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A STUDY OF HYDROGEN BONDS IN *p*-SUBSTITUTED CALIX[4]- AND CALIX[6]ARENES BY *AB INITIO* AND ELECTRON DENSITY FUNCTIONAL METHODS

A. N. Novikov and Yu. E. Shapiro

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RHF/3-21G and B3LYP/3-21G methods are used to calculate the hydrogen bond energies in calix[4]-, calix[6]-, *p*-fluorocalix[4]-, *p*-fluorocalix[6]-, *p*-chlorocalix[4]-, *p*-chlorocalix[6]-, *p*-bromocalix[4]-, *p*-bromocalix[6]-, *p*-iodocalix[4]-, *p*-iodocalix[6]-arenes and a number of other *p*-substituted calix[4]- and calix[6]arenes ($R = \text{Me, OMe, NO}_2, \text{Ac, NH}_2, \text{CN, N}_2^+$). The calculations along with the structural data give evidence of the cooperative effect of hydrogen bonding. Multiple correlation ($p \geq 0.9$) between the pairs of Hammett substituent constants and the calculated values of hydrogen bond energies in the corresponding *p*-substituted calixarenes is found. It is predicted that in the presence of weak bases and in aprotic solvents as well as in the gas phase, the nucleophilic substitution reaction involving *p*-halogen calix[6]arenes should proceed through diastereomeric transition states.

Keywords: *p*-substituted calixarene, *p*-halogenocalix[4]arene, *p*-halogenocalix[6]arene, hydrogen bond, Hartree–Fock method, electron density functional method, Hammett constants, multiple correlation, Grootenhuis et al. method

INTRODUCTION

Calixarene derivatives are a type of cavitands that along with crown ethers are used to model the mutual recognition processes of molecules in biological systems [1] and also to study the molecular and ionic transfer through cell membranes [2]. The presence of intramolecular hydrogen bonds is the characteristic feature of calixarenes. In a number of cases, typical hydrogen bonds (H-bonds) have considerable values of the dissociation energy (so-called strong symmetric hydrogen bonds [3]). However, these energies increase inadditively when oligomeric linear or cyclic chains of hydrogen bonds form (the so-called cooperative effect observed, for instance, in calixarenes [4, 5]). These hydrogen bonds can decisively affect the preference for a certain conformation both of the free host compound and its complex with an ion or neutral molecule acting as a guest [4]. They can also substantially affect the reactivity of calixarenes as a whole [4]. Therefore, it is important to study hydrogen bond parameters in calixarenes to get the insight into the formation of compounds of the guest–host type and to reveal the mechanism of any chemical transformations involving these compounds.

The $\angle \text{H}_i\text{C}_{1i}\text{H}_{i+1}\text{O}_{i+1}$, if $i > 1$, or $\angle \text{H}_6\text{C}_{16}\text{H}_1\text{O}_1$ dihedral angles in calixarenes (Fig. 1), according to the statement of atomic orbital hybridization theory, characterize the mutual spatial orientation of orbitals participating in the formation of strong hydrogen bonds, and correspondingly, the efficiency of their overlapping [6]. The index i takes values from 1 to 6 and

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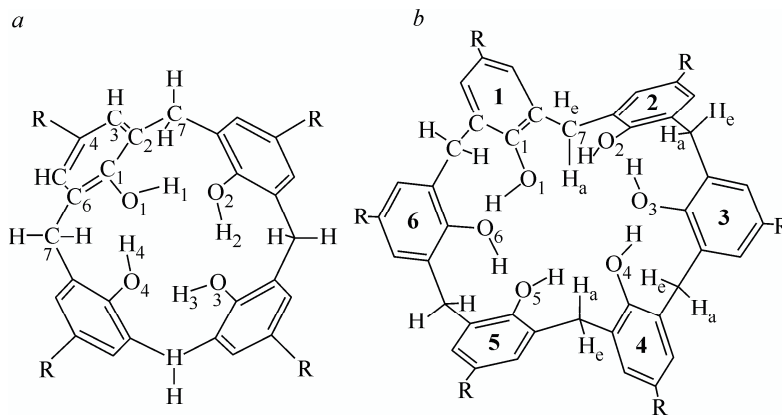


Fig. 1. Preferred cone conformer of calix[4]arene (*a*), $n = 4$: R = Hal (F, Cl, Br, I), Me, OMe, NO₂, Ac, NH₂, CN, N₂⁺; preferred pinched cone conformer of calix[6]arene (*b*), $n = 6$: R = Hal (F, Cl, Br, I), Me, OMe, NO₂, Ac (top view, i.e. from the upper rim side).

corresponds to carbon, oxygen, and hydrogen atoms of the i -th or $(i+1)$ -th monomeric fragment. In the index after the carbon atom, the first figure designates the number of the atom in the benzene ring, and the second is the number of the benzene ring. In this case, 1 means that the carbon atom is bonded to the hydroxyl group.

In the present work, we performed a quantitative analysis of the dependence between the energy parameters of hydrogen bonds in calixarenes and the values of $\angle \text{H}_i\text{C}_1\text{H}_{i+1}\text{O}_{i+1}$, if $i > 1$, or $\angle \text{H}_6\text{C}_{16}\text{H}_1\text{O}_1$ angles to find out whether the dependence is different or not for p -substituted derivatives of calix[4]- and calix[6]arenes and calix[4]- and calix[6]arenes without p -substituents [6].

CALCULATION METHODS

In the work, we studied the specificity of reactions involving p -substituted derivatives of calix[4]- and calix[6]arenes (calix[n]arenes, $n = 4, 6$; Fig. 1). Furthermore, we determined the possibility of applying the principle of linearity of free energies relative to the results of quantum chemical studies of these compounds. To this end, we calculated the following compounds: calix[4]arene (1), p -fluorocalix[4]arene (2), p -chlorocalix[4]arene (3), p -bromocalix[4]arene (4), p -iodocalix[4]arene (5), p -methylcalix[4]arene (6), p -methoxycalix[4]arene (7), p -nitrocalix[4]arene (8), calix[6]arene (9), p -fluorocalix[6]arene (10), p -chlorocalix[6]arene (11), p -bromocalix[6]arene (12), p -iodocalix[6]arene (13), p -methylcalix[6]arene (14), p -methoxycalix[6]arene (15), p -nitrocalix[6]arene (16), p -acetylcalix[4]arene (17), and p -acetylcalix[6]arene (18) and also monoanions of the mentioned p -substituted calix[4]arenes and monoanions 1, 2, and 3 of p -substituted calix[6]arenes (Fig. 1). For this purpose, we employed *ab initio* (Hartree–Fock, RHF) and electron density functional (B3LYP) methods [6]. In both cases, the split valence 3-21G basis set was used. The hydrogen bond energies of all p -substituted calix[4]arenes were calculated for cone conformers and for pinched cone conformers of all p -substituted calix[6]arenes, which were the main conformers of the above compounds, as previously confirmed by different theoretical and experimental methods [6, 7]. Moreover, we calculated p -aminocalix[4]arene (19), p -nitrile calix[4]arene (20), and calix[4]arene- p -diazonium (21) and their monoanions (Fig. 1) at the RHF/3-21G level of theory followed by the determination of the hydrogen bond energy in these compounds. All calculations were performed with full geometry optimization, as in the previous work [6], using the Firefly program package [8] that is partially based on the GAMESS US software [9]. The values of changes in the hydrogen bonding energy were found from the data of quantum chemical calculations, according to the method proposed by Grootenhuis et al. [5], which we applied in our previous calculations [6, 10].

Tables 1-3 summarize the calculation results for p -substituted calixarenes. Some structural parameters of the cone conformer of p -substituted calix[4]arenes and the pinched cone conformer of p -substituted calix[6]arenes, calculated at the

TABLE 1. Structural Parameters of the Cone Conformers of *p*-Substituted Calix[4]arenes Determined by the B3LYP/3-21G Method

Parameter, Å	Compound						
	2	3	4	5	6	7	8
C ₁ –O ₁	1.400	1.397	1.398	1.397	1.401	1.403	1.391
O _{<i>i</i>} –O _{<i>i</i>+1}	2.496	2.493	2.494	2.491	2.495	2.497	2.489
C ₄ –X	1.371	1.832	1.930	2.151	1.520	1.390	1.460

Note: 2 is *p*-Fluorocalix[4]arene; 3 is *p*-Chlorocalix[4]arene; 4 is *p*-Bromocalix[4]arene; 5 is *p*-Iodocalix[4]arene; 6 is *p*-Methylcalix[4]arene; 7 is *p*-Methoxycalix[4]arene; 8 is *p*-Nitrocalix[4]arene; X = Hal, C (Me), O (OMe), N (NO₂).

TABLE 2. Structural Parameters of the Pinched Cone Conformers of *p*-Substituted Calix[6]arenes Determined by the B3LYP/3-21G Method

Parameter, Å, deg	Compound						
	11	12	13	14	15	16	
O _{<i>i</i>} ...O _{<i>i</i>+1}	2.455	2.455	2.459	2.455	2.456	2.453	
	2.447	2.447	2.451	2.448	2.448	2.449	
	2.442	2.443	2.446	2.444	2.442	2.444	
O _{<i>i</i>} –H _{<i>i</i>}	1.093	1.092	1.090	1.092	1.092	1.093	
	1.095	1.095	1.093	1.095	1.095	1.094	
	1.099	1.099	1.097	1.099	1.100	1.097	
H ₆ –O ₆ ...H ₁	102.3	102.1	101.8	101.8	100.9	103.6	
H ₁ –O ₁ ...H ₂	123.6	123.7	123.6	124.0	124.4	123.7	
H ₂ –O ₂ ...H ₃	122.3	122.3	122.5	122.9	122.7	122.0	
O ₁ –C ₁ –C ₂	120.3	120.5	120.5	120.4	120.5	120.3	
	120.7	120.9	120.9	121.0	121.1	120.7	
	120.4	120.5	120.5	120.6	120.7	120.3	
H _{<i>i</i>+1} ...O _{<i>i</i>}	1.367	1.368	1.374	1.368	1.368	1.367	
	1.352	1.353	1.359	1.354	1.354	1.356	
	1.351	1.352	1.358	1.351	1.349	1.357	
H ₆ C ₁₆ H ₁ O ₁	–132.6	–132.3	–131.5	–132.2	–132.3	–132.2	
H ₁ C ₁₁ H ₂ O ₂	–175.8	–176.3	–175.8	–174.2	–173.1	–179.1	
H ₂ C ₁₂ H ₃ O ₃	–158.2	–157.9	–158.0	–157.7	–157.4	–154.9	
O ₁ –C ₁ –C ₆	118.1	118.2	118.2	118.4	118.6	117.9	
	117.9	118.0	118.0	118.0	118.2	117.7	
	118.2	118.4	118.4	118.4	118.7	118.0	
O _{<i>i</i>} ...H _{<i>i</i>+1} –O _{<i>i</i>+1}	172.5	172.4	172.1	172.4	172.8	171.6	
	176.7	176.9	177.0	176.9	176.1	177.6	
	170.8	170.7	170.5	171.1	171.2	169.6	
C ₄₁ –X ₁	1.832	1.931	2.152	1.520	1.390	1.461	
C ₄₂ –X ₂	1.832	1.931	2.152	1.520	1.390	1.460	
C ₄₃ –X ₃	1.832	1.931	2.152	1.520	1.390	1.460	

B3LYP/3-21G level of theory, are given in Tables 1 and 2 respectively, and the energy parameters of *p*-substituted calix[4]- and calix[6]arenes, calculated at RHF/3-21G and B3LYP/3-21G levels of theory, are given in Table 3. Monoanions 1 and 3 of calix[6]arenes represent monoanions formed when a proton is detached from the first and third monomeric fragments respectively in *p*-R-calix[6]arene (Fig. 1), whereas monoanion 2 is the anion formed when a proton is detached from the second monomeric fragment in *p*-R-calix[6]arene. For *p*-substituted calix[6]arenes the first row in Table 2 presents the value of each structural parameter (bond length or bond angle) in the first monomeric fragment, the next row gives this value in the

TABLE 3. Hydrogen Bonding Energies in the Cone Conformers of *p*-Substituted Calix[*n*]arenes

Compound, R, <i>n</i> , number of the corresponding monoanion	Calculation method	$\Delta\Delta E$, kcal/mol	ΔE_k , kcal/mol	Compound, R, <i>n</i> , number of the corresponding monoanion	Calculation method	$\Delta\Delta E$, kcal/mol	ΔE_k , kcal/mol
1, H, 4	RHF/3-21G	26.9	—	11, Cl, 6,	RHF/3-21G	44.2	8.8
	B3LYP*/3-21G	24.7	—	anion 3	B3LYP/3-21G	38.7	6.3
2, F, 4	RHF/3-21G	34.8	—	12, Br, 6,	RHF/3-21G	40.9	8.0
	B3LYP/3-21G	30.3	—	anion 1	B3LYP/3-21G	35.3	5.5
3, Cl, 4	RHF/3-21G	35.4	—	12, Br, 6,	RHF/3-21G	34.8	1.9
	B3LYP/3-21G	32.5	—	anion 2	B3LYP/3-21G	31.6	1.9
4, Br, 4	RHF/3-21G	32.9	—	12, Br, 6,	RHF/3-21G	40.9	8.0
	B3LYP/3-21G	29.8	—	anion 3	B3LYP/3-21G	35.3	5.5
5, I, 4	RHF/3-21G	32.4	—	13, I, 6,	RHF/3-21G	40.2	7.9
	B3LYP/3-21G	29.8	—	anion 1	B3LYP/3-21G	35.5	5.7
8, NO ₂ , 4	RHF/3-21G	35.7	—	13, I, 6,	RHF/3-21G	34.3	1.9
	B3LYP/3-21G	33.2	—	anion 2	B3LYP/3-21G	31.3	1.5
6, Me, 4	RHF/3-21G	26.0	—	13, I, 6,	RHF/3-21G	40.2	7.9
	B3LYP/3-21G	23.4	—	anion 3	B3LYP/3-21G	35.5	5.7
7, MeO, 4	RHF/3-21G	26.1	—	16, NO ₂ , 6,	RHF/3-21G	46.4	10.7
	B3LYP/3-21G	23.3	—	anion 1	B3LYP/3-21G	40.7	7.5
9, H, 6,	RHF/3-21G	32.7	5.8	16, NO ₂ , 6,	RHF/3-21G	41.7	6.0
anion 1	B3LYP/3-21G	28.6	3.9	anion 2	B3LYP/3-21G	38.3	5.1
9, H, 6,	RHF/3-21G	26.3	−0.6	16, NO ₂ , 6,	RHF/3-21G	46.4	10.7
anion 2	B3LYP/3-21G	24.7	0.0	anion 3	B3LYP/3-21G	40.7	7.5
9, H, 6,	RHF/3-21G	32.7	5.8	14, Me, 6,	RHF/3-21G	31.5	5.5
anion 3	B3LYP/3-21G	28.6	3.9	anion 1	B3LYP/3-21G	26.8	3.3
10, F, 6,	RHF/3-21G	43.1	8.3	14, Me, 6,	RHF/3-21G	25.0	−1.0
anion 1	B3LYP/3-21G	35.7	5.4	anion 2	B3LYP/3-21G	22.9	−0.5
10, F, 6,	RHF/3-21G	36.6	1.8	14, Me, 6,	RHF/3-21G	31.5	5.5
anion 2	B3LYP/3-21G	31.7	1.4	anion 3	B3LYP/3-21G	26.8	3.4
10, F, 6,	RHF/3-21G	43.1	8.3	15, MeO, 6,	RHF/3-21G	31.9	5.8
anion 3	B3LYP/3-21G	35.7	5.4	anion 1	B3LYP/3-21G	26.6	3.3
11, Cl, 6,	RHF/3-21G	44.2	8.8	15, MeO, 6,	RHF/3-21G	25.3	−0.8
anion 1	B3LYP/3-21G	38.7	6.3	anion 2	B3LYP/3-21G	22.6	−0.7
11, Cl, 6,	RHF/3-21G	38.3	2.9	15, MeO, 6,	RHF/3-21G	31.7	5.6
anion 2	B3LYP/3-21G	35.2	2.7	anion 3	B3LYP/3-21G	25.4	2.1

*In the work, we applied the Lee-Young-Parr correlation functional implemented in the form of an algorithm specially developed within the GAMESS US program package, which differs from the LYP algorithm embedded into the GAUSSIAN program package and also available in the PC GAMESS program.

second monomeric fragment, and the third row in the third one. The structural parameters of calix[4]- and calix[6]arenes, calculated by two different methods (RHF/3-21G and B3LYP/3-21G), are not very different, therefore for brevity, the information on the structural parameters of calix[4]- and calix[6]arenes, calculated by the RHF/3-21G method, is omitted in this work.

RESULTS AND DISCUSSION

We [6] and the other researchers [11] have previously shown that in hexahydroxycalix[6]arene the formation of three pairs of hydrogen bonds is observed, which have different structural characteristics. This, in general, corresponds to C_2 molecular symmetry. A similar picture was also observed for *p*-substituted calix[6]arenes studied in this work (Table 2). The structural parameters of hydrogen bonds (e.g., interatomic distances $d(O_i \dots O_{i+1})$) in the cone conformers of *p*-substituted calix[4]- and calix[6]arenes, calculated by RHF/3-21G and B3LYP/3-21G methods (Tables 1 and 2), give evidence of the cooperative effect of H-bonds. The effect is manifested in a decrease in the distances between oxygen atoms, involved in the formation of hydrogen bonds, with increasing chain length of these bonds (B3LYP/3-21G, Tables 1 and 2, [6, 10]). On the other hand, an increase in the energy of certain hydrogen bonds in *p*-substituted calix[6]arenes equal to ΔE_k (Table 3), as compared to the respective *p*-substituted calix[4]arenes, also indicates the presence of the cooperative effect with increasing length of the hydrogen bond circuit [10].

Cooperative effects in the hydrogen bond chains are due to the mutual polarization of these bonds [6]. For the quantitative estimation of the mutual effect of hydrogen bonds in compounds 10, 11, 12, 13, 15, 16, and 18 ($n = 6$, $R = F, Cl, Br, I, CH_3O, NO_2$, and CH_3CO), we performed multiple correlation between the energy values of hydrogen bonding and the average values of Mulliken partial charges on oxygen atoms of the neighboring and considered H-bonds based on the calculations by the RHF/3-21G method. The multiple correlation coefficient [6, 12] is rather large and is 0.988. In our opinion, the result, firstly, indicates that the neighboring hydrogen bonds substantially affect each other, and this effect can be characterized by a linear dependence. Secondly, it shows that the calculation method that we applied provides the correct estimation of not only the value of changes in the hydrogen bonding energy in calixarene molecules in general, which occur when a particular hydrogen bond breaks, but also the dissociation energy of an individual hydrogen bond. For brevity, this value is further called the hydrogen bond energy.

The formation of the intramolecular hydrogen bond affects the dissociation constants of hydroxy acid. This is explained by the stabilization of the initial state of the acid during dissociation with respect to the conjugated base [6]. The stronger the H-bond, the more stable the initial state is, and the lower the dissociation constant K_a (and correspondingly, higher pK_a). Hence, the strength of the intramolecular hydrogen bond can be estimated either by means of the dissociation constant of the acid participating in the formation of this hydrogen bond, or by the difference in the energies of the acid and conjugated base. As seen from Table 3, according to the method for calculating changes in the hydrogen bonding energy, a change in the dissociation energy of hydroxyl groups in *p*-substituted calix[6]arenes equal to the difference $\Delta E_1(p\text{-R-calix[6]arene}) - \Delta E_1(p\text{-R-calix[4]arene})$, in comparison with *p*-substituted calix[4]arenes, exactly corresponds to the cooperative effect ΔE_k of hydrogen bonds in the transition from *p*-R-calix[4]arene to *p*-R-calix[6]arene, where $R = H, Alk, Hal$, etc. As shown in Table 3 and Figs. 1 and 2, monoanions 1 and 3 represent enantiomers (protomers) that can transform into each other when the hydrogen bond breaks between the oxygen atoms of the third and fourth monomeric fragments in monoanion 3, and when the hydrogen bond breaks between the oxygen atoms of the second and third monomeric fragments in monoanion 1 respectively. The anions differ only in the orientation of the mentioned hydrogen bonds, whose parameters are identical (Tables 2 and 3). Monoanion 2 is simultaneously a protomer and diastereomer of monoanions 1 and 3 and has the achiral configuration.

Changes in the hydrogen bond energies in calix[4]- and calix[6]arenes under variation of *p*-substituents in benzene rings given in Table 3 are caused by a difference in the quantitative indices of inductive and mesomeric effects of these substituents, which differently affect the reaction centers, i.e. oxygen atoms of hydroxyl groups. This in turn is related to the different electronegativities of atoms binding *p*-substituents to benzene rings. Therefore, it seemed reasonable to estimate the pair correlation between the hydrogen bond energies in *p*-halogen calix[4]arenes and calix[4]arene (or, similarly, in *p*-halogen calix[6]arenes and calix[6]arene) and the electron affinity values of hydrogen and halogen atoms [13]. According to the calculations of calix[4]arenes by RHF/3-21G and B3LYP/3-21G methods, the pair correlation coefficient was 0.984 and 0.993 respectively, whereas for calix[6]arenes it turned out to be 0.975 and 0.958 respectively.

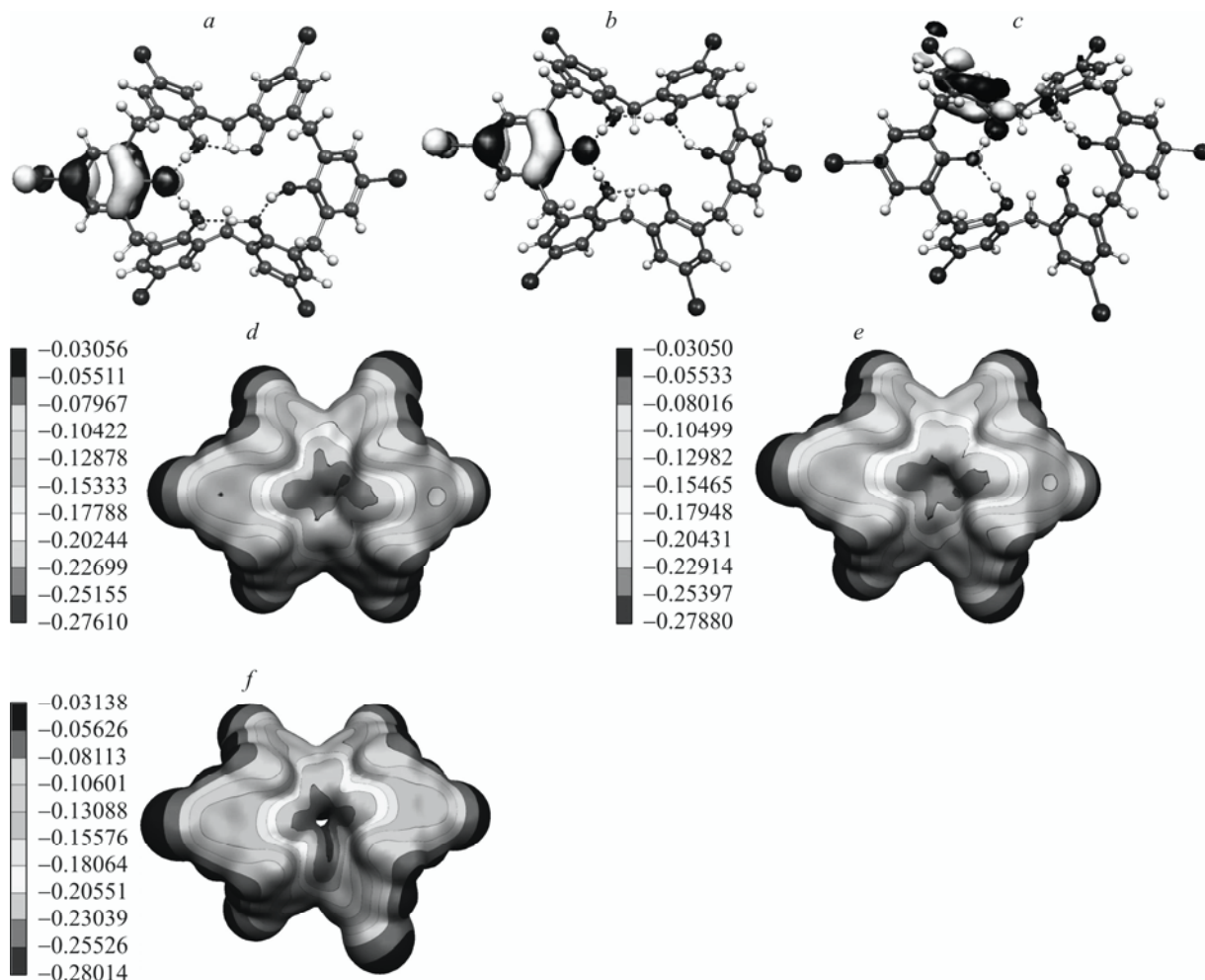


Fig. 2. Monoanions of *p*-iodocalix[6]arene, calculated by the RHF/3-21G method (bottom view): (a, b, c) HOMOs of monoanions 1, 3 and 2 *p*-iodocalix[6]arene respectively; (d, e, f) electrostatic potentials of monoanions 1, 3 and 2 *p*-iodocalix[6]arene respectively.

As RHF/3-21G and B3LYP/3-21G [6] methods predict (ΔE_k values in Table 3), *p*-halogen substituted calix[6]arenes and *p*-nitrocalix[6]arene have by lower conformational mobility as compared to calix[6]arene, *p*-methylcalix[6]arene, and *p*-methoxycalix[6]arene. This is because the ΔE_k value of the second hydrogen bond for the first group of compounds (*p*-halogen substituted calix[6]arenes and *p*-nitrocalix[6]arene) is positive, while it is negative for the second group of compounds (calix[6]arene, *p*-methylcalix[6]arene, and *p*-methoxycalix[6]arene). Consequently, the strength of the second hydrogen bond in the first group of compounds is higher than the strength of hydrogen bonds in the respective *p*-substituted calix[4]arenes. At the same time, the strength of the second hydrogen bond in the second group of compounds is lower than the strength of hydrogen bonds in the respective *p*-substituted calix[4]arenes. Therefore, the second hydrogen bond in calix[6]arene, *p*-methylcalix[6]arene, and *p*-methoxycalix[6]arene breaks easier than any other hydrogen bond in the respective *p*-substituted calix[4]arenes. However, the second hydrogen bond in *p*-halogen substituted calix[6]arenes and *p*-nitrocalix[6]arene breaks harder than any other hydrogen bond in the respective *p*-substituted calix[4]arenes.

Calculation results for different *p*-substituted derivatives of calix[4]- and calix[6]arenes allowed us to check if there is a correlation dependence (both pair and multiple) between the hydrogen bonding energy and Hammett constants as well as Swain–Lupton parameters that can replace 43 sets of different Hammett constants [14]. The values of Hammett (Brown) substituent constants σ and σ^+ characterizing the inductive and mesomeric effects of functional groups respectively, which affect the electron density on the reaction center (oxygen atoms of hydroxyl groups) may correlate with the hydrogen bond

TABLE 4. Multiple Correlation Coefficients Between the Pairs of Hammett Constants (Swain–Lupton parameters) and the Hydrogen Bond Energies in *p*-Substituted Calix[4]- And Calix[6]arenes Calculated by the RHF/3-21G Method

Number of monomeric links <i>n</i> , anion No.		4				6, anion 1 and anion 3			6, anion 2		
Compounds		1-8, 17, 19, 20	1-8	R=H, Hal	R=H, Hal, NO ₂	9-16, 18	R=H, Hal	R=H, Hal, NO ₂	9-16	R=H, Hal	R=H, Hal, NO ₂
Type of constants	σ_I and σ_R	0.93*	0.91	0.97	0.97	0.94	0.97	0.98	0.96	0.97	0.98
	F and R	0.89	0.93	0.96	0.97	0.89	0.96	0.97	0.97	0.96	0.97

*In pair correlation, the dependence of one parameter on another is found. In the simplest multiple correlation (as in this work), the simultaneous dependence of one parameter on the two other parameters is found. The parameters in turn may be dependent on each other. The multiple correlation coefficient can take values only from 0 to 1, i.e. it cannot be negative, whereas the pair correlation coefficient can take values from –1 to 1 [6, 12].

energy in the corresponding *p*-substituted calix[4]- and calix[6]arenes. We have estimated the multiple correlation between the mentioned Hammett constants of hydrogen atom, halogens, methyl, methoxy and nitro groups [14] on the one hand, and the hydrogen bonding energy in the respective *p*-substituted calix[4]arenes on the other. We have separately estimated the multiple correlation for Hammett constants σ_I and σ_R (and also separately of Swain–Lupton parameters) for the same substituents with the hydrogen bonding energies in the respective *p*-substituted calix[4]arenes (Table 4). The multiple correlation coefficients for Hammett substituent constants σ and σ^+ are, as a rule, somewhat smaller than the correlation coefficients for the other types of constants, therefore they are omitted for brevity. Moreover, we made similar calculations of the correlation coefficients for the H-bond energy in the corresponding *p*-substituted calix[6]arenes for both the strongest hydrogen bonds and weaker ones (Table 4). We also studied the correlation for larger and smaller groups of compounds (Table 4). All types of calculations only for *p*-halogen calix[*n*]arenes, *p*-nitrocalix[*n*]arenes, and calix[*n*]arenes (*n* = 4, 6) without substituents in the *p*-position yielded, in general, larger values for the multiple correlation coefficients as compared to calculations for the other groups of compounds. As seen from Table 4 data (only Hartree–Fock RHF/3-21G method), all multiple correlation coefficients have close values in a range from 0.89 to 0.98. The same can be said about the calculation results based on the B3LYP/3-21G method, which cannot be given here because of lack of room. This is almost the same value range previously noted in the published work [15] on the determination of pair correlation between σ^+ Hammett (Brown) substituent constants found experimentally and a number of parameters of isolated *p*-substituted benzyl cations theoretically calculated by quantum chemical methods.

Such a comparison allows the conclusion that there is an obvious dependence between the experimentally found Hammett constants and theoretically calculated values of the H-bond energy in calixarenes. The authors of the work [15] have come to the similar conclusion. The error of quantum chemical calculations of the hydrogen bond energy depends on the number of atoms (orbitals) in the calculated molecules: the higher the total energies of molecules and ions, from which the hydrogen bond energy is obtained by subtraction, the larger the error of this calculation [3]. Here the correlation coefficients for benzyl cations and calixarenes are close to each other. Therefore, taking into account that at the identical significance level the linear correlation coefficients for calixarenes could take smaller values than the similar correlation coefficients for benzyl cations, the correlation coefficients obtained in the calculations of calixarenes are in fact more significant. The Swain–Lupton parameters F and R [16] can replace almost any set of Hammett constants (here the term Hammett constant is used in a wide sense). Part of Hammett constants, with which the correlation analysis was performed, was developed for some specific types of reactions. Nonetheless, they characterize the certain types of the electronic effect of substituents (inductive or mesomeric), and as Swain and Lupton have shown [16], they are not completely linearly independent of each other. Consequently, the correlation of hydrogen bond energies is observed with different sets of Hammett constants, and the correlation coefficients take comparable values.

We have simultaneously calculated the multiple correlation between two structural parameters of hydrogen bonds (the distance between oxygen atoms $d(O_i...O_{i+1})$ that form hydrogen bonds, and $\angle H_iC_{1i}H_{i+1}O_{i+1}$ dihedral angles, where i is the index of the monomeric fragment, C_{1i} is the aromatic atom bonded to the oxygen atom in the corresponding monomeric fragment) in p -halogen and p -nitrocalix[4]- and calix[6]arenes on the one hand, and the energy parameters of hydrogen bonds on the other. For calix[6]arenes we considered only the strongest hydrogen bonds. The multiple correlation coefficients for ten values of the hydrogen bond energy, $d(O_i...O_{i+1})$ distance, and $\angle H_iC_{1i}H_{i+1}O_{i+1}$ dihedral angles, calculated by the RHF/3-21G method for ten compounds (2, 3, 4, 5, 8, 10, 11, 12, 13, and 16) being studied, takes a sufficiently large value of 0.941. Here the pair correlation coefficients between the energy parameter and the $d(O_i...O_{i+1})$ distance, the energy parameter and the $\angle H_iC_{1i}H_{i+1}O_{i+1}$ angle, and between the two mentioned structural parameters are also large and are -0.941 , -0.917 , and 0.978 respectively. The multiple correlation coefficient for twelve hydrogen bond energies (RHF/3-21G, including also p -methoxycalixarenes 11 and 41 in the consideration) is 0.914. The multiple correlation coefficient for ten values of the hydrogen bond energy, $d(O_i...O_{i+1})$ distance, and $\angle O_i...H_{i+1}-O_{i+1}$ angle, calculated by the RHF/3-21G method for ten considered compounds (2, 3, 4, 5, 8, 10, 11, 12, 13, and 16) is also large and is 0.942. Here the pair correlation coefficients between the energy parameter and the $d(O_i...O_{i+1})$ distance, the energy parameter and the $\angle O_i...H_{i+1}-O_{i+1}$ angle, and between the mentioned structural parameters are also large and are -0.941 , 0.896 , and -0.965 respectively. At the same time, the multiple correlation coefficient for ten values of the hydrogen bond energy, $d(O_i...O_{i+1})$ distance, and $\angle H_iC_{1i}H_{i+1}O_{i+1}$ dihedral angle, calculated by the B3LYP/3-21G method for ten p -halogen and p -nitrocalixarenes (2, 3, 4, 5, 8, 10, 11, 12, 13, and 16) is 0.910. This result, along with the calculation results of the correlation dependence between the hydrogen bond energy and the partial charges on atoms forming the neighboring hydrogen bonds, indicates that the calculated energy value is indeed the energy parameter of the hydrogen bond because it linearly depends on different structural parameters of this H-bond.

The strength of hydrogen bonds affects the electron density delocalization and distribution in the neighboring aromatic ring, and this in turn affects the reactivity of the compound in general, regardless of what transformations this compound undergoes. Therefore, the occurrence of a significant correlation between any Hammett constants and Swain and Lupton parameters on the one hand, and theoretically calculated hydrogen bond energies on the other, is a quite anticipated and explicable fact. The HOMA and NICS aromaticity indices proposed previously [17] represent a measure of π -electron delocalization. The work [15] shows that there is the linear correlation between the aromaticity indices and Hammett constants σ^+ characterizing the reactivity of benzyl cations. Hence, the occurrence of multiple correlations between the hydrogen bond energies and different Hammett constants gives evidence that hydrogen bonds decisively affect both the electron density distribution in calixarenes and their reactivity. Consequently, H-bonds affect the direction of reactions involving calixarenes and the mechanism of chemical transformations.

It has been noted above that intramolecular hydrogen bonds in calixarenes affect the acidic properties of hydroxyl groups participating in the formation of these H-bonds. Therefore, the strength of hydrogen bonds and basic as well as nucleophilic properties of both calixarenes *per se* and their monoanions are related. The work [6] shows that in reactions involving monoanions of calix[6]arene proceeding in aprotic nonpolar or weakly polar solvents and in the gas phase in the presence of weak bases the charge and orbital factors will promote the direction of the electrophilic attack to the same reaction center of the reagent. Moreover, it was also noted there that under the above mentioned conditions at a certain temperature it is possible to predict an intermediate associate with a minor prevalence of monoanion 2 of calix[6]arene followed by the electrophile attack of oxygen atoms of the first (or the fourth with allowance for the pinched cone symmetry of the conformer of calix[6]arene,) monomeric fragment. Here the formation of monoanions 1 and 3 is also possible. However, even in the presence of sufficiently strong bases, the electrophilic attack of oxygen atoms of the second (fifth) monomeric fragment is least probable.

In order to predict the mechanism and direction of reactions involving p -substituted calixarenes, we analyzed HOMOs of all monoanions of p -halogen substituted calix[6]arenes and p -nitrocalix[6]arene. Fig. 2 presents HOMOs of monoanions 1, 3, and 2 of p -iodocalix[6]arene respectively. According to the current generalized interpretation of the

Kornblum rule [14], an increase in the positive charge on the substrate reaction center leads to the charge control of the reaction. In this case, relative rates of the process depend on the total charge on atoms (e.g., on carbon and oxygen atoms in the enolate ion, or on oxygen atoms of different monomeric fragments of the monoanions of calix[6]arene). On the other hand, the lower the charge δ^+ on the carbon atom of the substrate (e.g., in alkylhalides, in particular, primary) in nucleophilic substitution reactions proceeding under S_N2 conditions, the greater the role of the orbital interaction is. It results in that the nucleophile interacts through the atom with the maximum HOMO coefficient, i.e., the orbital control is performed here. In the work, the calculation carried out similarly to the HOMO analysis of calix[6]arene [6] shows that in monoanion 2 of *p*-fluoro-, *p*-bromo-, *p*-iodo-, and *p*-nitrocalix[6]arenes 10, 12, 13, and 16, the coefficient is maximum at oxygen atoms of the second (and fifth, with allowance for the symmetry of conjugated acids) monomeric fragment. In monoanion 2 of *p*-chlorocalix[6]arene 11 as in monoanion 2 of calix[6]arene 9, this coefficient is maximum at oxygen atoms of the first (fourth) monomeric fragment, whereas in monoanions 1 and 3 of compounds 9, 10, 11, 12, 13, and 16, the HOMO coefficient is maximum at oxygen atoms of the third (sixth) monomeric fragment. Hence, under orbital control conditions in the presence of weak bases in aprotic nonpolar solvents and in the gas phase, the nucleophilic substitution reactions involving compounds 10, 12, 13, and 16 must proceed through the attack of the reaction center of the substrate by only oxygen atoms of the second (fifth) monomeric fragment, on the one hand, and oxygen atoms of the third (sixth) monomeric fragment, on the other.

At the same time, under orbital control conditions in the presence of weak bases in aprotic nonpolar solvents and in the gas phase, the nucleophilic substitution reaction involving compounds 9 and 11 must proceed through the attack of the reaction center of the substrate only by oxygen atoms of the first (fourth) monomeric fragment on the one hand, and oxygen atoms of the third (sixth) monomeric fragment on the other. The first type of the reaction proceeding with oxygen atoms of the first (fourth) (compounds 9 and 11) or second (fifth) (compounds 10, 12, 13, and 16) monomeric fragment should slightly dominate over the reaction proceeding by the second mechanism. The selectivity of the process is due to that it is much easier to break the weakest hydrogen bond formed by the oxygen atom of the first monomeric fragment and the hydrogen atom of the hydroxyl group of the second monomeric fragment, and also in accordance with conformer symmetry, the oxygen atom of the fourth monomeric fragment and the hydrogen atom of the hydroxyl group of the fifth monomeric fragment. Eventually, the dominant intermediate reaction product will correspond to the achiral configuration of monoanion 2 [18]. Nonetheless, the formed reaction products are also prone to conformational transformations as calix[6]arenes themselves. Therefore, the conclusion whether the nucleophilic substitution reaction involving compounds 9, 10, 11, 12, 13, and 16 is stereoselective or not can be drawn only based on the structural and configurational data for a particular substrate.

The obtained results give evidence that the method we applied to calculate the hydrogen bond energy (according to Grootenhuis) provides a sufficiently correct estimation of the energy of individual hydrogen bonds in a series of *p*-substituted calix[4]- and calix[6]arenes. The hydrogen bond energies calculated by this method can be considered as descriptors of the reactivity of calix[4]arene, calix[6]arene, and their *p*-substituted derivatives. Therefore, these values can be used for the theoretical prediction of reactivity of the studied calixarenes and the other ones close in structure. On the whole, the conclusion can be drawn that the nucleophilic substitution reaction involving *p*-substituted calix[6]arenes in the presence of weak bases and in aprotic solvents or in the gas phase, under orbital control conditions should proceed through the diastereomeric transition states [18]. Here the achiral calix[6]arene derivative should mainly form as an intermediate product of the reaction with a substrate without asymmetric centers.

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