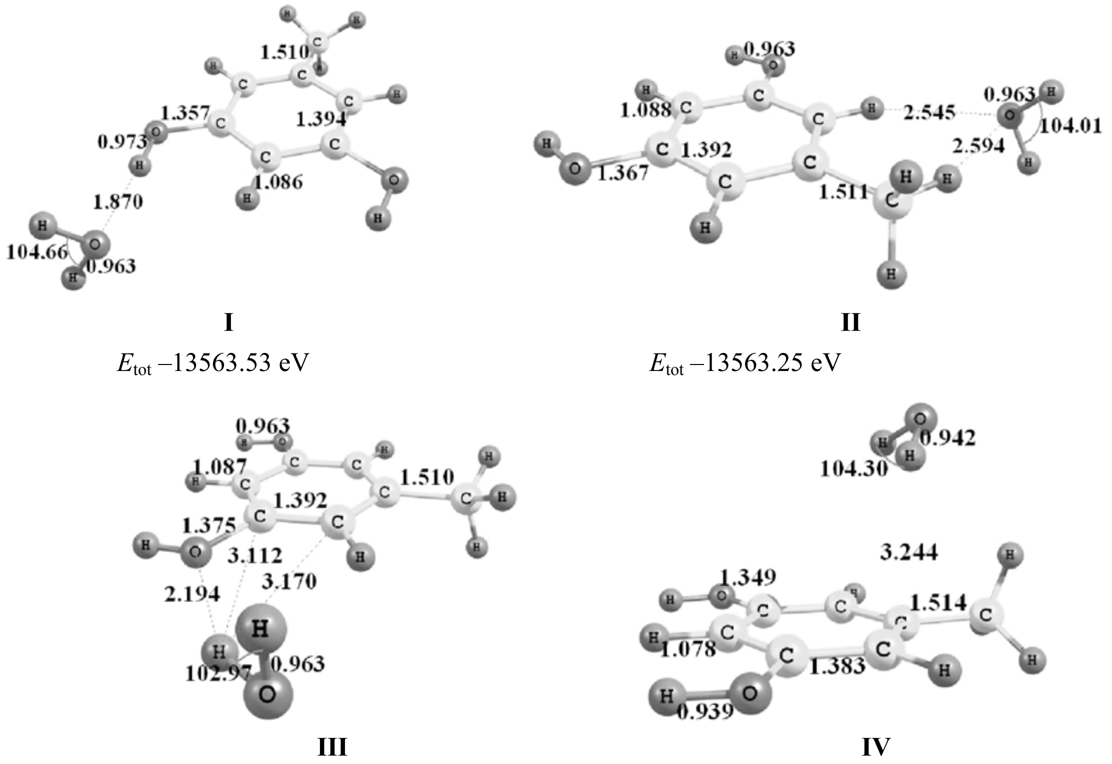
Results of computation of equilibrium geometry parameters of the four most probable conformations of C_1-AOB aquatic complex are shown in Fig. 1.

The most energetically stable conformation of H_2O–C_1-AOB was **I**, where water oxygen atom was oriented towards OH group of C_1-AOB, at a distance of 1.87 Å. In the conformation **II,** water molecule was located near the CH_3 group, at a distance of 2.59 Å. In the conformation **III,** water molecule was located under the C_1-AOB benzene ring plane, near the OH group, the shortest distance between water and C_1-AOB equaled 2.20 Å. In the ground equilibrium state of the conformation **IV,** water molecule was located above the aromatic ring and was shifted towards the CH_3 group, the shortest distance between water and C_1-AOB in this case equaled 2.80 Å.

To determine the dependence of C_n-AOB hydrophobic properties on the alkyl chain length, two conformations of the H_2O–C_4-AOB complex and two conformations of the H_2O–C_6-AOB complex were simulated, where the water molecule was oriented either towards hydrogen atom of the hydroxy group, or towards hydrogen atom of the alkyl CH_3 group (Fig. 2).

It is noteworthy that in various conformations of the C_n-AOB complexes the geometric parameters of the aromatic ring and of the alkyl group did not change significantly with increasing alkyl chain length.

As a result of computation of thermodynamic potentials ΔH_{298}, ΔS_{298}, ΔG_{298} of alkyloxybenzenes interaction with water (Table 1), it was found that the total entropy S_{298} of the system decreased in this process. The formation of the H_2O–C_1-$AOB_{conf.\mathbf{II}}$ complex was accompanied with the decrease in enthalpy ($\Delta H_{298} < 0$), whereas during the formation of the H_2O–C_1-$AOB_{conf.\mathbf{I}}$, H_2O–C_4-$AOB_{conf.\mathbf{I},\ conf.\mathbf{II}}$, and H_2O–C_6-$AOB_{conf.\mathbf{I},\ conf.\mathbf{II}}$ complexes $\Delta H_{298} > 0$. The change in the Gibbs free potential ΔG_{298} was positive for the formation of all complexes. Thus, the interaction of alkyloxybenzene molecule with H_2O was thermodynamically unfavorable, this was in line with



I

E_{tot} –13563.53 eV

II

E_{tot} –13563.25 eV

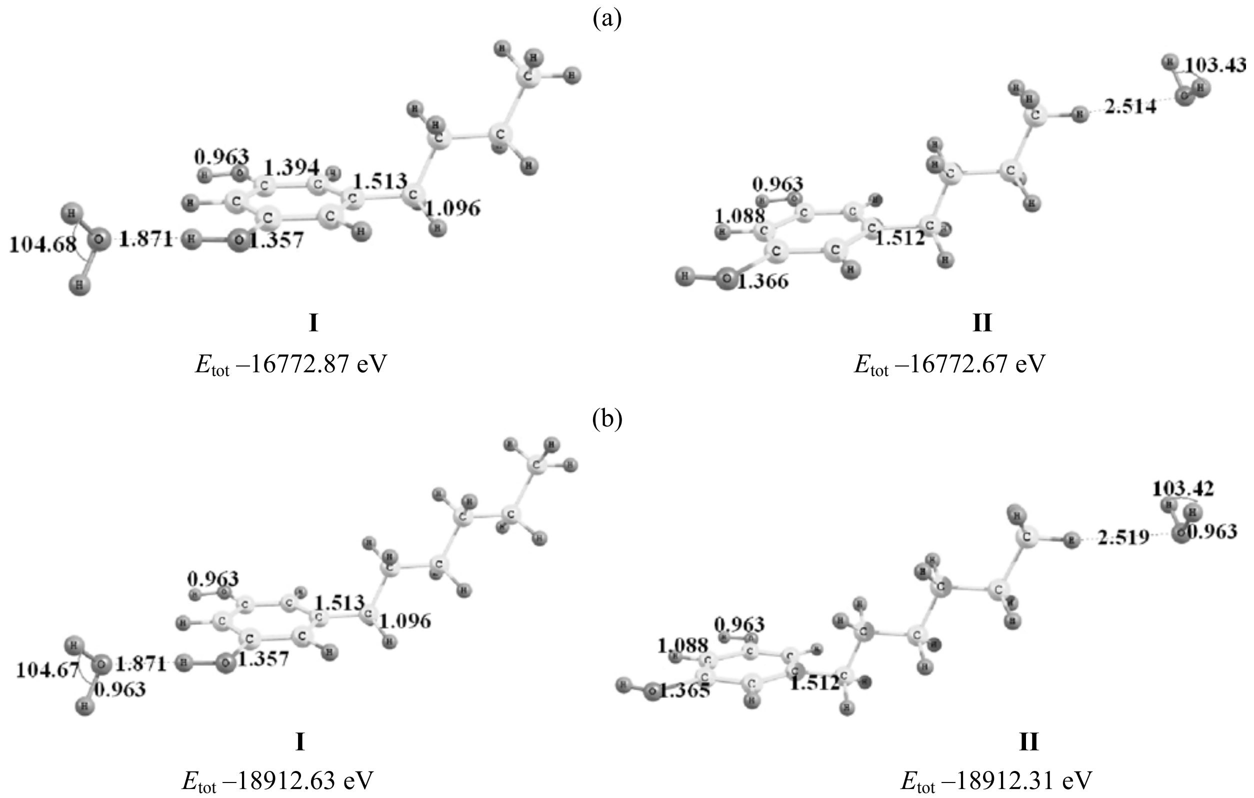
III

E_{tot} –13563.37 eV

IV

E_{tot} –13563.22 eV

Fig. 1. Geometric parameters and total energy of the four conformations (**I**, **II**, **III**, **IV**) of the H_2O–C_1-AOB complex computed by means of the DFT/ROB3LYP/6-31G(2p,2d) method.



I
E_{tot} –16772.87 eV

II
E_{tot} –16772.67 eV

I
E_{tot} –18912.63 eV

II
E_{tot} –18912.31 eV

Fig. 2. Geometric parameters and total energy of **I** and **II** conformations of the (a) H_2O–C_4-AOB complex and (b) of the H_2O–C_6-AOB complex, computed by means of the DFT/ROB3LYP/6-31G(2p,2d) method.

common conception of hydrophobic interaction occurring during transfer into water of the hydrophobic part of the molecule as processes with the negative change in the entropy ΔS_{298} and the positive change in the Gibbs energy ΔG_{298} [9].

To estimate the molecule hydrophobicity, its aquatic complex dissociation energy was compared with the bond energy in H_2O–H_2O dimer. If the calculated dissociation energy of the H_2O–C_n-AOB was higher that the H_2O–H_2O bond energy, this molecule or part of the molecule was considered hydrophilic, as it was more favorable to form the H_2O–C_n-AOB bond than H_2O–H_2O bond. In the opposite case, the analyzed structural fragment was considered hydrophobic.

The energy of hydrogen bond in H_2O–H_2O dimer (as determined experimentally by field mass spectrometry, radioscopy, far infrared spectroscopy, or derived from the second virial coefficient, or from the

Table 1. Thermodynamic functions ΔH_{298}, ΔS_{298}, and ΔG_{298} of the C_n-AOB + H_2O → C_n-AOB–H_2O reactions, as determined from functions computed be means of the DFT/ROB3LYP/6-31G(2p,2d) method

Reaction	ΔH_{298}, kJ mol^{-1}	ΔS_{298}, J mol^{-1} K^{-1}	ΔG_{298}, kJ mol^{-1}
C_1-AOB + H_2O → C_1-AOB–$H_2O_{conf.\mathbf{I}}$	1.77	–0.14	44.71
C_1-AOB + H_2O → C_1-AOB–$H_2O_{conf.\mathbf{II}}$	–5.68	–0.14	37.11
C_4-AOB + H_2O → C_4-AOB–$H_2O_{conf.\mathbf{I}}$	4.70	–0.13	42.87
C_4-AOB + H_2O → C_4-AOB–$H_2O_{conf.\mathbf{II}}$	5.98	–0.09	32.65
C_6-AOB + H_2O → C_6-AOB–$H_2O_{conf.\mathbf{I}}$	6.28	–0.13	43.78
C_6-AOB + H_2O → C_6-AOB–$H_2O_{conf.\mathbf{II}}$	7.73	–0.09	34.47

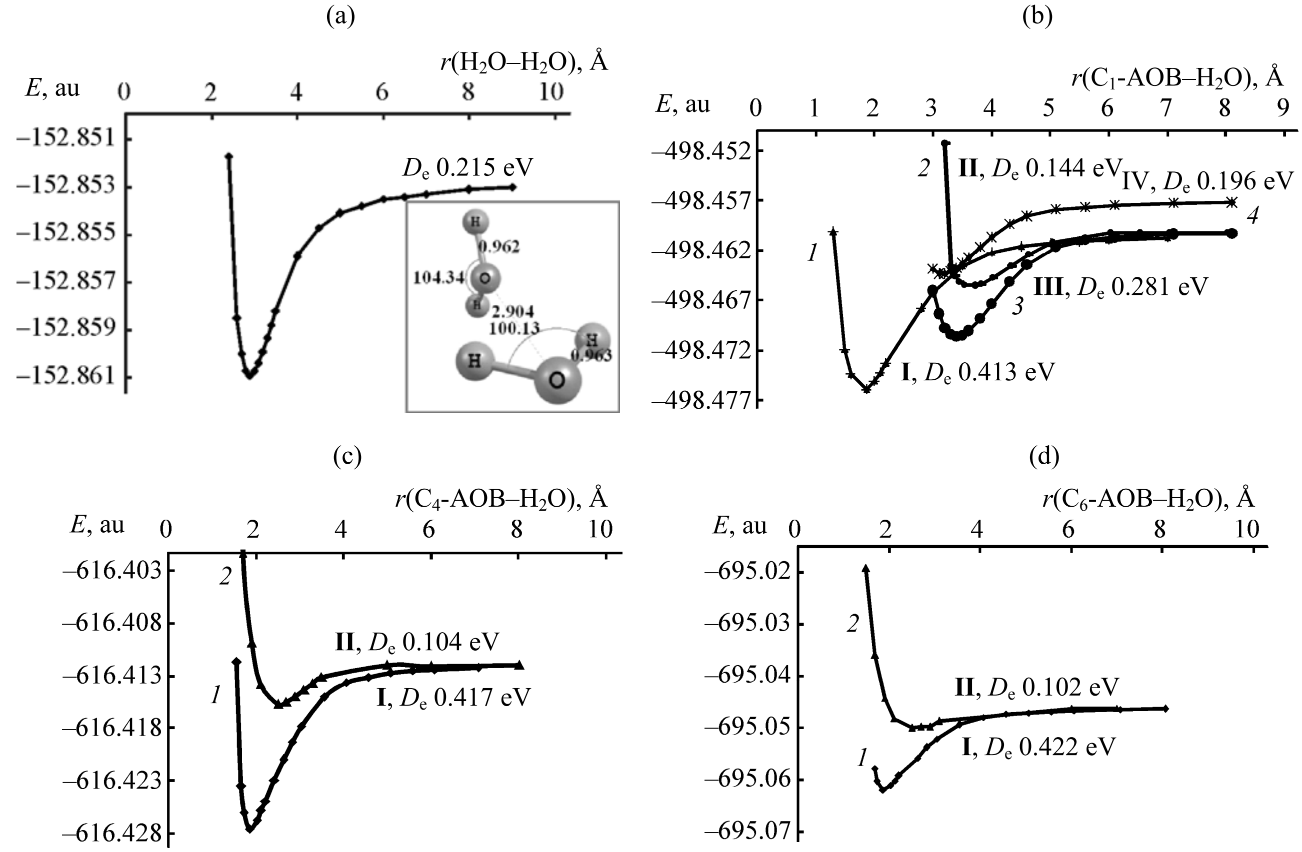


Fig. 3. Sections of the potential energy surface of the reactions of formation of intermolecular complexes and dissociation energy D_e of the complexes: (a) H_2O–H_2O; (b) H_2O–C_1-AOB; (c) H_2O–C_4-AOB; (d) H_2O–C_6-AOB [DFT/ROB3LYP/6-31G(2p,2d)].

vapor thermal conductivity) was found to be 21.8± 6.3 kJ mol^{-1} (0.23±0.07 eV). The hydrogen bond energy with respect to a single water molecule increased as the water molecules number in the cluster increased from 2 to 4, further increase of the cluster size did not influence the hydrogen bond energy, the latter being equal 35–39 kJ mol^{-1} [10]. Our computations of the bond energy in the water dimer by means of DFT/ROB3LYP/6-31G(2p,2d) gave 0.21 eV (20.74 kJ mol^{-1}) (Fig. 3a) that was in good agreement with the experimental data. The dissociation energy of the H_2O–C_n-AOB complexes were determined from the sections of corresponding potential energy surfaces (Figs. 3b–3d). Computations revealed that for the conformations **II** and **IV** of the H_2O–C_1-AOB complex and for conformation **II** of the H_2O–C_4-AOB and H_2O–C_6-AOB complexes the hydrogen bond strength was less than that in the water dimer. Thus, the water molecules oriented around the alkyl group tended to form cavities with the size depending on the substituent length.

The contributions of various atomic groups to the alkyloxybenzenes hydrophobicity are listed in Table 2. These contributions were calculated as difference of the water dimer H_2O–H_2O dissociation and that of the H_2O–C_n-AOB complexes, with respect to a single water molecule.

Total hydrophobicity should be considered as a sum of the hydrophilic contribution from hydrogen bonds of two OH groups and of hydrophobic contribution from each of CH_2 groups and from CH_3 group of the alkyl group. Each of OH groups formed two hydrogen bonds with H_2O (conformations **I** and **III** of the H_2O–C_1-AOB complex). Thus, the hydrophilic contribution from alkyloxybenzene OH groups was constant in the C_n-AOB series and equaled $2H(C_1\text{-OH})_1 + H(C_1\text{-OH})_2 = -0.54$ eV.

The hydrophobic contribution from different units of the alkyl chain varied between 0.07 and 0.19 eV (Table 2). The average contribution with respect to a single unit of linear hydrocarbon chain equaled

Table 2. Contributions (H, eV) into the total hydrophobicity of various atomic groups of alkyloxybenzenes, with respect to a single water molecule [DFT/ROB3LYP/6-31G(2p,2d)]

Complex	Contribution alias	Contribution to total hydrophobicity H, eV
C_1-AOB–$H_2O_{conf.I}$	$H(C_1–OH)_1$	–0.20
C_1-AOB–$H_2O_{conf.II}$	$H(C_1–CH_3)_1$	+0.07
C_1-AOB–$H_2O_{conf.III}$	$H(C_1–OH)_2$	–0.07
C_1-AOB–$H_2O_{conf.IV}$	$H(C_1–CH_3)_1$	+0.19
C_4-AOB–$H_2O_{conf.I}$	$H(C_4–OH)$	–0.20
C_4-AOB–$H_2O_{conf.II}$	$H(C_4–CH_3)$	+0.11
C_6-AOB–$H_2O_{conf.I}$	$H(C_6–OH)$	–0.20
C_6-AOB–$H_2O_{conf.II}$	$H(C_6–CH_3)$	+0.11

$[H(C_1\text{-}CH_3)_1 + H(C_1\text{-}CH_3)_1 + H(C_4\text{-}CH_3) + H(C_6\text{-}CH_3)]/4 = 0.12$ eV.

Thus, the alkyloxybenzene molecule was hydrophobic (in other words, the hydrophobic contribution exceeded the hydrophilic one) when the alkyl group contained more than four carbon atoms (0.54 eV/0.12 eV = 4.5), and C_n-AOB should have been completely or partially soluble in water at $n \leq 4$. This was in line with the result of [11]: C_2-AOB was moderately soluble in water, while C_6-AOB was a poorly soluble hydrophobic substance.

The intermolecular bonding energy of the H_2O–C_1-AOB complex was also estimated using different functionals (Table 3). Notwithstanding the functional form, the hydrophobicity estimations coincided with each other.

Table 3. Dissociation energy D_e (eV) of the four conformations of the H_2O–C_1-AOB complex computed by means of the DFT/6-31G(2p,2d) method with different functionals

Complex	B3LYP	BLYP	B3PW91
C_1-AOB–$H_2O_{conf.I}$	0.417	0.473	0.365
C_1-AOB–$H_2O_{conf.II}$	0.144	0.197	0.153
C_1-AOB–$H_2O_{conf.III}$	0.281	0.330	0.274
C_1-AOB–$H_2O_{conf.IV}$	0.196	0.246	0.211

To additionally confirm the applicability of the introduced method of alkyloxybenzenes hydrophobicity estimation according to the H_2O–C_n-AOB hydrogen bond dissociation energy, the complexes of C_n-AOB (n = 1, 4, 6, 12) with octanol-1 (Fig. 4) and their dissociation energy were computed by means of semi-empirical PM3 method.

The hydrophobicity coefficient H was calculated according to $H = \log (P_{oct}/P_w)$, with solubility in octanol-1 P_{oct} and in water P_w was substituted with the respective values of D_e, as they were considered to be proportional. The plot of hydrophobicity coefficient $H = [\log (D_{e(oct)}/D_{e(w)})]$ dependence on n for the C_n-AOB complexes (Fig. 5) was linear and demonstrated the increase of hydrophobic properties with increasing length of alkyl chain in the unbranched alkyloxybenzenes. This was qualitatively in line with our results.

EXPERIMENTAL

Geometry parameters of the H_2O–C_n-AOB complexes (n = 1, 4, 6) were computed by means of DFT/ROB3LYP/6-31G(2p,2d) method [12, 13]. The dissociation energy of complexes D_e was estimated from the shape of the intermolecular C_n-AOB + H_2O

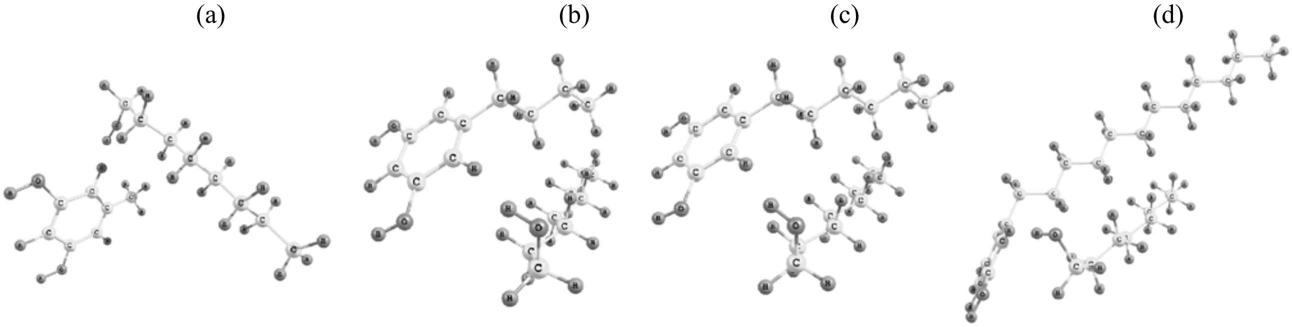


Fig. 4. Intermolecular complexes of alkyloxybenzenes with octanol-1: (a) $C_8H_{17}OH$–C_1-AOB, (b) $C_8H_{17}OH$–C_4-AOB, (c) $C_8H_{17}OH$–C_6-AOB, (d) $C_8H_{17}OH$–C_{12}-AOB (PM3 computation method).

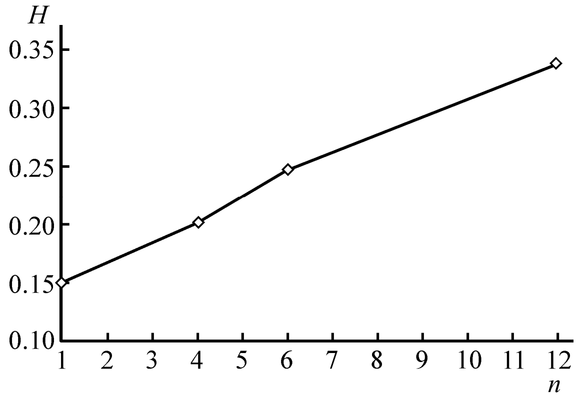


Fig. 5. Hydrophobicity coefficient H dependence on the carbon atoms number n in the alkyl group, for the unbranched C_n-AOB.

interaction potential. Along with B3LYP, other functionals (BLYP and B3PW91) were used for estimation of D_e for the H_2O–C_1-AOB complex.

Thermal effect ΔH_{298} of the C_n-AOB + H_2O ($n = 1$, 4, 6) reaction, entropy ΔS_{298} and Gibbs free energy ΔG_{298} changes in those processes were calculated using corollaries of the Hess law and the computed values of S_{298}, H_{298}, G_{298}.

Hydrophobicity of alkyloxybenzenes was calculated as sum of the constant hydrophilic contribution estimated from the OH groups and water interaction energy, and of the variable hydrophobic contribution (function of n) estimated from the energy of water bonding with CH_3 and CH_2 groups of alkyloxybenzenes. The H_2O–C_n-AOB bond energy was compared with that of the hydrogen bond in water dimer H_2O–H_2O. All computation were performed in PC GAMESS software [14], partially based on the source code of GAMESS (US) software [15].

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