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RESEARCH ARTICLE

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Thermodynamic and kinetic analysis of the reaction between biological catecholamines and chlorinated methylperoxy radicals

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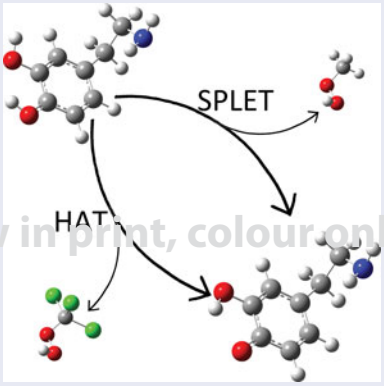
ABSTRACT

The antiradical potency of catecholamines (dopamine, epinephrine, norepinephrine, L-DOPA), metabolites of dopamine (homovanillic acid, 3-methoxytyramine and 3,4-dihydroxyphenylacetic acid) and catechol towards substituted methylperoxy radicals is investigated. The thermodynamic parameters, together with the kinetic approach, are used to determine the most probable mechanism of action. The natural bond orbital and quantum theory of atoms in molecules are utilised to explain the highest reactivity of trichloromethylperoxy radical. The preferred mechanism is dependent both on the thermodynamic and kinetic parameters and a number of chlorine atoms on radical, but also the presence of intra-molecular hydrogen bond and a number of hydroxy groups attached to the aromatic ring. The results suggest that sequential proton loss electron transfer (SPLET) is the most probable for reaction with methylperoxy and hydrogen atom transfer (HAT) for reaction with trichloromethylperoxy radicals, with a gradual transition between SPLET and HAT for other two radicals. Due to the significant deprotonation of molecules containing the carboxyl group, the respective anions are also investigated. The HAT and SPLET mechanisms are highly competitive in reaction with MP radical, while the dominant mechanism towards chlorinated radicals is HAT. The reactions in methanol and benzene are also discussed.



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Introduction

The extended amounts of free radicals in the human body, due to the environmental and modern factors, can cause diseases such as cancer, inflammation, hypertension and cardiovascular disorders [1,2]. The neurodegenerative disorders, in the first line Parkinson's, Alzheimer's and Huntingdon's, can also have a basis in oxidative stress and changes at the molecular level [2]. The processes include lipid peroxidation and a decrease in the concentration of neurotransmitters. Most of the natural and artificial antioxidants cannot pass the blood–brain barrier, so the molecules locally produced are gaining more and more attention [3]. Because more than 20% of oxygen is used in the brain, it is clear that the species present there are under constant exposure to the reactive oxygen species. Therefore, there is a persistent need for better understanding of mechanisms and reactivity of neurotransmitters [4–7]. The importance of neurotransmitters and their metabolites has been proven

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in vitro, experimentally towards superoxide anion [8], singlet oxygen [9,10], hydroxyl [11] and DPPH [9,12,13] radical.

Dopamine, epinephrine and norepinephrine are hormones in the central nervous system, and they are involved in the movement control, mood modulation, emotions, sleeping and other important functions. They are produced from 3,4-dihydroxy-L-phenylalanine (L-DOPA). The common structural element for the mentioned molecules is the catechol moiety, and that is the reason why this molecule is included in the study. The catechol moiety is a significant structural element for the antiradical scavenging activity, as shown in our previous examination [13,14]. Dopamine is decomposed into several metabolites, which also have an extensive role in the human body, and some of them are included in this contribution: 3-methoxytyramine (3-MT), homovanillic acid (HVA), 3.4-dihydroxyphenylacetic acid (DOPAC).

There are numerous attempts to quantify the antioxidant activity by employing various quantum-mechanical methods [15–18]. The reactions between the antioxidant molecule and free radical can proceed by either hydrogen atom transfer (HAT) or radical adduct formation (RAF). For the first process, there are three mechanisms discussed: HAT, single electron transfer followed by the proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET). It should be noted that the net reactions are the same. HAT mechanism is characterised by the rapid hydrogen atom abstraction from antioxidant to radical species (Equation (1)). One possibility of HAT mechanism is also the proton-coupled electron transfer, and, although biologically very important, it will not be considered in this contribution. SET-PT consists of two steps, first one being the electron transfer from the antioxidant to free radical and formation of cation radical which enters the second reaction and exchanges proton (Equations (2) and (3)). SPLET is also a two-step process, but the exchange of particles is a reverse of SET-PT (Equations (4) and (5)). Here it is assumed that some of the antioxidant molecules are in anionic form and the electron is transferred to the radical. The reaction enthalpies for the process are taken as the first step in the determination of the preferability of the process. Kinetic parameters for reactions, calculated by the Marcus and Transition State Theory approach, also present valuable data for comparison with experiment [19]. RAF is a simple mechanism of radical adduct formation between free radical and antiradical species (Equation (6)). This mechanism is important for systems containing the π conjugated systems, which is the case with the investigated molecules in this study [19,20]. The following notations,AOH,$AOH^{\bullet+}$,AO^- and $AO^\bullet$, are adopted for the neutral antiradical molecule, radical cation, anion and radical, respectively. The notation for species originated from free radical is analogous.

$$AOH + RO^\bullet \rightarrow AO^\bullet + ROH \quad (1)$$

$$AOH + RO^\bullet \rightarrow AOH^{\bullet+} + RO^- \quad (2)$$

$$AOH^{\bullet+} + RO^- \rightarrow AO^\bullet + ROH \quad (3)$$

$$AOH + RO^- \rightarrow AO^- + ROH \quad (4)$$

$$AO^- + RO^\bullet \rightarrow AO^\bullet + RO^- \quad (5)$$

$$AOH + RO^\bullet \rightarrow [AOH - RO]^\bullet \quad (6)$$

As the model system in this study, the differently substituted methylperoxy radicals, namely methylperoxy (MP), chloromethylperoxy (CMP), dichloromethylperoxy (DCMP) and trichloromethylperoxy (TCMP), were chosen to investigate the effects of electronegative element substitution on reaction parameters. Alkyl radicals also have an important role in free radical reactions in body, and chlorinated methylperoxy radicals are often studied as the model systems [21–23]. The carbon tetrachloride is a xenobiotic substance with hepatotoxic effect, which can be reduced in the human body by cytochrome P-450 [24]. This leads to the formation of trichloromethyl radical and, in the presence of oxygen, to TCMP radical [25]. Liver is not the only organ that can be a target of chlorinated peroxy radicals, but also other tissues such as heart, lung, brain and blood, kidneys (acute and chronic) and testis [26–28]. The reactions of chlorinated methylperoxy radicals are also examined experimentally towards the biologically important molecules and antioxidants [22,29–31], lycopene [32], other carotenoids [23] and non-steroidal anti-inflammatory drugs [33]. It was proven that these reactions are solvent polarity dependent [34]. On the other hand, methylperoxy radical and its reactions with good antiradical scavengers have been investigated both experimentally and theoretically [35,36].

In this contribution, the reactions between catecholamines and differently substituted methylperoxy radicals (mono, di, trichloro-) are investigated theoretically. The thermodynamic parameters for common mechanisms are calculated and discussed. Electron transfer reaction rates were also determined. The most favourable mechanism is therefore elucidated both from thermodynamic and kinetic parameters, and appropriability of their separate application is discussed.

Methods

The structures of the following molecules: dopamine, epinephrine, norepinephrine, catechol, L-DOPA, 3-MT, HVA, DOPAC, methylperoxy (MP), CMP, DCMP, TCMP radicals and adducts were optimised at the M06-2X/6-311G(d,p) level of theory in the Gaussian Program package [37]. The mentioned functional was chosen because it is recommended for the calculation of the thermodynamic parameters by various authors [38,39]. The solvent effects (water ($\varepsilon = 78.35$), methanol ($\varepsilon = 32.67$) and benzene ($\varepsilon = 2.27$)), as described by the Solute Electron Density Solvation Model (SMD) [40], were encountered to mimic the environment of the reactions. The solvents were chosen to investigate reaction in two polar (water and methanol) and one nonpolar (benzene) solvent. Five of the most stable structures of the antioxidant molecules were taken from literature and reoptimised at the given level [41–47]. The most stable conformer was taken for the calculation, and from this structure the radical cation, radical and anion structures were obtained. All of the structures were optimised without any geometrical constrains and the absence of the imaginary frequencies proved that the obtained conformers were the minima of the potential energy surface. The natural bond orbital (NBO) [48] analysis allowed the analysis of the donor–acceptor interaction within the structure of free radicals and calculation of the charges on their constituent atoms. Quantum theory of atoms in molecules (QTAIM) [49] was applied, using AIMAll Program package [50], for the investigation of the influence of substituents on the bond critical points (BCP) in the radical structure.

Thermodynamic parameters calculation

The thermodynamic parameters, namely bond dissociation enthalpy (BDE), ionisation potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), electron transfer enthalpy (ETE) and RAF enthalpy, defined within the four mechanisms, can be calculated as follows [51]:

$$\Delta H_{\mathrm{BDE}} = H(\mathrm{AO}^{\bullet}) + H(\mathrm{ROH}) - H(\mathrm{AOH}) - H(\mathrm{RO}^{\bullet}) \quad (7)$$

$$\Delta H_{\mathrm{IP}} = H(\mathrm{AOH}^{\bullet+}) + H(\mathrm{RO}^{-}) - H(\mathrm{AOH}) - H(\mathrm{RO}^{\bullet}) \quad (8)$$

$$\Delta H_{\mathrm{PDE}} = H(\mathrm{AO}^{\bullet}) + H(\mathrm{ROH}) - H(\mathrm{AOH}^{\bullet+}) - H(\mathrm{RO}^{-}) \quad (9)$$

$$\Delta H_{\mathrm{PA}} = H(\mathrm{AO}^{-}) + H(\mathrm{ROH}) - H(\mathrm{AOH}) - H(\mathrm{RO}^{-}) \quad (10)$$

$$\Delta H_{\mathrm{ETE}} = H(\mathrm{AO}^{\bullet}) + H(\mathrm{RO}^{-}) - H(\mathrm{AO}^{-}) - H(\mathrm{RO}^{\bullet}) \quad (11)$$

$$\Delta H_{\mathrm{RAF}} = H([\mathrm{AOH} - \mathrm{RO}]^{\bullet}) - H(\mathrm{AOH}) - H(\mathrm{RO}^{\bullet}) \quad (12)$$

Fukui functions

In this contribution, the Fukui functions are used for determination of the most probable reaction site for the radical attack. These parameters, as proposed by Parr and Yang, present the differential change in electron density when the total number of electrons is changed [52,53]. If the frozen orbital approximation is assumed, the electron densities for neutral molecule (ρ_N), radical cation (ρ_{N-1}) and radical anion (ρ_{N+1}) can be used to calculate the Fukui function for the radical attack:

$$f^0 = \frac{\rho_{N+1} - \rho_{N-1}}{2} \quad (13)$$

When Equation (13) is integrated for individual atoms, the so-called Fukui functions are obtained [54]. The radical attack site can be calculated as the difference between the charge on atom A of cationic (q^A_{N-1}) and anionic (q^A_{N+1}) species:

$$f^0_A = \frac{q^A_{N-1} - q^A_{N+1}}{2} \quad (14)$$

Electron-transfer reaction rate constant calculation

In the various contributions, the electron transfer reaction was proven to be a determining step. This type of reaction is present in two out of four most commonly investigated mechanisms: the first step of SET-PT and the second step of SPLET. The calculation of the reaction rate is based on the Marcus approach [55], as described here [13]. The reaction rate (k_{ET}) is dependent on the free energy of reaction (ΔG^0_{ET}) and the nuclear reorganisation energy (λ).

$$k_{\mathrm{ET}} = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}_{\mathrm{ET}}}{RT}} \quad (15)$$

$$\Delta G^{\ddagger}_{\mathrm{ET}} = \frac{\lambda}{4}\left(1 + \frac{\Delta G^0_{\mathrm{ET}}}{\lambda}\right)^2 \quad (16)$$

In Equation (15), k_B is the Boltzmann constant, h is the Planck's constant, T is temperature, R is the gas constant, $\Delta G^{\ddagger}_{\mathrm{ET}}$ is the activation energy. The reorganisational energy is defined as the difference between non-diabatic energy difference between reactants (ΔE_{ET}) and vertical products and the change in Gibbs free energy of reaction

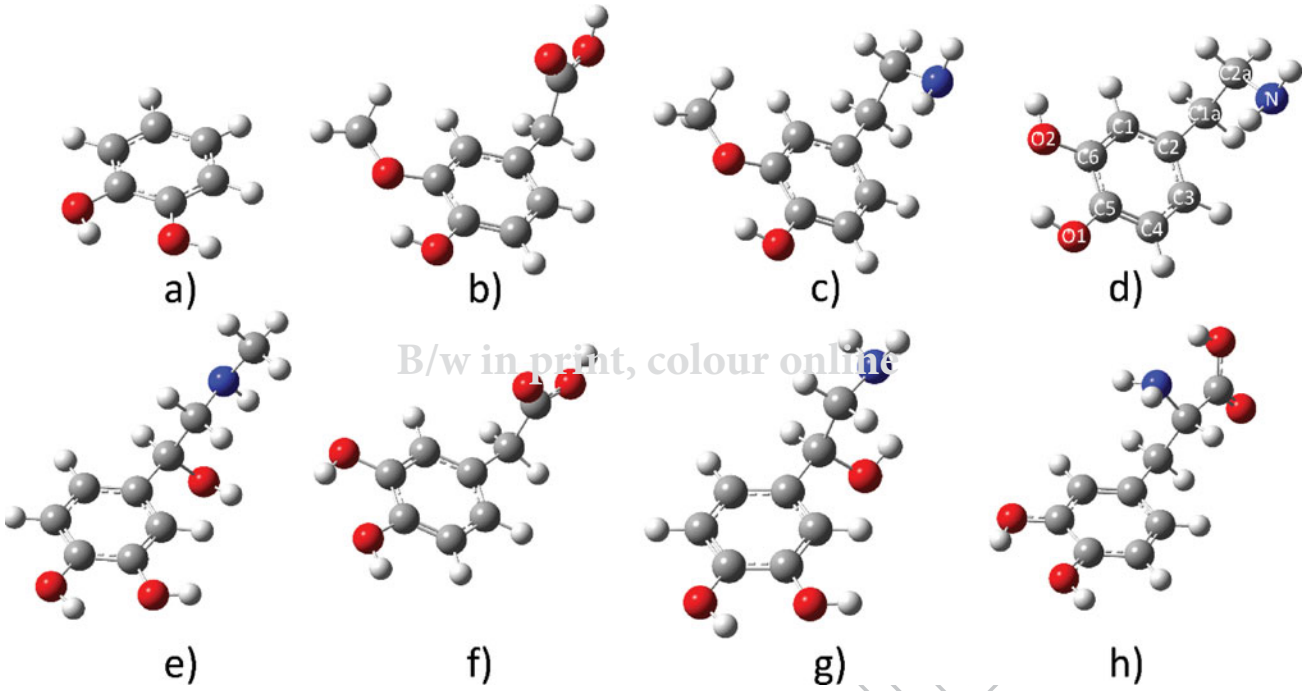

Figure 1. The most stable conformers of (a) catechol, (b) homovanillic acid, (c) 3-MT, (d) dopamine, (e) DOPAC, (f) epinephrine, (g) norepinephrine, (h) L-DOPA. The atoms numbering scheme is given for dopamine.

(ΔG^0_{ET}) [56,57].

$$\lambda \approx \Delta E_{ET} - \Delta G^0_{ET} \quad (17)$$

The calculated reaction rate is usually comparable to the diffusion-limited rate constant. The apparent rate constant (k_{app}) is then calculated as the correction to this value, according to the Collins–Kimball theory [58]:

$$k_{app} = \frac{k_D k_{ET}}{k_D + k_{ET}} \quad (18)$$

The steady-state Smoluchowski rate constant (k_D) [59], under the assumption of the irreversible bimolecular diffusion controlled reaction, is calculated in order to encounter diffusion as parameter. The diffusion-limited rate constant depends on the reactant distance (R), the diffusion coefficient of reactants (D_{AB}) and Avogadro's constant (N_A).

$$k_D = 4\pi \mathrm{R} D_{AB} N_A \quad (19)$$

The Stokes–Einstein theory allows the calculation of the diffusion coefficient (D_{AB}) from the diffusion constants of reactants A and B (D_A and D_B). These parameters can be estimated from Boltzmann's constant (k_B), temperature (T), viscosity of solvent (η) and radius of solvent (a) (Equation (10)) [59]. All of the reactions were investigated at 298 K.

$$D = \frac{k_B T}{6\pi \eta a} \quad (20)$$

Results and discussion

Thermodynamic investigation of the preferred mechanism in water

The most stable conformers of the investigated antiradical molecules are given in Figure 1. Based on the representation of their structures, it can be concluded that catecholamines and metabolites of dopamine possess various structural elements that can be significant for their good antiradical activity. Five molecules contain catechol moiety as mentioned in the 'Introduction' section; 3-MT and HVA have significantly lower activity towards radicals, as determined experimentally [13], because one of the hydroxy groups is substituted by the methoxy group. Epinephrine and norepinephrine also contain the side chain, hydroxy group. The ending group of the aliphatic chain can be used to divide investigated molecules into two distinct groups of those containing carboxyl group (DOPAC, L-DOPA and HVA) and amino group (epinephrine, norepinephrine, dopamine and 3-MT). The significant activity from these groups is not expected, as calculated in one of our previous contributions [13].

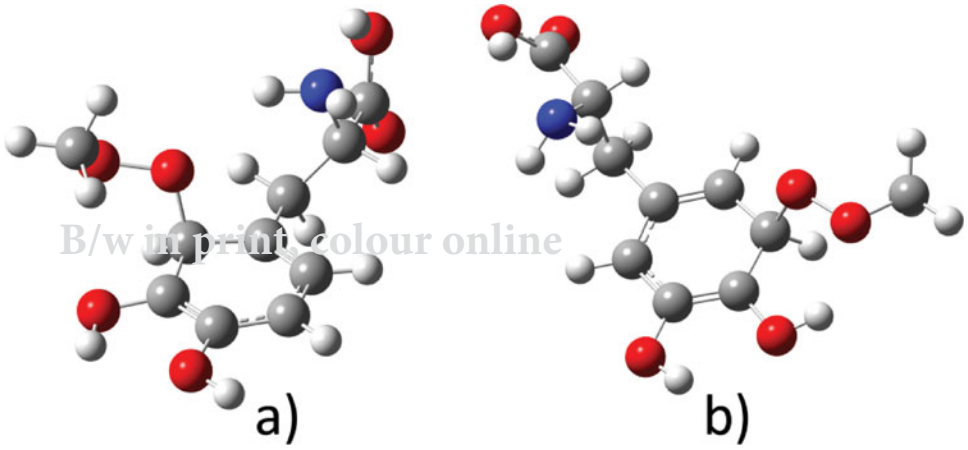

Figure 2. The radical adducts between methylperoxy radical and L-DOPA at positions (a) C1 and (b) C4.

Q7 The Fukui functions, described in the 'Methods' section, were employed to determine the most probable reaction sites for the RAF. The values of these parameters for the selected atoms are given in Supplementary material (Table S1). These results show that the *ortho*-positioned carbon on one side (denoted as C1) and *meta* on the other side (denoted as C4) to the aliphatic chain are the most suitable reaction sites for radical attacks. These two positions were further investigated and radical adducts optimised. The structures of methylperoxy adducts with L-DOPA are given in Figure 2 as an example. Based on the reaction enthalpies for these two positions, it was concluded that more stable radicals are formed at position 4, and these values are further used for the analysis and discussion.

The thermodynamic parameters for the reaction between dopamine and radicals in water, according to Equations (7)–(12), are presented in Table 1, in kJ mol^{-1}.

In general, the change in Gibbs free energy determines the spontaneity and preferability of different mechanisms. But the differences in calculated change in Gibbs free energy and enthalpy of reaction are small. Therefore, it is common to discuss the preferability of the mechanism based on the value of the second. The lower values represent the more probable reaction mechanisms. From the data presented in Table 1, it can be concluded that all investigated mechanisms give endothermic reactions (except for RAF with MP and CMP), but the value of enthalpy depends both on the investigated molecule and radical. The HAT mechanism enthalpies show that as the number of chlorine atoms increases, the spontaneity increases, with the difference between reaction enthalpies with methylperoxy and TCMP radicals of 40 kJ/mol. The first step of the SET-PT mechanism is very unfavourable, but the value lowers with the increase in a number of chlorine atoms. At the same time, the favourability of the second step increases. It is interesting to observe that the value of the enthalpy change for the first step of SPLET mechanism becomes positive as the number of chlorine atoms increases, proving that this reaction becomes more and more unfavourable. The enthalpies for RAF mechanism also change sign as the number of chlorine atoms increases (from 29 to −19 kJ mol^{-1}). When the values for RAF, BDE, IP and PA are compared, it can be concluded that HAT mechanism is the preferred mechanism for the reaction, with exception of methylperoxy radical when HAT and SPLET mechanisms are highly competitive. Because of that, the special attention to the kinetic investigation of the first step of SPLET is given in the second part of the paper. The value of IP is significantly higher than the other two, and the possible explanation is given in the last section of this contribution.

Table 1. Thermodynamic parameters for the reaction between dopamine and differently substituted methylperoxy radicals (in kJ mol^{-1}).

	Aqueous phase					
	RAF	HAT	SET-PT		SPLET	
	RAF	BDE	IP	PDE	PA	ETE
MP	29	−24	120	−144	−29	5
CMP	0	−34	89	−123	−8	−26
DCMP	−4	−53	51	−104	12	−65
TCMP	−19	−63	27	−90	25	−88

NBO and QTAIM analyses of free radicals

According to Bent's rule, s-character is concentrated in orbitals directed toward more electropositive substituents [60]. In these cases, the carbon is more electropositive than chlorine. It means that the bonds between chlorine and carbon have more s-character around the

Table 2. Spin density and charge distribution on oxygen atoms in radicals).

	Spin density		Charge	
	O1[a]	O2	O1	O2
MP	0.66	0.34	− 0.22	− 0.16
CMP	0.70	0.30	− 0.17	− 0.19
DCMP	0.73	0.27	− 0.13	− 0.20
TCMP	0.75	0.24	− 0.10	− 0.22

[a] O1 represents atom further from the methyl group, and O2 atom directly attached to side group.

Table 3. QTAIM parameters for the BCP of interest in radicals.

	$\rho(r)$ (a.u.)		$\nabla^2\rho(r)$ (a.u.)	
	O1-O2	O2-C	O1-O2	O2-C
MP	0.424	0.233	− 0.376	− 0.179
CMP	0.423	0.244	− 0.365	− 0.444
DCMP	0.420	0.259	− 0.357	− 0.598
TCMP	0.423	0.262	− 0.360	− 0.646

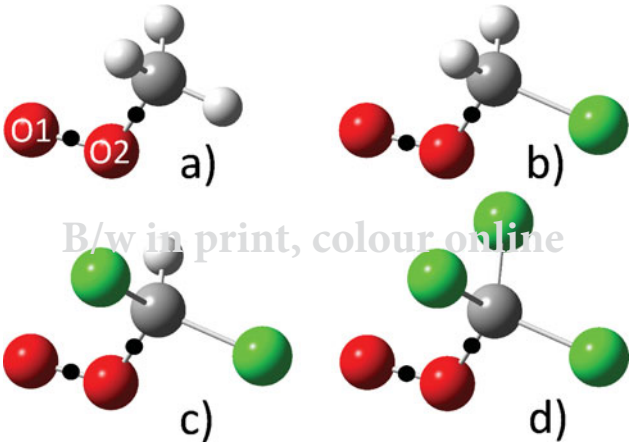

Figure 3. Structures of radicals: (a) methylperoxy (MP), chloro- (CMP), dichloro- (DCMP) and trichloromethylperoxy (TCMP). Black dots represent the bond critical points (BCP) of interest.

chlorine and more p-character around the carbon atom in CMP, DCMP and TCMP. This s-character concentrated toward the chlorine affects the bond angle and bond length. Bigger p-character around the carbon in these compounds weakens the carbon–chlorine bond relative to the bond in carbon tetrachloride. The average carbon–chlorine bond lengths in CMP, DCM and TCMP are 1.763, 1.759 and 1.753 Å, while the Cl-C-Cl angles in the last two are 112.4° and 111.5°. As it can be observed with the increased number of chlorine atoms, the bonds are stronger and the s-character increases. The different reactivity towards radicals is further explained by means of the NBO analysis of the radicals. The spin density and charge distribution on oxygen atoms of free radicals are given in Table 2. Figure 3 shows the positions of O1 and O2, as well as the optimised structures of radicals.

The spin density and charge distribution on oxygen atoms change uniformly as chlorine atoms are added. The most electronegative oxygen atom is in MP and the charge decreases as a number of chlorine atoms are added. The charge in radicals is shifted to the second oxygen atom because of the electronegative substituents from MP to TCMP. If data for spin density are considered, the same trend is observed. The oxygen atom directly attached to the methyl group has lower spin density than the one further from this group. This table shows that the reactivity of the radicals increases with chlorine atoms addition due to the strong inductive effect of this atom and a relative deficiency in electrons in the other parts of the molecule. The spin density is concentrated on oxygen atom further from methyl group, which makes it the most reactive site of the molecule. The change in spin density and charge of O1 is not as drastic as expected with the change in substituents. It can be assumed that the addition of chlorine atoms does not change the charge and spin density significantly because of the distance between O1 and methyl group. To verify this result, the QTAIM analysis is performed for the BCP of O1-O2 and O2-C1 bonds in radicals (Table 3 and Figure 3). By this analysis, proposed by Bader [61], two types of interactions are possible: shared interactions (covalent bonds) with electron density of the order of 0.1 eA and large negative Laplacian, and closed shell interactions (ionic bonds, hydrogen bonds and van der Walls interactions) with electron density in the range between 0.001 and 0.040 eA and positive Laplacian.

Based on the QTAIM analysis parameters, both of the bonds fall into the category of the covalent bonds. The electron density in O2-C bond increases with the addition of chlorine atoms, while the Laplacian decreases. The BCP parameters are almost constant for all of the radicals, with slight variations that are much lower than for the previously discussed bond. This proves that O2-C bond is much more affected by the presence of the electronegative chlorine atoms. The change in electron density and Laplacian can be used as the measure of the bond strength change. Therefore, the bond strength between O2 and C1 is affected by the presence of substituents, while the bond between O1 and O2 is almost intact [62]. The results of QTAIM analysis have shown that the addition of chlorine atoms changes the bond strength and the structure of radicals, but the O1 atom is not influenced significantly.

Based on both NBO and QTAIM analyses, the reactivity of radicals is the consequence of both spin density and charge distribution, which might also determine different mechanisms for the antiradical activity of catecholamines and their metabolites.

Table 4. Thermodynamic parameters for the reaction between investigated molecules and radical species (reaction site *p*-OH, in kJ mol^{-1}).

	MP						TCMP					
	RAF	HAT	SET-PT		SPLET		RAF	HAT	SET-PT		SPLET	
	ΔH_{RAF}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}	ΔH_{RAF}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}
3-MT	29	−17	116	−133	−15	−3	−20	−56	23	−79	40	−96
HVA	39	−13	123	−136	−18	5	−9	−51	30	−81	37	−88
DOPAC	33	−20	128	−148	−34	12	−9	−59	35	−94	22	−81
Dopamine	29	−24	122	−146	−29	5	−19	−63	27	−90	25	−88
Catechol	39	−18	131	−149	−33	15	−1	−57	38	−95	22	−79
Epinephrine	39	−22	124	−146	−32	10	−7	−61	31	−92	22	−83
Norepinephrine	31	−21	125	−146	−32	11	−13	−60	31	−91	22	−82
L-DOPA	24	−34	113	−147	−41	7	−20	−73	20	−92	14	−86

Influence of the structure of antiradical scavenger on the reactivity towards differently substituted methylperoxy radicals

The thermodynamic parameters for the reaction of investigated molecules towards methylperoxy and TCMP radicals are given in Table 4. These two are chosen to examine the behaviour towards the most distinct radicals. The values for the other two radicals are given in Supplementary Material (Tables S3–S6). The introspection of Table 4 leads to the conclusion that the net reactions towards both the radicals are mainly exothermic for all of the investigated species, although there are variations in the preferability of the mechanisms. Only the RAFs between antiradical species with MP are endothermic, but the value for reaction enthalpy changes sign when three chlorine atoms are added. Solely based on BDE values molecules with one hydroxy group attached to the aromatic ring have a lower probability of being good radical scavengers. The most potent antiradical molecule is L-DOPA, with a difference of 20 kJ mol^{-1} between this molecule and HVA. The formation of the intra-molecular hydrogen bond, when the anion is formed, is one of the reasons for lower values of thermodynamic parameters for molecules with a catechol moiety. This result is in accordance with the experimental antiradical activity comparison of the investigated molecules [8,9,11,63]. The enthalpy of the first step of SPLET is comparable to BDE value for all of the investigated molecules. The difference between PA and BDE is between 5 and 13 kJ mol^{-1}. It should be beared in mind that the proton transfer is very fast process, and therefore it is never the limiting factor. This is expected because in a polar solvent the formation of intermediate ionic species is promoted, and the electron transfer process is highly favoured [59]. In the next section, the preferability of SPLET is discussed from the mechanistic point of view because the second step is endothermic. The least favourable mechanism is SET-PT because IP values are of the order of 120 kJ mol^{-1}.

The situation is changed when the reaction with TCMP is considered. The BDE value is much lower than the IP and PA, on average 40 kJ mol^{-1}. This proves that thermodynamically HAT is the most probable mechanism. On the contrary to the previous radical, the values for PA and IP are almost the same, and both are positive. Based on the Bell–Evans–Polanyi principle, the reactions that are endothermic are not expected to occur at significant rates. The second step of both mechanisms is of the order of −90 kJ mol^{-1}. The values for BDE are lower for the molecules containing catechol moiety, like L-DOPA. Dopamine, epinephrine and norepinephrine have the values of BDE within 2 kJ mol^{-1}, which verifies the experimentally determined similar antioxidant activity [8,9,12,13]. The RAF mechanism is becoming more and more important with the addition of chlorine atoms, but the values for enthalpy are still higher than BDE. Therefore, it can be concluded that RAF is not the dominant mechanism in this model system and it would not be further discussed in this contribution.

Just based on the values presented in Table 4 it is not possible to determine the absolute order of the scavenging activity of selected molecules. These findings suggest that the thermodynamic parameters can be ambiguous if only the enthalpies are compared. But is should be beared in mind that molecules containing the catechol moiety can donate hydrogen atom from both hydroxy groups. The results for the thermodynamic parameters for the *m*-OH group breakage, concerning the aliphatic chain, are given in Table 5 to thermodynamically investigate the reaction from this site as well.

Reaction enthalpies presented in Table 5 demonstrate that the *m*-positioned hydroxy group plays an important role for the antiradical activity, comparable to that of *p*-OH. The values for thermodynamic parameters are still lower than for the molecules with one hydroxy group directly attached to the aromatic ring, which also confirms the importance of intra-molecular hydrogen bond

Table 5. Thermodynamic parameters for the reaction between investigated molecules and radical species (reaction site *m*-OH, in kJ mol^{-1}).

	MP					TCMP				
	HAT	SET-PT		SPLET		HAT	SET-PT		SPLET	
	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}
DOPAC	− 19	128	−148	−33	14	−58	35	−93	21	−79
Dopamine	−19	120	−139	−31	12	−58	27	−85	24	−81
Catechol	−18	131	−149	−33	15	−57	38	−95	22	−79
Epinephrine	−20	124	−144	−33	13	−59	31	−90	21	−80
Norepinephrine	−18	125	−142	−32	14	−56	32	−88	22	−79
L-DOPA	−31	113	−144	−42	11	−70	20	90	12	−82

for radical and anion stability. When these values are compared with enthalpies from Table 4 for *p*-OH, it can be concluded that for the reaction with MP, these two positions are competitive because of the similar value of PA (which on average differ for 1 kJ mol^{-1}). On the other hand, for the reactions that happen via HAT mechanism, the more favourable position is *p*-OH because of the lower BDE value. Although *m*-OH is important for the antiradical activity, the kinetic investigation in the next section will be performed only for the *p*-position. These results also suggest that highest antiradical activity is expected for molecules with two OH groups attached to the aromatic ring.

Galano and Alvarez-Idaboy discussed that, when reaction pathways are concerned, protonated/deprotonated forms should also be investigated [19]. For the molecules of interest, only those containing the carboxyl group are expected to be significantly deprotonated at physiological pH (7.4). Based on the procedure suggested in reference [19] and experimental values of p*Ka* [64], this percentage was determined. The amount of deprotonated form was estimated to be 99.8% for HVA, 99.5% for DOPAC and 97.5% for L-DOPA, which proves the necessity to investigate the thermodynamics of the reaction between radicals and respective carboxylate anions. The changes in enthalpy for all possible species formed from anions and MP/TCMP are given in Table 6, while for the other two radicals data are shown in Table S7.

The values shown in Tables 6 and S7 demonstrate that the formation of anions does not influence the spontaneity of the process significantly. Only reaction enthalpies for the RAF mechanism with MP radical are positive. When thermodynamic parameters for the first step of each mechanism are compared, it can be concluded the HAT and SPLET mechanisms are highly competitive for reaction of carboxylate anions with MP radical, while the most probable mechanism for other presented radicals is HAT. These results are similar to those obtained for the protonated species. Results presented in Table 6 also justify that *p*-OH position is slightly more reactive than *m*-OH group. Due to the reduced probability of SPLET mechanism for reactions with carboxylate anions, the reaction rates are not calculated. But it is important to conclude that molecules that contain carboxyl group are almost fully deprotonated at physiological pH and that there is a competition between HAT and SPLET for non-chlorinated methylperoxy radical. On the other hand, HAT is the most probable mechanism when chlorine atoms are added.

Kinetic investigation of the electron-transfer reactions in water

According to Marcus' approach, the important parameters for the investigation of the electron transfer reactions are the change in Gibbs free energy of reaction, reorganisational energy and diffusion rate constant. The calculated values of the electron transfer reactions in the second step of SPLET are presented in Table 7. The rate constants for the first step of SET-PT are given in Table S8.

Table 6. Thermodynamic parameters for the reaction between formed carboxylate anions and radical species (in kJ mol^{-1}).

		MP						TCMP					
		RAF	HAT	SET-PT		SPLET		RAF	HAT	SET-PT		SPLET	
		ΔH_{RAF}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}	ΔH_{RAF}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}
DOPAC-COO$^-$	*m*-OH	31	−24	112	−136	−28	4	−11	−63	19	−82	26	−89
	p-OH		−28	112	−140	−26	−2		−67	19	−86	28	−95
L-DOPA-COO$^-$	*m*-OH	34	−23	114	−137	−28	5	−9	−62	21	−83	27	−89
	p-OH		−27	114	−142	−26	−1		−66	21	−87	28	−94
HVA-COO$^-$	*p*-OH	37	−20	108	−127	−12	−8	−11	−58	15	−73	43	−101

Table 7. Rate constants for the reaction between investigated molecules and MP radical.

	MP			
	ΔG^0_{ET} (kJ mol^{-1})	Λ (kJ mol^{-1})	k_{ET} (M^{-1} s^{-1})	k_{app} (M^{-1} s^{-1})
3-MT	− 6	18.0	3.0×10^{10}	3.2×10^{9}
HVA	8	63.9	1.8×10^{9}	1.2×10^{9}
DOPAC	13	67.7	3.7×10^{8}	3.3×10^{8}
Dopamine	12	60.5	9.9×10^{8}	7.6×10^{8}
Catechol	15	66.9	2.7×10^{8}	2.5×10^{8}
Epinephrine	12	71.0	1.0×10^{9}	3.4×10^{8}
Norepinephrine	12	70.2	3.7×10^{8}	3.3×10^{8}
L-DOPA	7	68.2	1.5×10^{9}	1.0×10^{9}

Based on the data presented in Table 7, it can be concluded that the values for the change in Gibbs energy for reaction with MP are positive, except for 3-MT. This is consistent with Table 5 where reaction enthalpies are considered. The thermodynamic parameters suggest that this reaction is not spontaneous and the reaction rate constants were calculated as discussed previously. The electron transfer rate constant is of the order 10^8-10^9 M^{-1} s^{-1} for molecules with catechol moiety and 10^{10}-10^{11} M^{-1}s^{-1} for molecules with one OH group. When the apparent rate constant is corrected for diffusion, the values are of the order of 10^9. Several orders of magnitude lower rate constant is the consequence of the diffusion limited rate. Results presented in Table 7 suggest that the limiting factor in reaction with catecholamines and their metabolites with MP is diffusion, so it can be concluded that this is a kinetically driven process. These rate constants are of the same order of magnitude as those calculated by other authors who investigated the protonated form of dopamine, epinephrine and norepinephrine [15,59,65]. These findings suggest that the protonation of the antiradical molecule does not play an important role because the reactive sites are not the protonated groups. Only with the results for thermodynamic parameters, as presented in Tables 4 and 5, it can be confirmed that SPLET is the most probable mechanism with MP radical. One more validation for this finding is the charge distribution on free radical presented in Table 2. Because of high electronegativity of the first oxygen atom it is reasonable to conclude that proton is transferred in the first step and then followed by electron in second. The electron transfer reaction as the first step of SET-PT is also investigated, and the rate constants are given in Table S8, of the order of 10^{-10}-10^{-11}, are in good accordance with the assumption that this is the least favourable mechanism of the antiradical activity.

On the other hand, the reaction with TCMP, according to thermochemistry of the SET-PT and SPLET, is highly unfavourable because of the exothermic first step, as given in Table 8. The reaction rates are calculated to verify the preferability of HAT mechanism and demonstrate the ambiguity of the use of kinetic parameters without thermodynamic ones.

The values for electron transfer reaction rates in two different mechanisms (Table 8) for the reaction between antioxidants and TCMP suggest that this process is diffusion controlled in the case of SPLET, while the limiting factor in the first step of SET-PT is the thermodynamics of process. The electron transfer as the second step of SPLET is highly exergonic with rate constants of the order 10^9, which is comparable to the previously examined reaction. The rate constants for electron transfer in SET-PT are endergonic with values that are four orders of magnitude slower. High reaction rates for electron transfer and formation of respective radical cations are expected because of the favourability of the ion formation in polar media. Therefore, it can be concluded that these two mechanisms are kinetically and solvent polarity favourable, but thermodynamically not. The results for spin density and charge distribution (Table 2) show that the spin density is the highest on the first oxygen atom while the charge distribution is pulled towards the electronegative substituent. Therefore, it is expected that the reduction of free radical happens through the exchange of hydrogen atom. These findings lead to the conclusion that the most favourable mechanism for reaction with TCMP is HAT.

The important question raised in this contribution is the low preferability of SET-PT mechanism for all of the investigated reactions. In the first step, the radical cation is formed and electron transferred on radical species. In polar solvent, this type of reaction should be spontaneous because of the ion formation and it is somewhat analogous to SPLET.

The NBO analysis is used to obtain the possible explanation based on the stabilisation interaction formed within molecule that stabilises the newly formed species. The stabilisation interaction between *p*-O and *m*-OH is observed in all of the investigated species, except in anionic form of 3-MT and HVA because of the proton

Table 8. Rate constants for the reaction between investigated molecules and TCMP radical.

	SET-PT				SPLET			
	$G_{ET}^{0\Delta}$ (kJ mol^{-1})	Λ (kJ mol^{-1})	k_{ET} (M^{-1} s^{-1})	k_{app} (M^{-1} s^{-1})	ΔG_{ET}^{0} (kJ mol^{-1})	Λ (kJ mol^{-1})	k_{ET} (M^{-1} s^{-1})	k_{app} (M^{-1} s^{-1})
3-MT	19	79.1	2.8×10^{7}	2.7×10^{7}	−98	72.9	2.8×10^{12}	3.2×10^{9}
HVA	31	83.4	8.0×10^{5}	8.0×10^{5}	−88	72.7	4.5×10^{12}	3.7×10^{9}
DOPAC	37	83.3	1.4×10^{5}	1.4×10^{5}	−82	76.5	5.9×10^{12}	3.7×10^{9}
Dopamine	28	82.0	2.3×10^{6}	2.3×10^{6}	−84	69.2	4.6×10^{12}	3.2×10^{9}
Catechol	39	82.7	1.0×10^{5}	1.0×10^{5}	−81	75.7	6.0×10^{12}	3.2×10^{9}
Epinephrine	34	86.0	3.2×10^{5}	3.2×10^{5}	−84	79.8	6.1×10^{12}	3.2×10^{9}
Norepinephrine	35	82.8	2.9×10^{5}	2.9×10^{5}	−83	79.0	6.1×10^{12}	3.2×10^{9}
L-DOPA	16	105.7	5.0×10^{6}	5.0×10^{6}	−89	77.0	5.2×10^{12}	3.2×10^{9}

Table 9. The energy (in kJ mol^{-1}) of donor–acceptor interactions between hydroxy groups of catechol moiety or hydroxy and methoxy group in neutral, radical and anion species of investigated molecules.

	Neutral species	Radical cation	Anion
3-MT	5.19	2.34	2.26
HVA	5.23	2.17	/
DOPAC	3.14	1.46	/
Dopamine	3.09	1.63	2.21
Catechol	3.14	1.33	2.23
Epinephrine	3.22	1.55	2.26
Norepinephrine	3.43	1.84	2.29
L-DOPA	4.01	1.38	2.23

loss (values are given in Table 9). The hydrogen bond interaction is much stronger in neutral form of these two molecules because of the charge distribution and electronegativity of *p*-O. This interaction is more than two times weaker in the radical form, which leads to the lower stability of this type of species and thermodynamically lower preferability of mechanism in which radical is formed. The hydrogen bond is weaker in anionic form as well, but still stronger than in radical cation. Because of the lower stability of the species, the mechanism of antiradical activity depends significantly on the stability of species formed from free radical. With all that is previously mentioned, it is important to conclude that the preferability of the mechanism depends both on the stability and charge distribution in formed molecules.

Thermodynamic investigation of the preferred mechanism in methanol and benzene

The results for thermodynamic parameters in methanol and benzene are given in Tables S1–S4, except for the RAF which is not investigated in solvents other than water. The reaction enthalpies in methanol, as polar solvent, are analogous to those obtained for water; the actual values are different for 3–5 kJ mol^{-1}. The reaction enthalpy of the PA is comparable with BDE in methanol. Therefore, it can be concluded that for this radical the actual mechanism is ambiguous. As the number of chlorine atoms increases, the preferability of HAT mechanism is enhanced and for the reaction with TCMP, this is the most preferred mechanism in methanol (Table S4). The IP values are higher than PA and BDE for all the investigated molecules, so SET-PT is not a plausible mechanism in methanol either. In nonpolar solvent, the SPLET and HAT mechanisms are usually competitive [66]. In the chosen system, the values for PA are lower than BDE for the first investigated radical for more than 60–80 kJ mol^{-1} and this difference decreases, which makes SPLET the preferred mechanism in benzene. The order is reversed for the reaction with TCMP, and the values of BDE are lower for 40–60 kJ mol^{-1}. This is in accordance with the results obtained for reactions in water, proving that the reaction mechanism is dependent on the structural parameters of radicals. The average values of IP are 400 kJ mol^{-1}, for the reaction with MP, and 260 kJ mol^{-1} for the reaction with TCMP. HAT is the dominant mechanism with CMP and DCMP in all solvents.

Conclusions

In this contribution, the natural antioxidant molecules present in the body (dopamine, epinephrine, norepinephrine, catechol, DOPAC, L-DOPA, HVA and 3-MT) were investigated for the reactivity towards differently substituted chlorinated methylperoxy radicals (MPs). These radicals were chosen to determine the dependence of thermodynamic and kinetic parameters on the number of chlorine atoms. The reactions with MPs are exothermic in most cases, proving the possible antiradical activity that is dependent on the structure of radical. Through the calculation of charge density and spin distribution, it was shown that the oxygen further from methyl group is the most reactive site. The spin density increases and charge decreases with a number of chlorine atoms leading to the highest reactivity of TCMP radical. The QTAIM analysis showed that

the bond between two oxygen atoms is not significantly affected by the substituents. The preferability of the mechanism was discussed based on the reaction enthalpies and reaction rates for the electron transfer. RAF was investigated based on the Fukui functions of the reaction sites. The enthalpies for adduct formation are positive for methylperoxy radical, but their value becomes negative with the addition of chlorine atoms. The adduct formation cannot be considered as a dominant process because reaction enthalpies are higher than for the other three investigated mechanisms. The values of thermodynamic parameters for reaction with methylperoxy radical are comparable for SPLET and HAT. Since the reaction rates for the first step of SPLET are of the order 10^9 $M^{-1}s^{-1}$ it was concluded that this is the most probable mechanism. The charge distribution on oxygen atom in free radical also favours the proton transfer followed by the electron transfer. In spite of the fact that the electron transfer rates are high in the case of TCMP radical, by the reaction enthalpies, the dominant mechanism is HAT. The spin density on oxygen atoms promotes the rapid exchange of hydrogen atom. The low preferability of SET-PT is a consequence of the lower stability of the formed radical cation due to the decrease in hydrogen bond strength, as determined by NBO analysis. The molecules with two neighbouring OH groups attached directly to aromatic ring have significantly higher antiradical activity because of the hydrogen bond formed and a higher number of active sites. The reactions in methanol and benzene were also investigated. The percentage of deprotonated forms of molecules containing carboxyl group was estimated to be 99.8% for HVA, 99.5% for DOPAC and 97.5% for L-DOPA. Due to this high percentage, the reactions between radicals and carboxylate anions were investigated. The most probable mechanisms in reaction with MP are HAT and SPLET, while HAT is the dominant mechanism with CMP, DCMP and TCMP. The results in methanol are analogous to those in water, with values being within 10 kJ mol^{-1}. The thermodynamic parameters in benzene are even more prominent in favour of the discussed preferred mechanisms in water, proving that SPLET is the dominant mechanism for reaction with methylperoxy and HAT for the reaction with TCMP radicals.

Disclosure statement

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