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Active components of frequently used β-blockers from the aspect of computational study

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Abstract The aim of this study is to investigate the active components of representative drugs for blood pressure regulation by applying quantum mechanical computer codes and comparison of the same for the sake of obtaining knowledge about the properties associated with the electronic structure of given molecules. The study included three well-known, but not theoretically investigated enough, active components of β-blockers: acebutolol, metoprolol and atenolol. The results are in agreement with the experimental data and were used for initial assumptions concerning the degradation of these compounds.

Keywords Aromaticity · β-blockers · NBO · NMR parameters · NPA · Stability

Introduction

The appearance of drugs in the environment is considered as the result of a combination of a partial removal in sewage treatment plant (STP) and of the refractoriness with respect to abiotic and biotic (natural) transformations. Although the concentrations at which they are normally found in the aquatic environment are in the range of micrograms per liter to nanograms per liter [1, 2], no indications exist for the most part of them that allow to rule out possible interactions with living organisms. Hundreds of tons of pharmaceuticals are annually prescribed in Europe and consequently discharged modified or as metabolites in sewage effluents [3].

Amongst the considerable number of pharmaceuticals that can be detected in receiving effluents, β-blockers are characterized by increasing use in recent years, and, as a consequence, an increasing presence in aqueous effluents is envisaged. They belong to the group of cardiovascular pharmaceuticals and are generally used for treatment of hypertension, angina, arrhythmia and acute myocardial infarction. β-blockers show slow direct phototransformation and/or hydrolysis, although indirect photolysis and photo-induced biodegradation can be the main sources of its depletion in the environment [4, 5].

Low levels of human medicines (pharmaceuticals) have been detected in many countries in sewage treatment plant effluents, surface waters, seawaters, groundwater and some drinking waters [6]. Concentrations of β-blockers in surface waters in Europe and North America range from a few ng/L up to 2.2 mg/L [5]. Consequently, great attention is paid to the stability of the studied group of compounds and intermediaters that arise during their removal from the aqueous environment [5, 7–9].

The stability of the mentioned group of compounds was tested in the photo-degradation processes with or without the presence of catalysts which proposed some possible intermediers [4, 10, 11].

However, the toxicity of degradation by products/intermediates of individual compounds is still unknown. Although the presence and extent of ecological impact of environmental

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β-blockers is uncertain, more study may be needed to confirm generation of potentially intermediates.

That is why this work is of importance for research in the field of stability of the mentioned group of compounds and their intermediers.

NMR parameters, chemical shift and chemical shielding [12] are parameters that are very sensitive to the change of charge density; therefore, they are ideal parameters for comparison of similar or in some way perturbed systems. In addition, the calculations of (NMR) parameters using *ab initio* techniques have found the ability of quickly evaluating and correlating the magnitude of the chemical shielding (CS) tensors with variations in bond angles, bond lengths, and the nearest neighboring interactions and then have increased the significance of utilizing these parameters in investigations of molecular structures [13–15].

For the evaluation of aromaticity Schleyer et al. [16] introduced nucleus independent chemical shifts (NICS) as a negative value of absolute magnetic shielding calculated at the aromatic ring center or one angstrom above the molecular plane. NICS are very important parameters because they are closely related to the energetic, structural and magnetic properties of molecules.

The molecular electrostatic potential (MEP) represents an important tool in the primary qualitative analysis of degradation. The most negative parts of MEP surface are ideal for electrophilic attacks.

Bioactivity of molecules can be further evaluated based on the charge of some important atoms. Reliable data is obtained in the natural population analysis (NPA) whose results are presented in this paper. In particular, for the high bioactivity, high negative value of the charge of the atoms in the molecule is necessary.

In general a good insight of the stability of these molecules can be obtained by natural bond order (NBO) analysis presented here and implemented.

Computational details

The paper uses the Hartree-Fock (HF) method [17] with 6-31G(d) basis set. The structures are optimized by implementation of the WinGamess code, revision 09 [18]. For result visualization we used the WinMacMolPlt [19]. Input files were prepared with Avogadro [20].

NMR parameters, chemical shift and chemical shielding, were calculated within GIAO method [21] at the same level

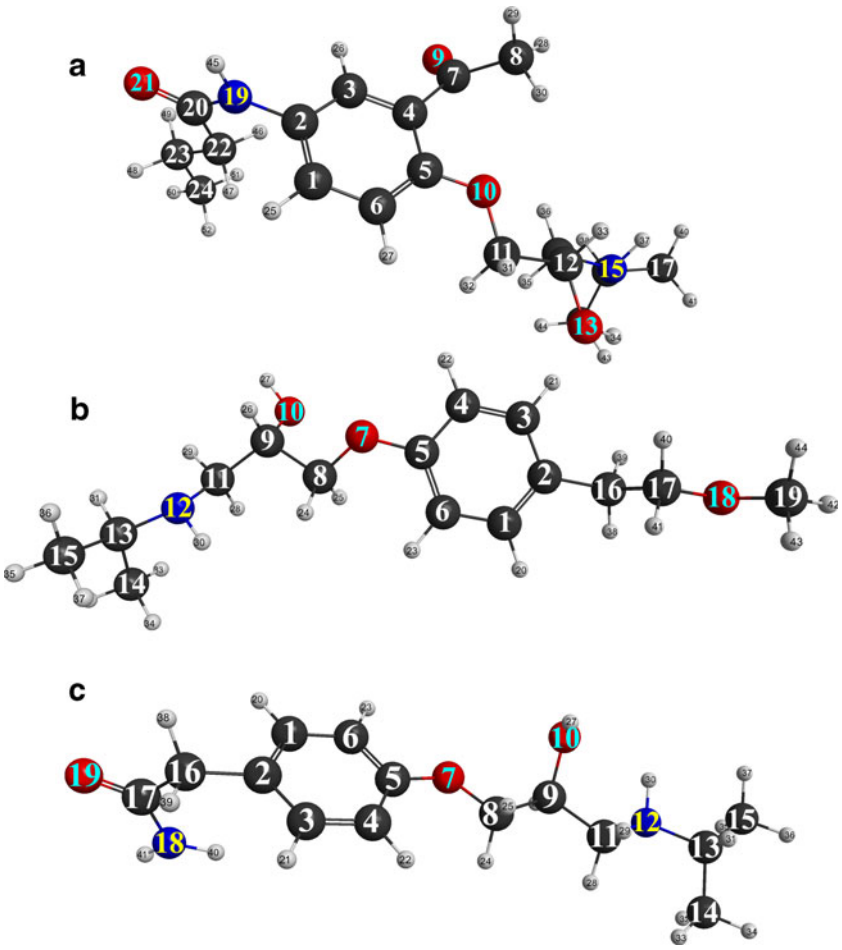

Fig. 1 Optimized geometries of investigated structures (**a**) Acebutolol (**b**) Metoprolol and (**c**) Atenolol

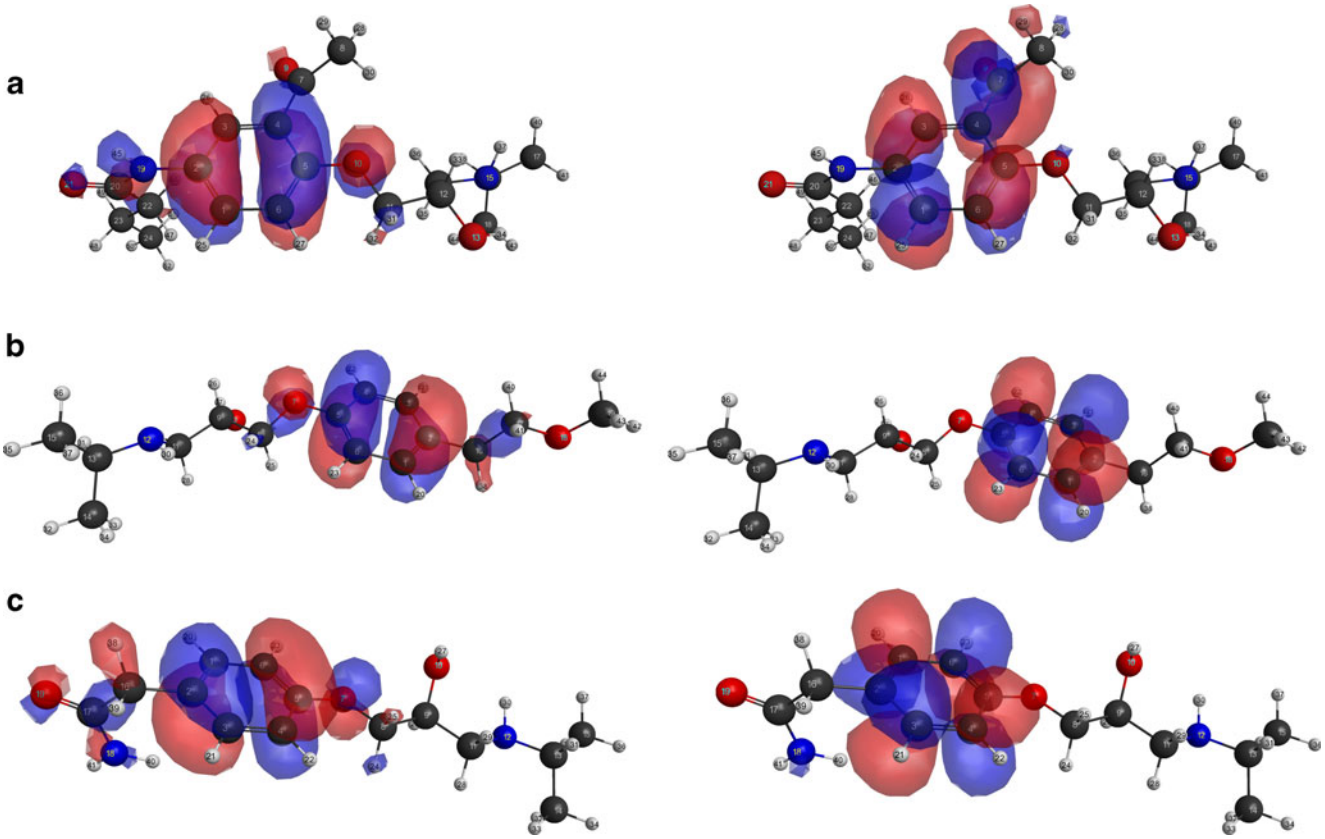

Fig. 2 HOMO and LUMO orbitals of investigated compounds (**a**) Acebutolol, (**b**) Metoprolol and (**c**) Atenolol

of theory. For NICS calculations we placed ghost atoms in ring centers and than we took negative value of absolute magnetic shielding of that ghost atom as NICS value.

The effects of solvent, DMSO, H2O, and chloroform on the NMR parameters are obtained within the default polarizable continuum model (PCM) model [22].

For calculations of NMR parameters, NICS, effects of solvents, as well as for NBO analysis we used Gaussian 03 [23].

Results and discussion

HOMO, LUMO, stability, sensitivity and chemical hardness

By optimizing the structures we obtained data on the HOMO and LUMO energies that we continue to utilize to calculate the parameters that indicate the stability / reactivity / sensitivity, such as the chemical potential χ_m and chemical hardness η. Within the Koopmans' theorem these parameters can be calculated as follows:

$$\eta = +0.5(E_{LUMO} - E_{HOMO}), \quad (1)$$

$$\chi_m = -0.5(E_{HOMO} + E_{LUMO}). \quad (2)$$

These parameters are important as a measure of stability and sensitivity of organic compounds and predicting reactivity, or sensitivity in the general case, of a molecule is very important for the stability analysis of a compound and its degradation.

The HOMO represents the ability to donate an electron, LUMO as an electron acceptor represents the ability to

Table 1 Main stability/sensitivity parameters

Compound	Equilibrium energy (Hartrees)	HOMO	LUMO	ΔE (eV)	Chemical hardness, η	Chemical potential, χ_m
Acebutolol	−1106.284	−9.001	2.639	11.644	5.820	3.181
Atenolol	−876.446	−8.570	3.483	12.053	6.027	2.544
Metoprolol	−861.571	−8.136	4.000	12.136	6.068	2.068

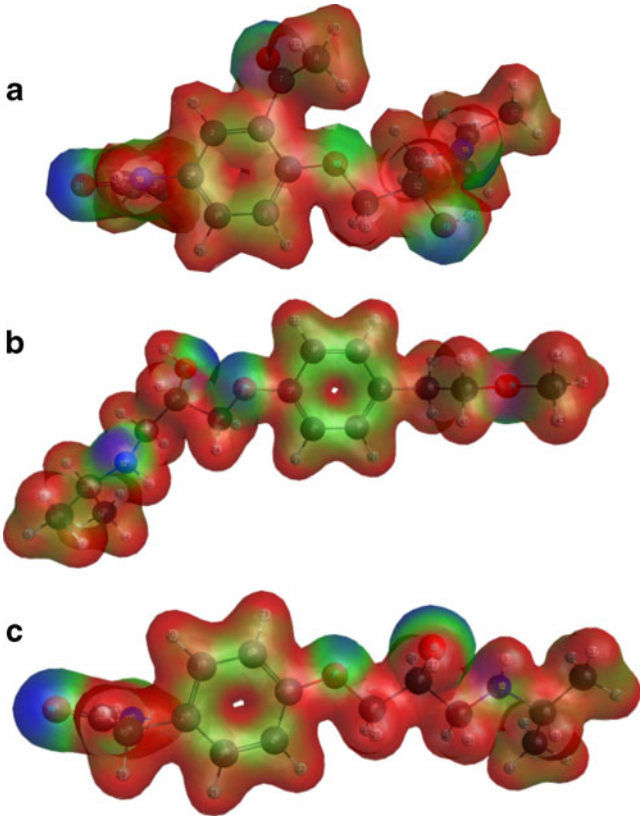

Fig. 3 Representative MEP surfaces of investigated compounds (**a**) Acebutolol, (**b**) Metoprolol and (**c**) Atenolol

obtain an electron. HOMO and LUMO are the main orbitals that take part in chemical stability [24]. The eigenvalues of LUMO and HOMO and their energy gap reflect the chemical activity of the molecule. The decrease in the HOMO and LUMO energy gap explains the intramolecular charge transfer (ICT) interaction taking place within the molecule which is responsible for the activity of the molecule. The HOMO-LUMO energy separation has served as a simple measure of kinetic stability. A molecule with a small or no HOMO-LUMO gap is chemically reactive. Pearson showed that the HOMO-LUMO gap represents the chemical hardness of the molecule [24]. In Fig. 1, optimized structures of investigated compounds are given. HOMO-LUMO orbitals of investigated compounds are given in Fig. 2, while HOMO-LUMO gap values are given in Table 1.

Chemical hardness has been used as an electronic property to characterize the relative stability of molecules. Hardness is interpreted as the resistance toward change in number of electrons. According to the principle of maximum hardness [25], the hardness of a system becomes maximal at equilibrium geometries [26], and the stability is directly related to the higher values of hardness [27]. Obtained results concerning chemical hardness are given in Table 1.

Bearing this in mind, and the results given in Table 1 show that in terms of thermodynamic the most stable compound is acebutolol, with the lowest equilibrium energy of −1106 a.u., but according to HOMO-LUMO gap and the chemical hardness (which are in mutual agreement) that compound is more reactive than others. A similar conclusive situation also applies in the paper [28].

MEP surfaces

Molecular electrostatic potential and electrostatic potential are useful quantities to illustrate the charge distributions of molecules and are used in our work to visualize variably charged regions of a molecule. Therefore, the charge distributions can give the information about how the molecules interact with another molecule. At any given point in the vicinity of a molecule, the MEP, $V(r)$ is defined in terms of the interaction energy between the electrical charge originated from the molecule electrons and nuclei and a positive test charge (a proton) located at r [29, 30]. The molecular electrostatic potential is related to the electronic density and is a very useful descriptor for determining sites for electrophilic attack and nucleophilic reactions as well as hydrogen-bonding interactions [31]. In Fig. 3, representative pictures of MEP surfaces, which are used for degradation analysis, are given.

Blue color indicates atractivity to the positive charge, red indicates repulsion to the positive charge, while green indicates neutrality.

The oxygen atom bearing the free electron pairs, is very obvious on the MEP surfaces (Fig. 3), as a strong nucleophilic

Scheme 1 Degradation scheme of investigated compounds

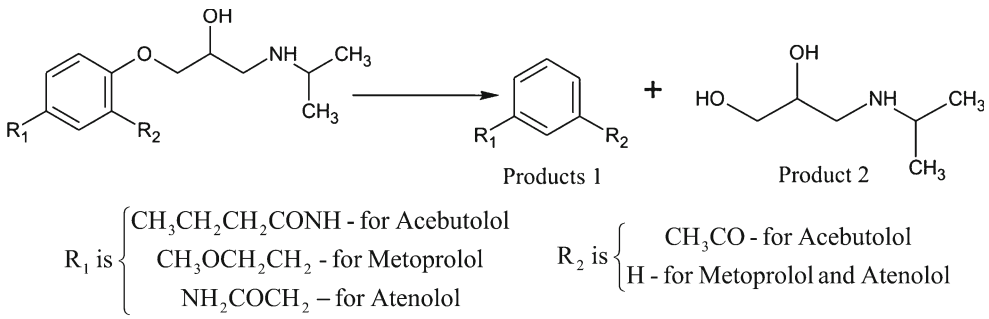

Table 2 Main stability/sensitivity parameters of degradation products

Products	Equilibrium energy [Hartrees]	HOMO	LUMO	ΔE (eV)	Chemical hardness, η(eV)	Chemical potential, χ_m(eV)
MET1[a]	−422.647	−8.735	3.973	12.708	6.354	2.381
ATE1[a]	−437.522	−9.143	3.538	12.681	6.340	2.802
ACE1[a]	−515.590	−8.218	3.946	12.164	6.082	2.136
PRO2[a]	−440.080	−9.633	5.714	15.347	7.674	1.960

[a] PRO2 is product 2 which is the same for all three compounds. MET1, ATE1 and ACE1 are products of metoprolol, atenolol and acebutolol, respectively, which contain aromatic ring

atom (likes the nucleus) can be the center of a relatively high chemical reactivity, thereby determining the overall reactivity of molecule. The characteristic functional ether bond is one of the most important bonds in terms of transformation of molecules [32].

As a result, product 2 (Scheme 1) is one of the expected products in the system regarding a group of the observed compounds. Based on the chemical hardness parameter (Table 2), which is higher in the proposed degradation products, it can be seen that the proposed products are more stable than the starting compounds.

The obtained results are a consequence of the amino-diol separation as an alifatic part of the molecule, which leads to a reduction in the molecule surface.

In Table 2 the basic parameters of stability/sensitivity of degradation products of investigated compounds are given.

NMR parameters

Schleyer et al. [16] introduced a nucleus independent chemical shift (NICS) as the negative value of the absolute magnetic shielding calculated in ring centers or one angstrom above molecular plane. This approach was used in our work to estimate aromaticity of investigated molecules. Aromaticity results are given in Table 3. As expected all compounds are aromatic.

Table 3 Aromaticity of investigated compounds

	NICS (ppm)	$NICS_{zz}$ (ppm)	Chemical hardness, η(eV)
Compound			
Acebutolol	−12.893	−13.609	5.820
Metoprolol	−12.447	−14.683	6.068
Atenolol	−11.287	−13.899	6.027
Products			
ACE1	−12.086	−15.282	6.340
MET1	−11.400	−15.694	6.354
ATE1	−11.205	−12.351	6.082

However, based on the work of [33] the component corresponding to the principal axis perpendicular to the ring plane, NICSzz, is found to be a good measure for the characterization of the π system of the ring, because isotropic NICS values at ring centers contain large influences from the σ system and from all three principal components of the NICS tensor. At large distances from the ring center, zz-component of NICS, which is dominated by contributions from the π system, characterizes NICS better than isotropic value.

Because of this, in Table 3, we give the results of the isotropic NICS and zz NICS component of magnetic shielding.

In order to determine which value of NICS to use for evaluation of examined compounds aromaticity we will refer to, that in some works, such as [34] the stability of a compound is related with compound aromaticity. If we compare the values of isotropic NICS, and zz component of the NICS depending on the chemical hardness we see that an increasing trend from acebutolol to atenolol applies exactly for the zz component of the NICS. The same situation exists for the aromatic products of examined compounds, except that an increasing trend of the NICSzz component and chemical hardness is going from the atenolol product to the metoprolol product.

In this paper, the GIAO method [21] was used to determine the NMR parameters of chemical shift and magnetic shielding implemented in Gaussian 03. The obtained parameters are compared with experimental values and results in the form of correlation between the calculated and experimental values are shown in Fig. 4.

The effects of solvent, DMSO, H2O, and chloroform on the NMR parameters are obtained in the framework of default polarizable continuum model (PCM) model [22] and the results are compared with experimental results for all (Fig. 4 and Table 4.).

Experimental results for atenolol and acebutolol were taken from reference [35], while the experimental data for the chemical shift of metoprolol are taken from reference [36].

In Table 5 results of the effect of different solvents on 13C NMR parameters are given.

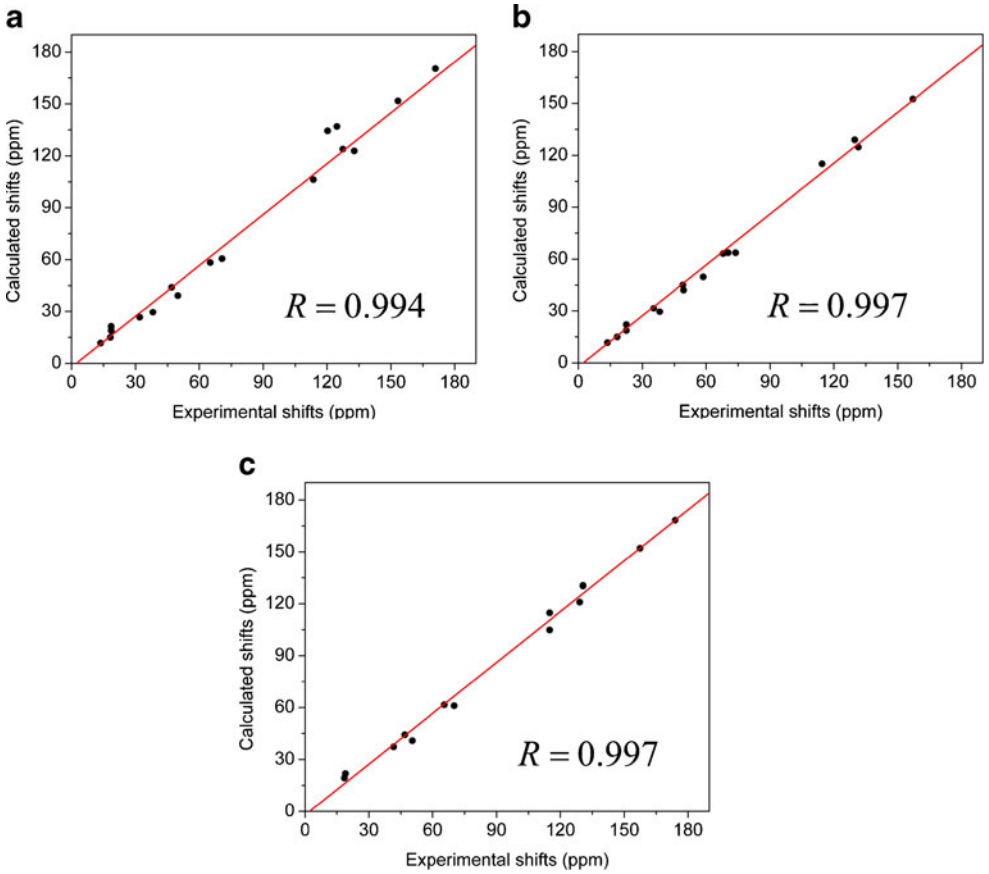

Fig. 4 Correlation between experimental and calculated C NMR chemical shifts (**a**) Acebutolol, (**b**) Metoprolol and (**c**) Atenolol. *R* is correlation coefficient

Table 4 Comparison of theoretical and experimental values of NMR chemical shift (ppm)

Acebutolol, DMSO			Metoprolol, $CHCl_3$			Atenolol, DMSO		
#	Theoretical	Experimental	#	Theoretical	Experimental	#	Theoretical	Experimental
1	136.99	124.67	1	128.41	–	1	130.6	130.65
2	122.87	132.78	2	124.83	131.5	2	120.77	129.1
3	134.47	120.3	3	129.02	129.8	3	130.83	130.65
4	123.93	127.47	4	115.17	114.5	4	105.25	114.88
5	151.69	153.28	5	152.52	157.1	5	152.06	157.38
6	106.36	113.62	6	109.08	–	6	114.14	114.88
7	195.12	198.55	8	63.74	70.34	8	60.82	70.11
8	26.66	31.93	9	63.23	67.98	9	61.72	65.52
11	60.6	70.66	11	45.16	49.1	11	43.86	46.87
12	58.34	65.13	13	42.14	49.44	13	40.58	50.39
14	44.03	46.9	14	18.73	22.48	14	19.28	18.54
16	39.26	49.83	15	22.12	22.48	15	21.88	19.02
17	21.38	18.57	16	31.58	35.28	16	37.24	41.6
18	18.95	18.59	17	63.71	73.84	17	169.63	173.93
20	170.38	170.97	19	49.8	58.66			
22	29.61	38.13						
23	15.00	18.19						
24	11.72	13.62						

Table 5 Effects of different solvents on 13C NMR parameters

Acebutolol				Metoprolol				Atenolol			
#	None	Water	$CHCl_3$	#	None	Water	DMSO	#	None	Water	$CHCl_3$
1	135.10	137.06	136.38	1	127.88	128.85	128.79	1	130.33	130.57	130.59
2	123.55	122.86	123.00	2	124.53	125.01	124.98	2	121.63	120.9	120.94
3	135.35	134.34	134.73	3	128.92	129.06	129.06	3	129.19	130.91	130.22
4	125.69	123.81	124.49	4	116.08	114.59	114.68	4	104.38	105.34	104.86
5	150.94	151.76	151.52	5	152.73	152.28	152.34	5	151.95	151.94	152.11
6	105.39	106.43	106.07	6	108.73	109.41	109.33	6	115.75	114.02	114.76
7	189.93	195.4	193.6	8	63.63	63.81	63.8	8	61.50	60.82	61.04
8	26.28	26.68	26.54	9	63.38	63.3	63.25	9	61.55	61.73	61.57
11	60.96	60.65	60.7	11	45.83	44.85	44.86	11	45.01	43.83	44.28
12	58.92	58.29	58.56	13	42.62	41.89	41.92	13	41.32	40.58	40.87
14	44.23	44.01	44.06	14	19.09	18.51	18.54	14	19.41	19.29	19.31
16	39.71	39.26	39.38	15	22.26	22.09	22.07	15	22.04	21.87	21.91
17	21.73	21.37	21.48	16	32.02	31.35	31.38	16	37.51	37.23	37.32
18	19.04	18.97	18.95	17	64.22	63.42	63.44	17	164.58	169.78	168.32
20	166.57	170.58	169.39	19	50.06	49.67	49.68				
22	29.91	29.47	29.71								
23	15.12	15.00	15.01								
24	12.22	11.71	11.86								

From Table 5 it can be seen that the major changes of chemical shifts occurred in metoprolol (C4 atom), acebutolol (atoms C1, C4, C7 and C20), atenolol (C17 atom).

NBO analysis

An efficient method for studying intra and inter molecular bonding and interaction among bonds is represented by natural bond order (NBO) analysis [37, 38]. It provides an efficient method for studying intra and inter molecular bonding and interaction among bonds; it is a convenient basis for investigation of charge transfer or conjugative interactions in molecular system [39].

NBO analysis is carried out by energetic examination of all possible interactions between 'filled' (donor) NBOs and 'empty' (acceptor) NBOs, and estimating their energetic

Table 6 Metoprolol NBO analysis

Donor NBO (i)	Acceptor NBO (j)	$E(2)$ kcal/mol	$E(i) - E(j)$ a.u.	$F(i, j)$ a.u.
BD (2) C1–C2	BD*(2) C3–C4	44.79	0.50	0.134
BD (2) C1–C2	BD*(2) C5–C6	35.48	0.49	0.119
BD (2) C3–C4	BD*(2) C1–C2	36.07	0.51	0.122
BD (2) C3–C4	BD*(2) C5–C6	44.47	0.50	0.135
BD (2) C5–C6	BD*(2) C1–C2	46.57	0.51	0.138
BD (2) C5–C6	BD*(2) C3–C4	35.18	0.51	0.120
LP (2) O7	BD*(2) C5–C6	30.14	0.68	0.137
LP (2) O10	BD*(1) C9–C11	10.26	1.14	0.097
LP (1) N12	BD*(1) C11–H28	11.69	1.16	0.105
LP (1) N12	BD*(1) C13–C14	11.09	1.08	0.098
LP (2) O18	BD*(1) C17–H40	8.52	1.19	0.091
LP (2) O18	BD*(1) C17–H41	8.63	1.19	0.091
LP (2) O18	BD*(1) C19–H43	8.97	1.19	0.093
LP (2) O18	BD*(1) C19–H44	8.34	1.18	0.090
BD*(2) C5–C6	BD*(2) C1–C2	627.11	0.01	0.124

Table 7 Atenolol NBO analysis

Donor NBO (i)	Acceptor NBO (j)	$E(2)$ kcal/mol	$E(i) - E(j)$ a.u.	$F(i, j)$ a.u.
BD (2) C1–C6	BD*(2) C2–C3	33.99	0.51	0.119
BD (2) C1–C6	BD*(2) C4–C5	43.16	0.50	0.134
BD (2) C2–C3	BD*(2) C1–C6	42.61	0.51	0.132
BD (2) C2–C3	BD*(2) C4–C5	31.55	0.50	0.114
BD (2) C4–C5	BD*(2) C1–C6	31.84	0.52	0.115
BD (2) C4–C5	BD*(2) C2–C3	46.65	0.51	0.139
LP (2) O7	BD*(2) C4–C5	38.98	0.67	0.154
LP (1) N12	BD*(1) C11–H29	12.08	1.12	0.105
LP (1) N12	BD*(1) C13–H31	11.04	1.16	0.102
LP (1) N18	BD*(2) C17–O19	59.39	0.73	0.186
LP (1) O19	RY*(1) C17	23.61	1.88	0.188
LP (2) O19	BD*(1) C16–C17	28.59	1.05	0.156
LP (2) O19	BD*(1) C17–N18	35.37	1.18	0.185
BD*(2) C4–C5	BD*(2) C1–C6	568.79	0.01	0.125
BD*(2) C17–O19	BD*(1) C17–O19	17.73	0.52	0.260

importance by 2nd-order perturbation theory. In this manner we obtained the energies of delocalization of electrons from filled NBOs into empty NBOs, e.g., we obtain stabilization energies gained by donation from the donor NBO to the acceptor NBO. In this way we are able to conclude which interactions among all possible interactions produce stability of certain molecule.

For each donor NBO (i) and acceptor NBO (j), the stabilization energy associated with $i \rightarrow j$ delocalization can be estimated on the basis of second order perturbation theory as:

$$E(2) = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_i \varepsilon j}, \tag{3}$$

where q_i is the donor orbital occupancy, ε_i, ε_j are diagonal elements (orbital energies) and $F(i,j)$ is the off-diagonal NBO Fock matrix element.

Table 8 Acebutolol NBO analysis

Donor NBO (i)	Acceptor NBO (j)	$E(2)$ kcal/mol	$E(i) - E(j)$ a.u.	$F(i, j)$ a.u.
BD(2) C1–C2	BD*(2) C3–C4	51.80	0.51	0.145
BD(2) C1–C2	BD*(2) C5–C6	31.10	0.50	0.112
BD(2) C3–C4	BD*(2) C1–C2	33.17	0.50	0.115
BD(2) C3–C4	BD*(2) C5–C6	49.19	0.49	0.140
BD(2) C3–C4	BD*(2) C7–O9	13.14	0.57	0.083
BD(2) C5–C6	BD*(2) C1–C2	53.12	0.51	0.146
BD(2) C5–C6	BD*(2) C3–C4	32.23	0.51	0.115
BD(1) C8–H29	BD*(2) C7–O9	10.09	0.93	0.087
LP(1) O9	RY*(1) C7	21.97	1.92	0.184
LP(2) O9	BD*(1) C4–C7	28.84	1.13	0.162
LP(2) O9	BD*(1) C7–C8	26.57	1.09	0.154
LP(2) O10	BD*(2) C5–C6	39.18	0.68	0.155
LP(2) O13	BD*(1) C12–H33	11.95	1.21	0.108
LP(1) N19	BD*(2) C20–O21	85.83	0.61	0.204
LP(1) O21	RY*(1) C20	23.12	1.88	0.186
LP(2) O21	BD*(1) N19–C20	35.57	1.18	0.185
LP(2) O21	BD*(1) C20–C22	28.25	1.07	0.157
BD*(2)C3–C4	BD*(2) C7–O9	16.36	0.07	0.065
BD*(2)C5–C6	BD*(2) C3–C4	646.00	0.01	0.126

In Tables 6, 7 and 8, the perturbation energies of significant donor-acceptor interactions are presented and significant interaction energies are given in bold and are commented. The larger the $E(2)$ value, the more intensive the interaction between electron donors and electron acceptors.

For metoprolol, we see that there is a much stronger interaction between BD * (2) C5–C6 and BD * (2) C1–C2, which has a value of 627 kcal mol^{-1}. Other significant interactions have values of 30–40 kcal mol^{-1}. Lone pair on O7 has the most significant interaction between interactions containing lone pairs, while the mean value of the significant interactions containing lone pairs is 12 kcal / mol.

For atenolol again we have a much stronger interaction than the other, between BD * (2) C4–C5 and BD * (2) C1–C6, whose energy is 569 kcal mol^{-1}, which is similar to, but not the same as that of metoprolol. Compared with metoprolol the most important interaction is weaker, about 10 %. Other significant interactions are in the range of 30–50 kcal mol^{-1}. Atenolol has six interactions containing lone pairs and significant amounts of energy on average 25 kcal mol^{-1}. The highest contribution to the interaction which has a lone pair is LP (1) with N18 BD * (2) C17–O19, with energy of 60 kcal mol^{-1}.

Concerning acebutolol, again we have one much stronger interaction with value of 646 kcal mol^{-1} (between BD*(2) C5–C6 and BD*(2) C3–C4). Other significant interactions have values ranging from 10 to 53 kcal mol^{-1}. This molecule is interesting because it has interaction including lone pair with highest contribution to stabilization of molecule among all investigated molecules, that is lone pair on N19 with corresponding energy of interaction of 86 kcal mol^{-1}. Average value of significant interactions including lone pairs is 33 kcal mol^{-1}, the highest among investigated molecules.

NPA analysis

To study the charge distribution of some molecule it is better to use natural population analysis (NPA) than Milliken one, since NPA do not exhibit dependence on basis set [40]. NPA is a part of full NBO analysis and results are presented in Table 9.

Acebutolol and atenolol have the two N atoms, rich in negative charge. One N atom is located almost in the same place in the molecule for all three molecules and the value of the charge of that N atom is about 0.75 e. However, in the acebutolol and atenolol the charge of the other two N atoms are significantly different and to almost 0.2 e. In the work [41] based on [42] is stated that the N atoms are rich in negative electric charge and significant for the overall bioactivity of some compounds. On this basis it is concluded that the examined compounds are highly bioactive. On the other hand, all hydrogen atoms have a positive electrical charge.

Table 9 NPA analysis—NPA charges of atoms

#	Acebutolol		Atenolol		Metoprolol	
	Atom	Charge	Atom	Charge	Atom	Charge
1	C	−0.1645	C	−0.1872	C	−0.1920
2	C	0.0935	C	−0.1077	C	−0.0816
3	C	−0.1465	C	−0.1881	C	−0.1947
4	C	−0.2141	C	−0.3288	C	−0.2680
5	C	0.4197	C	0.3855	C	0.3766
6	C	−0.3280	C	−0.2701	C	−0.3117
7	C	0.6939	O	−0.6062	O	−0.6182
8	C	−0.7241	C	−0.0586	C	−0.0481
9	O	−0.6292	C	0.1309	C	0.1370
10	O	−0.6293	O	−0.7962	O	−0.8033
11	C	−0.0462	C	−0.2297	C	−0.2309
12	C	0.1411	N	−0.7428	N	−0.7467
13	O	−0.8166	C	−0.0112	C	−0.0130
14	C	−0.2350	C	−0.6411	C	−0.6539
15	N	−0.7650	C	−0.6372	C	−0.6355
16	C	−0.0121	C	−0.5280	C	−0.4486
17	C	−0.6398	C	0.8489	C	−0.0153
18	C	−0.6399	N	−0.9238	O	−0.6456
19	N	−0.7523	O	−0.7245	C	−0.2209
20	C	0.8680				
21	O	−0.7227				
22	C	−0.5303				
23	C	−0.4222				
24	C	−0.6324				

Conclusions

This paper presents a computational study of representative β-blockers, which will in the relatively near future represent a significant environmental problem, since they are already significantly present in all types of water. The increasing use of drugs to control blood pressure leads to a situation where it is necessary to find effective ways of their elimination from the environment, which should always be preceded by computational theoretical analysis. Investigated compounds are quite stable and are among the group of mid aromatic compounds.

Aromaticity, estimated on the basis of nucleus independent chemical shift, was brought into correlation with the stability and the results obtained follow information related to the chemical harness.

Based on the MEP surfaces the products proposed have also been determined to be very stable, even more stable than their parent compounds, and the same case is seen with aromaticity which increase is followed by the increase of chemical hardness.

The calculated parameters of the 13C NMR chemical shifts are fully consistent with experimental results.

NBO analysis revealed which interaction contributed most to the stabilization of molecules, which is important considering experimentally determined persistence of these compounds.

NPA analysis confirmed enrichment by negative charge of N atoms.

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