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Adrenaline and Noradrenaline: Protectors against Oxidative Stress or Molecular Targets?

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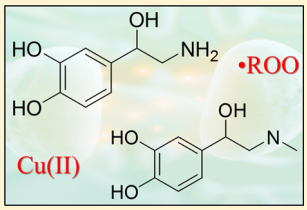
Supporting Information

ABSTRACT: Density functional theory was used to investigate the potential role of neurotransmitters adrenaline and noradrenaline regarding oxidative stress. It is predicted that they can be efficient as free radical scavengers both in lipid and aqueous media, with the main reaction mechanism being the hydrogen transfer and the sequential proton loss electron transfer, respectively. Despite the polarity of the environment, adrenaline and noradrenaline react with •OOH faster than Trolox, which suggests that they are better peroxyl radical scavengers than the reference compound. Both catecholamines are also proposed to be capable of efficiently inhibiting the oxidative stress induced by copper(II)−ascorbate mixtures, and the •OH production via Haber−Weiss reaction, albeit the effects on the later are only partial. They exert such beneficial effects by sequestering Cu(II) ions. In summary, these catecholamines can be capable of reducing oxidative stress, by scavenging free radicals and by sequestering metal ions. However, at the same time they might lose their functions in the process due to the associated structural modifications. Consequently, adrenaline and noradrenaline can be considered as both protectors and molecular targets of oxidative stress. Fortunately, under the proper conditions, both catecholamines can be regenerated to their original form so their functions are restored.

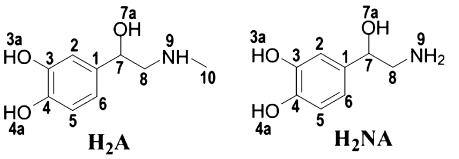


INTRODUCTION

From a chemical point of view oxidative stress (OS) can be defined as a chemical imbalance between the production and consumption of oxidants, particularly free radicals (FRs).[1] There are numerous reports providing evidence on the role of OS, and excess of FRs, in the onset and development of a large number of health disorders. OS has been associated with pulmonary,[2−4] renal,[5−7] and ocular[8−10] diseases; rheumatoid arthritis;[11−13] fetal growth restriction; and preeclampsia.[14−16] It has also been established that oxidative damage is responsible, at least partially, for cancer development.[17−19] OS has been reported to be involved in several neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, memory loss, and depression.[20−26] There is also evidence supporting the role of OS in several cardiovascular diseases including atherosclerosis, ischemia, cardiac hypertrophy, cardiomyopathy, hypertension, and congestive heart failure.[27−30] OS can be associated with chemical damage to essential biomolecules including lipids, proteins, DNA, enzymes, and neurotransmitters, etc. Thus, studying in detail the chemical reactions involved in such damages is an important, and active, area of research.

Adrenaline ((*R*)-4-(1-hydroxy-2-(methylamino)ethyl)-benzene-1,2-diol) and noradrenaline (4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol) are catecholamine neurotransmitters produced by the nervous system. They are also known as epinephrine and norepinephrine, and herein they are referred to as H_2A and H_2NA, respectively (Scheme 1). Adrenaline is released by the sympathetic nervous system and adrenal medulla and is involved in several physiological functions including regulation of blood pressure, vasoconstriction, cardiac stimulation, and regulation of the blood glucose levels.[31−34] It also has multiple clinical applications such as treating anaphylaxis,[35,36] angioedema,[37] acute asthma,[38] and cardiac arrest.[39] Noradrenaline is mainly produced by neurons within the locus coeruleus (LC) and takes part in diverse motor and mental functions including locomotion control, motivation, attention, cognition, and memory formation.[40] It also regulates the differentiation, plasticity, and survival of neurons in both developing and adult brains.[41−44] In addition, it seems that the LC−noradrenaline system plays a crucial role in compensatory mechanisms responding to acute brain injuries, and in defining the progression of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.[45]

Scheme 1. Structures and Site Numbering of Adrenaline (H_2A) and Noradrenaline (H_2NA)



Regarding the relationship of these molecules with OS, two possible outcomes can be anticipated. They can be involved in OS related processes as protectors but also as vulnerable

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targets. There is evidence on their potential role as protectors against the deleterious effects of OS. It has been reported that adrenaline can behave as an efficient antioxidant, and FR scavenger, in several in vitro assays including reducing power, 2,2-diphenyl-1-picrylhydrazyl radical ($DPPH^{\bullet}$), 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation ($ABTS^{\bullet+}$), dimethyl-4-phenylenediamine radical cation ($DMPD^{\bullet+}$), and $O_2^{\bullet-}$ radical scavenging, hydrogen peroxide scavenging, and metal chelating activities.[31] Noradrenaline has been reported to be able of providing short-term protection against the β-amyloid-induced neurotoxicity associated with the Alzheimer's disease (AD).[46] Accordingly, it was proposed that noradrenaline, or other catecholamines, and thiol-reducing antioxidants might be considered as a supplementary therapeutic strategy to reduce neural death in patients with AD. There is also evidence that intracellular reactive oxygen species are significantly reduced by treatments with noradrenaline, indicating that it can also exhibit antioxidant properties.[47] Based on this finding it was proposed that noradrenaline provides long-term protection to dopaminergic neurons, probably by reducing oxidative stress. Moreover, it was hypothesized that OS prevention may be one of the mechanisms by which neurotransmitters could exert neuroprotective functions in the brain.[47] This hypothesis is in line with the idea that pharmacological protocols designed to increase extracellular levels of noradrenaline, and probably of other catecholamines, might be useful in treating neurodegenerative disorders currently associated with OS, such as Parkinson's disease.

The antioxidant protection exerted by catecholamines can be rationalized based on their molecular structures. The presence of a catechol moiety has been previously demonstrated to be crucial for the free radical scavenging activity of other compounds that share this structural feature such as esculetin, fraxetin, propyl gallate, piceatannol, 6-hydroxydaidzein, 8-hydroxyglycitein, hydroxytyrosol, and caffeic, dihydrocaffeic, ellagic, protocatechuic, and hypogallic acids.[48−57] Moreover, it has been proposed that catecholic compounds can be regenerated, under physiological conditions, scavenging several radical equivalents in the process, two per cycle,[48,51,53−57] which is expected to increase their antioxidant capacity. Accordingly, it is logical to assume that catecholamine neurotransmitters can also efficiently scavenge free radicals, reducing the associated OS.

On the other hand, the high reactivity of catecholamines toward free radicals also means that these molecules would be degraded over time, losing their functions due to OS and becoming a health risk. For example, postmortem studies of AD brains have shown that degeneration of the LC may be an early maker of the AD pathology.[58,59] The consequent noradrenaline depletion has been associated with cognitive changes in AD patients.[60−65] In addition, it has been proposed that under OS conditions catecholamines are oxidized yielding a variety of products including 6-nitroadrenaline, 6-nitronoradrenaline, and *o*-quinones which in turn may be involved in cyclization and chain breakdown pathways.[66−69] This has been related to catecholaminergic neuron loss in some incapacitating neurodegenerative diseases, especially Parkinson's.[70]

According to the gathered data it becomes evident that further studies dealing with both antioxidant activity and oxidative damage of catecholamine neurotransmitters are still needed. For example, there are no reports on the kinetics of the reactions between these compounds and free radicals. There is no quantitative information related to the different reaction mechanism involved, nor on the site selectivity and branching ratios. The influence of the environment has not been assessed. There is also a lack of information on their potential interactions with metal ions, and on their possible regeneration, under physiological conditions. Consequently, providing some information on these particular aspects is the main purpose of the present work. It is expected that such information may contribute to a better understanding of the chemical fate of adrenaline and noradrenaline under OS.

The reactions of adrenaline and noradrenaline with the hydroperoxyl radical ($^{\bullet}OOH$) have been chosen to explore their potential free radical scavenging activity. This choice has been made because of the following reasons:

(i) Peroxyl radicals ($ROO^{\bullet}$) are of biological relevance and can be successfully scavenged to retard OS,[71] since their half-lives are long enough to ensure that they can be efficiently intercepted by phenolic compounds.[72]

(ii) Within the context of oxidative stress, $ROO^{\bullet}$ are among the most important reaction partners for phenolic compounds.[72] In fact, it has been suggested that their key antioxidant function is just to deactivate peroxyl radicals.[73,74]

(iii) $ROO^{\bullet}$ radicals have low to moderate reactivity, which is considered a desirable characteristic for studying trends in free radical scavenging activities.[75,76] This is because highly reactive radicals are typically involved in reactions with diffusion-limited rates. Thus, using the kinetic data from these reactions as the comparative criteria might lead one to misconclude that all of the studied compounds have similar antioxidant capacity.

(iv) $^{\bullet}OOH$ is the smallest member of the peroxyl family. It has been proposed that this radical plays an essential role in the toxic side effects associated with aerobic respiration.[77] In the same work it was also pointed out that more information is still needed on the reactivity of this particular radical.

On the other hand, copper has been chosen for investigating the reactions of adrenaline and noradrenaline with metal ions because it is widely distributed in the human body and can induce cellular toxicity, albeit it is also crucial for the proper function of most living systems.[78] There is evidence supporting the role of copper in the pathogenesis of several neurodegenerative disorders,[79] which has been attributed to its involvement in the formation of oxidative species,[80] in particular the very harmful $^{\bullet}OH$ radical.[79] In addition, it has been reported that under identical experimental conditions the toxicity of Cu(II), in terms of oxidative damage, is larger than that of Fe(III).[81,82]

COMPUTATIONAL DETAILS

The Gaussian 09 package of programs[83] was used for all of the electronic calculations. Geometry optimizations and frequency calculations were performed with the 6-311+G(d,p) basis set and the SMD continuum model,[85] using the M06-2X and M06 functionals[84] for the systems without and with Cu, respectively. For the free radical scavenging activity pentyl ethanoate and water were used as solvents to mimic lipid and aqueous environments, respectively, while the metal chelation study was carried out only in aqueous solution, because this is the phase where ions are expected to be found. The M06-2X functional has been chosen because their developers recommend it for kinetic calculations,[84] and also because several independent authors have used it successfully for that purpose.[86−94] In addition, it has been identified among the best performing functionals for calculating relative energies of chemical reactions involving free radicals,[95] as well as for kinetic

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calculations in solution.[96] The M06 functional was chosen to study the Cu involving systems because it was parametrized including both transition metals and nonmetals while M06-2X was parametrized only for nonmetals. Thus, M06 is recommended for both organometallic and inorganometallic systems.[97] SMD has been chosen for mimicking the solvent effects because it can be safely used for estimating solvation free energies for any charged or uncharged solute with relatively low errors.[85]

The number of imaginary frequencies (0 or 1) was used to identify local minima and transition states, respectively. In addition, intrinsic coordinate calculations (IRCs) were carried out to verify that the imaginary frequency of the transition states actually corresponds to the expected motion along the reaction coordinate. Unrestricted calculations were used for open shell systems. Relative energies were calculated including thermodynamic corrections at 298.15 K. The solvent cage effects have also been included according to the corrections proposed by Okuno,[98] and the free volume theory.[99] The conventional transition state theory (TST)[100−102] together with the zero curvature tunneling corrections (ZCTs),[103] and the 1 M standard state, were used to calculate the rate constants (k). These computational details are in line with the quantum mechanics based test for overall free radical scavenging activity (QM-ORSA) protocol.[104] It was validated by comparisons with experimental results and proven to produce uncertainties no larger than those arising from experiments.[104]

RESULTS AND DISCUSSION

Acid−Base Equilibria in Aqueous Solution. Based on the structures of adrenaline and noradrenaline (Scheme 1), they are expected to present at least three acid−base equilibria when they are protonated at site 9, i.e., those corresponding to this site and also to the phenolic sites (3a and 4a). There are several experimental values reported for the associated pK_as (Table 1). Using the average values, the molar fractions of the acid−base species of adrenaline and noradrenaline have been estimated, namely, protonated (H_3A^+, H_3NA^+), neutral (H_2A, H_2NA), monoanionic (HA^-, HNA^-), and dianionic (A^{2-}, NA^{2-}). The dominant species for both compounds are the protonated ones (Table 2), with population ∼94.7%, at physiological pH, Under such conditions, the populations of the H_2A and H_2NA are small but not negligible (∼5.3%), while those of the anions are almost zero.

Table 1. pK_a Values for Protonated Adrenaline (H_3A^+) and Noradrenaline (H_3NA^+)

pK_{a1}	ref	pK_{a2}	ref	pK_{a3}	ref
		Adrenaline			
8.66	105	9.95	105	∼13	105
8.75	106	9.89	106		
8.52	107	10.04	107	11.99	107
8.67	108	9.91	108		
8.66	108	9.88	108		
8.64	109	9.84	109	13.1	109
8.63	110	9.87	110	13.15	110
8.74	111	10.01	111	12.1	111
8.59	112	8.65	112	9.67	112
8.65	av	9.78	av	12.00	av
		Noradrenaline			
8.64	105	9.70	105	∼13	105
8.73	107	9.59	107	11.56	107
8.58	109	9.53	109	12.9	109
8.57	113	9.73	113	11.13	113
8.72	114	10.30	114	11.69	114
8.65	av	9.77	av	12.06	av

Table 2. Molar Fractions (mf) of the Different Acid−Base Species of Adrenaline and Noradrenaline, at pH = 7.4

adrenaline	mf	noradrenaline	mf
H_3A^+	0.9467	H_3NA^+	0.9466
H_2A	0.0531	H_2NA	0.0532
HA^-	0.0002	HNA^-	0.0002
A^{2-}	∼0.0000	NA^{2-}	∼0.0000

Accordingly, in the present study, the species used for the reactions in aqueous solution are H_3A^+, H_3NA^+ and H_2A, H_2NA. On the other hand, there are different possible deprotonation routes for both catecholamines. For the first pK_a, the potential acid sites are 3a, 4a, and 9 (Scheme 1), with the latter corresponding to the deprotonation with the lowest Gibbs free energy (Table 1S, Supporting Information). For the second pK_a, only the phenolic sites, 3a and 4a, remain as potential acid sites, and for both catecholamines the anion formed at site 3a is the lowest in energy. Based on these results, deprotonation routes have been proposed for adrenaline and noradrenaline (Scheme 2), which allows identification of the most probable structures for all of their acid−base species.

Free Radical Scavenging Activity. To investigate the reactions of adrenaline and noradrenaline with the hydroperoxyl radical (•OOH), different reaction mechanisms have been included in this study. This is because the free radical scavenging activity of these catecholamines can take place through a variety of chemical pathways, as it is the case for other compounds.[115−119] The reaction mechanisms considered in this work are the radical adduct formation (RAF), the hydrogen transfer (HT), the single electron transfer (SET), and the sequential proton loss electron transfer (SPLET). The SPLET mechanism was proposed by Litwinienko and Ingold for the reactions of the DPPH radical with substituted phenols.[120−123]

All of the previously mentioned mechanisms have been considered for the reactions in aqueous solution, while only RAF and HT are included for reactions in nonpolar media. SPLET has not been taken into account in this case because nonpolar (lipid) solutions are not expected to provide the necessary solvation for the ionic species yielded by deprotonation; i.e., such a process is not expected to occur to a significant extent in this kind of environment. For the same reason, the SET mechanism has not been included either. To prove this assumption, the Gibbs free energy of reaction (ΔG) for the SET processes in pentyl ethanoate (PE) solution were calculated. They were found to be higher than 72 kcal/mol (Table 3) for both studied catecholamines, which definitively rules out SET in lipid media. In aqueous solution, the endergonicity of the SET process is reduced, albeit it is still too large (>31 kcal/mol) for this mechanism to make significant contributions to the overall reactivity. The SPLET process, on the other hand, was found to be only slightly endergonic (1.8 and 1.7 kcal/mol for adrenaline and noradrenaline, respectively); thus it may contribute to the •OOH scavenging activity of these catecholamines, in aqueous solution.

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Scheme 2. Deprotonation Routes for Adrenaline and Noradrenaline

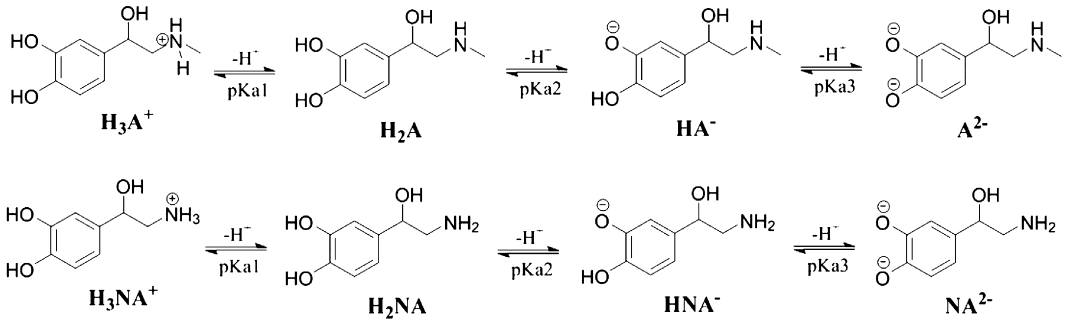

Table 3. Gibbs Free Energies of Reaction (ΔG, kcal/mol) at 298.15 K

	H_2NA	H_2NA	H_3NA^+	H_2A	H_2A	H_3A^+
	PE[a]	water	water	PE[a]	water	water
SET	73.72	30.20	32.23	72.07	27.21	31.20
SPLET		1.68			1.81	
RAF1	15.57	12.65	12.37	8.04	12.60	11.86
RAF2	15.88	14.66	14.21	10.64	15.20	14.74
RAF3	12.70	10.54	10.47	4.10	8.66	11.74
RAF4	11.00	10.04	10.00	5.75	10.31	10.66
RAF5	15.70	14.85	15.15	11.12	15.68	15.25
RAF6	15.60	14.27	12.92	8.43	12.99	13.50
HT-3a	−6.04	−4.89	−4.66	−6.33	−6.17	−4.85
HT-4a	−6.63	−5.75	−4.38	−6.81	−6.68	−4.50
HT-7	−3.42	−3.73	−1.10	−3.90	−6.08	−1.42
HT-8	6.98	5.22	17.25	6.30	3.11	17.29
HT-9	14.18	10.87	16.92	6.90	3.42	17.03
HT-10				6.74	4.74	18.65

[a]PE = pentyl ethanoate.

In all of the tested solvents, and for all the dominant acid/base species in aqueous solution, the RAF pathways are predicted to be endergonic (Table 3). For that reason, this mechanism has been ruled out as feasible for the peroxyl radical scavenging activity of adrenaline and noradrenaline. The HT pathways are the only ones that were found to be exergonic, in particular those involving sites 3a, 4a, and 7a. Thus, they are expected to play a crucial role in the antioxidant capacity of these compounds. In general, the largest exergonicities correspond to the neutral species, not to the most abundant (protonated) ones in aqueous solution. This finding suggests that deprotonation may have a promoting role on the peroxyl scavenging activity of adrenaline and noradrenaline, in aqueous solution. On the other hand, the polarity of the environment was found to have only a minor influence on the reactivity of these compounds toward $^{\bullet}$OOH. In addition the ΔG values for adrenaline and noradrenaline are rather similar, comparing similar sites, acid species, and environment's polarity. Accordingly, it seems that the presence of a methyl group, at the terminal site of the adrenaline side chain, does not influence its free radical scavenging activity. In fact, for the reactions with $^{\bullet}$OOH, the reaction pathway involving this site (10) was found to be endergonic (Table 3).

The reaction pathways described earlier as endergonic were not included in the kinetic study because they would be reversible to a significant extent, albeit they may take place at a significant rate, and consequently the corresponding products will not be experimentally observed. On the other hand, endergonic processes might still represent significant reaction pathways, provided that the products evolve into other species through fast enough reactions. The contributions of such reactions to the overall activity of a particular compound would become particularly important when the later stages are significantly exergonic, i.e., they provide a driving force, and the associated reaction barriers are rather low. These features are expected to be fulfilled by the SPLET mechanism, since the intermediates involved frequently are highly reactive radicals. Therefore, it was also included in the kinetic analyses.

The fully optimized geometries of the transition states (TSs) are provided in Figures 1S and 2S, Supporting Information, for adrenaline and noradrenaline, respectively. The corresponding imaginary frequencies are provided in Table 2S, Supporting Information. In general the geometrical features of the TS, i.e., the distances around the transferred H, are similar for both catecholamines in both solvents and for both reacting acid−base species (neutral and protonated) in aqueous solution. The TSs involving site 3a become earlier (more reactant-like) in aqueous solution, suggesting that such a medium should favor HT from this site. For the TS associated with HT from site 7a, the aspect influencing the most geometrical features seems to be the reacting acid−base form of the catecholamines with the protonated ones leading to the most product-like TS. This seems to be a logical finding, since the site involved in the H transfer, in this case, is close to the protonated amino site. On the other hand, the effects of solvent, and pH in aqueous solution, were found to have only minor effects on the geometries of the TSs involving site 4a.

The rate constants for each reaction pathway, as well as the overall rate coefficients ($k_{overall}$) are reported in Table 4. The Gibbs free energies of activation ($\Delta G^{\ddagger}$) and the tunneling corrections used to obtain the rate constant of each individual path are provided as Supporting Information (Tables 3S and 4S, respectively). The $k_{overall}$ values, in lipid solution, were calculated as the sum of the rate constants of each individual

Table 4. Rate Constants of Each Individual Pathway and Overall Rate Coefficients[a] (M^{-1} s^{-1}), at 298.15 K

	H_2NA	H_2NA	H_3NA^+	H_2A	H_2A	H_3A^+
	PE	Water	Water	PE	Water	Water
SPLET		7.40E+09			7.48E+09	
HT-3a	3.97E+03	5.17E+04	4.30E+04	5.93E+03	7.74E+04	8.60E+03
HT-4a	1.25E+05	7.05E+04	6.57E+05	1.60E+05	5.68E+05	3.64E+04
HT-7	8.84E+01	9.95E+01	3.61E+01	2.52E+02	6.94E+02	2.48E+01
Overall	1.29E+05	2.15E+06		1.66E+05	1.57E+06	

[a]Where, for example, 7.40E+09 represents 7.40×10^9. PE = pentyl ethanoate.

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pathway. In aqueous solution, on the other hand, they were obtained by taking into account the molar fractions of the different acid−base species, at the pH of interest (physiological pH, 7.4):

$$k_{\text{overall}}^{\text{PE}} = \sum_{i=1}^{n} k_i^{\text{H}_2\text{X}} \quad (1)$$

$$k_{\text{overall}}^{\text{W,pH=7.4}} = \text{mf}_{(\text{HX}^-)}^{\text{pH=7.4}} k_{\text{SPLET}} + \text{mf}_{(\text{H}_2\text{X})}^{\text{pH=7.4}} \sum_{i=1}^{n} k_i^{\text{H}_2\text{X}} + \text{mf}_{(\text{H}_3\text{X}^+)}^{\text{pH=7.4}} \sum_{i=1}^{n} k_i^{\text{H}_3\text{X}^+} \quad (2)$$

where X = A or NA, PE = pentyl ethanoate, and W = aqueous solution.

The values of k_{overall} obtained this way are expected to be directly comparable with the experimental data for the reactions of interest.

The reactions of both catecholamines with $^{\bullet}$OOH were found to be faster in aqueous solution than in lipid media, by about 9.5 and 16.6 times for adrenaline and noradrenaline, respectively. This suggests that polar, protic, solvents promote the reactivity of these catecholamines toward peroxyl radicals. In addition, such a reactivity is further increased in aqueous solution by deprotonation, with the individual rate constants or each pathway being systematically higher for H_2A and H_2NA, compared to H_3A^+ and H_3NA^+. Among the HT pathways, that involving site 4a is the fastest one, regardless of the polarity of the environment and of the reacting catecholamine (adrenaline vs noradrenaline, or neutral vs protonated). However, in aqueous solution the fastest process corresponds to the SPLET mechanism. This finding suggests that deprotonation not only alters the reactivity of the studied compounds toward free radicals but also the relative importance of the different mechanisms involved in their scavenging activity.

The contributions of the different mechanisms and reaction pathways to the overall HOO$^{\bullet}$ scavenging activity of adrenaline and noradrenaline have been further investigated by estimating the corresponding branching ratios (Γ):

$$\Gamma_i^{\text{PE}} = \frac{k_i}{k_{\text{overall}}} \times 100 \quad (3)$$

$$\Gamma_i^{\text{W,pH=7.4}} = \frac{\text{mf}_i^{\text{pH=7.4}} k_i}{k_{\text{overall}}^{\text{W,pH=7.4}}} \times 100 \quad (4)$$

where i represents each individual reaction pathway.

It was found that in nonpolar, lipid, media HT from site 4a is responsible for most of the peroxyl radical scavenging activity of both adrenaline and noradrenaline, with contributions to the overall rate coefficients higher than 96% (Table 5). HT from site 3a has minor, but significant, contributions (about 3%), while the contributions of HT from site 7a are almost negligible (lower than 0.2%). In aqueous solution at physiological pH, on the other hand, SPLET is the reaction mechanism contributing the most to the overall peroxyl scavenging activity of the studied catecholamines. Its importance is higher for adrenaline than for noradrenaline, with branching ratios equal to 95.1% and 68.9%, respectively. In the case of noradrenaline HT from site 4a in H_3NA^+ has relatively important contributions to the overall activity (about 29%), while for adrenaline the equivalent process contributes by only ∼2%.

Table 5. Branching Ratios (%), at 298.15 K

	H_2NA	H_2NA	H_3NA^+	H_2A	H_2A	H_3A^+
	PE[a]	water	water	PE[a]	water	water
SPLET		68.86			95.11	
HT-3a	3.06	0.13	1.90	3.57	0.26	0.52
HT-4a	96.87	0.17	28.94	96.28	1.92	2.19
HT-7	0.07	0.00	0.00	0.15	0.00	0.00

[a]PE = pentyl ethanoate.

To analyze the potential protective effects of adrenaline and noradrenaline, their overall rate coefficients have been compared with that reported for the HOO$^{\bullet}$ damage to polyunsaturated fatty acids, which has been estimated to be in the range of $(1.18-3.05) \times 10^3$ M^{-1} s^{-1}.[77] The k_{overall} values of both catecholamines are about 2 and 3 orders of magnitude faster than the previously mentioned threshold value, in lipid and aqueous media, respectively. Accordingly, it can be stated that these compounds can efficiently act as free radical scavengers, in both phases.

To quantify such protection, it has been compared with that exerted by Trolox.[124] It was found that in nonpolar media adrenaline and noradrenaline reacts with $^{\bullet}$OOH about 49 and 38 times faster, respectively, than the reference compound, while in aqueous solution these ratios become 17 and 24. Therefore, it can be concluded that the studied catecholamine neurotransmitters are better peroxyl radical scavengers than Trolox. Compared to those of other known antioxidants, the peroxyl radical scavenging activity of both adrenaline and noradrenaline, in lipid media, was found to be higher than those of resveratrol,[125] ascorbic acid,[104] caffeic acid,[50] and melatonin.[126] In aqueous solution they surpass the protection exerted by gallic acid,[127] dopamine,[128] ellagic acid,[53] and α-mangostina.[129] On the other hand, piceatannol,[56] for example, is predicted as better peroxyl radical scavengers in both lipid and aqueous media than the studied catecholamines. This suggests that piceatannol may act as a protector of these neurotransmitters in biological systems.

Copper Chelation and Inhibition of $^{\bullet}$OH Production. Ionic copper exists in both Cu(I) and Cu(II) oxidation states. They can be interconverted by oxidation and reduction reactions, which makes copper a likely candidate to be involved in the formation of hydroxyl radicals ($^{\bullet}$OH) by the Fenton reaction:[130]

$$\text{Cu(I)} + \text{H}_2\text{O}_2 \rightarrow \text{Cu(II)} + \text{OH}^- + {}^{\bullet}\text{OH}$$

Another route for $^{\bullet}$OH production is the Haber−Weiss reaction:

$$\text{O}_2^{\bullet-} + \text{H}_2\text{O}_2 \rightarrow \text{O}_2 + \text{OH}^- + {}^{\bullet}\text{OH}$$

However, it is too slow to be of any physiological importance, unless it is catalyzed by metal ions. In the case of copper, the Haber−Weiss reaction can be reformulated as the combination of the following steps:

$$\text{Cu(II)} + \text{O}_2^{\bullet-} \rightarrow \text{Cu(I)} + \text{O}_2$$

$$\text{Cu(I)} + \text{H}_2\text{O}_2 \rightarrow \text{Cu(II)} + \text{OH}^- + {}^{\bullet}\text{OH}$$

(Fenton reaction)

At this point it seems worthwhile to call attention to the fact that, during the whole Haber−Weiss process, only $O_2^{\bullet-}$ and H_2O_2 are consumed while the copper ions act only as catalyst; i.e., Cu(II) is fully regenerated. Accordingly, a large number of $^{\bullet}$OH radicals can be produced with very small amounts of

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Table 6. Gibbs Free Energies of Reaction (kcal/mol), of the Complexes of Copper(II) with Noradrenaline, at 298.15 K

	H_2NA			H_3NA^+		
	DCM[a]	CDCM[b]		DCM[a]	CDCM[b]	
site	$\Delta G^\circ = \Delta G'$	ΔG°(pH=0)	$\Delta G'$(pH=7.4)	$\Delta G^\circ = \Delta G'$	ΔG°(pH=0)	$\Delta G'$(pH=7.4)
O3a	5.26	5.22	−4.88	6.50	5.81	−4.29
O4a	4.71	4.55	−5.55	4.09	4.25	−5.85
O3a, O4a	5.87	3.68 (3a)	−6.42 (3a)	6.84	3.89 (3a)	−6.21 (3a)
		3.76 (4a)	−6.34 (4a)		3.01 (4a)	−7.09 (4a)
		9.98 (3a, 4a)	−10.21 (3a, 4a)		7.89 (3a, 4a)	−12.30 (3a, 4a)
N9	−8.32	17.67	7.57			
O7a	−0.10	11.96	1.86	7.06	11.29	1.19
O7a, N9	−13.56	13.00 (9)	2.90 (9)			
		−2.08 (7)	−12.17 (7)			
		33.31 (9, 7)	13.12 (9, 7)			

[a]DCM = formed via direct-chelation mechanism. [b]CDCM = formed via coupled-deprotonation-chelation mechanism (deprotonation site in CDCM pathways involving more than one acid site).

copper. In addition, Cu(II) is the most abundant and stable oxidative state of copper, so it is more likely that this ion is involved in a catalyzed Haber−Weiss reaction, than Cu(I) in a direct Fenton reaction. However, Cu(II) can be reduced to Cu(I) by other species in physiological systems, such as the ascorbate ion, facilitating the •OH production. Fortunately, it has been found that the feasibility of the Cu(II) reduction into Cu(I) can be reduced by metal chelation, inhibiting the •OH formation, with respect to the same reactions when they involve free copper ions.[131−133] Evidently, it is essential that chelation yields stable complexes to ensure the success of this kind of protection against OS; i.e., the chelation reactions must be exergonic. Thus, their thermochemical viabilities have been the first aspect explored in this work.

To that purpose, we have considered both the neutral and protonated forms of the studied catecholamines, since they would be the most relevant ones under physiological conditions. In addition, the calculations have been performed only for aqueous solution because this is the phase where ionic Cu is expected to be found. Copper ions were modeled coordinated to water molecules because they are expected to be hydrated in aqueous phase within biological systems. Thus, this model is more adequate to represent "free" copper under such conditions than the naked ions. Four water molecules were chosen, since it was previously reported that the most likely configuration of Cu(II) water complexes, in the aqueous phase, corresponds to an almost square-planar four-coordinate geometry.[134] For consistency purposes, the hydrated Cu(I) ions were modeled with the same amount of water molecules, albeit in this case the linear two-coordinate configuration is preferred; i.e., Cu(I) is coordinated only to two water molecules, and the other two are solvating the system. The linear, two-coordinated, structure found for Cu(I) complexes in aqueous solution is consistent with previous experimental evidence.[135−137]

The chelation reactions involving hydrated copper actually represent ligand substitutions; one water molecule is replaced in the copper coordination shell by one molecule of catecholamines when these compounds act as monodentate ligands, while two water molecules are replaced when they act as bidentate ligands. Regarding the chelation sites, all of those involving N and O atoms in the studied compounds (Scheme 1) have been explored. The structures of the different complexes are provided in Figures 3S−10S (Supporting Information).

In addition, two different chelation pathways have been analyzed, the direct chelation (DCM) and the coupled-deprotonation-chelation (CDCM) mechanisms. CDCM becomes relevant when some of the sites in the studied compounds are acidic. As a result, they are susceptible to deprotonation at the same time that the chelation processes take place. For adrenaline and noradrenaline the catechol sites (3a and 4a), as well as N9 and O7a, are all susceptible to being involved in these kinds of processes, i.e., concurrently involving Cu chelation and deprotonation of the reactive site in the ligand. The two chelation mechanisms considered in this work can be schematically represented as

DCM:

$$Cu(H_2O)_4^{2+} + H_nX \rightleftharpoons Cu(H_nX)(H_2O)_{4-j}^{2+} + jH_2O$$

CDCM:

$$Cu(H_2O)_4^{2+} + H_nX \rightleftharpoons Cu(H_{n-m}X)(H_2O)_{4-j}^{2-m} + jH_2O + mH^+$$

where X = A and NA, for adrenaline and noradrenaline, respectively.

These equilibria show that the equilibrium constants, and the corresponding Gibbs energies, of the DCM processes do not depend on the pH. On the contrary those corresponding to the CDCM mechanism are influenced by the pH of the environment. When the pH is not explicitly considered, the calculated ΔG values would correspond to the standard conditions (pH = 0), with the equilibrium constant equal to

$$K = \frac{[Cu(H_{n-m}X)(H_2O)_{4-j}^{2-m}][H^+]^m}{[X_nH][Cu(H_2O)_4^{2+}]} = e^{-\Delta G^\circ/RT} \quad (5)$$

However, we are interested on the chelation processes when they take place with the pH buffered to 7.4, i.e., under physiological conditions. In such a case $[H^+]$ remains constant, with $[H^+] = 10^{-pH} = 3.98 \times 10^{-8}$ M. Therefore, it is possible to define conditional equilibrium constants (K')[138,139] as

$$K' = \frac{K}{[H^+]^m} = \frac{e^{-\Delta G^\circ/RT}}{10^{-m(pH)}} = e^{-\Delta G'/RT} \quad (6)$$

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Table 7. Gibbs Free Energies of Reaction (kcal/mol), of the Complexes of Copper(II) with Adrenaline, at 298.15 K

	H_2A			H_3A^+		
	DCM[a]	CDCM[b]		DCM[a]	CDCM[b]	
site	$\Delta G^\circ = \Delta G'$	ΔG°(pH=0)	$\Delta G'$ (pH=7.4)	$\Delta G^\circ = \Delta G'$	ΔG°(pH=0)	$\Delta G'$ (pH=7.4)
O3a	4.42	3.40	−6.69	5.90	4.37	−5.72
O4a	4.31	4.86	−5.24	5.68	5.86	−4.24
O3a, O4a	5.01	3.12 (3a)	−6.98 (3a)	7.47	4.53 (3a)	−5.56 (3a)
		3.46 (4a)	−6.64 (4a)		2.90 (4a)	−7.19 (4a)
		9.60 (3a, 4a)	−10.60 (3a, 4a)		7.87 (3a, 4a)	−12.32 (3a, 4a)
N9	−8.81	14.05	3.95			
O7a	−1.45	9.90	−0.20	6.62	11.30	1.20
O7a, N9	−14.05	−2.86 (7)	−12.96 (7)			
		12.73 (9)	2.63 (9)			
		32.25 (7, 9)	12.06 (7, 9)			

[a]DCM = formed via direct-chelation mechanism. [b]CDCM = formed via coupled-deprotonation-chelation mechanism (deprotonation site in CDCM pathways involving more than one acid site).

Then the conditional Gibbs energy of reaction can be calculated, at each particular buffered pH, using the following equation:

$$\Delta G' = \Delta G^\circ - 2.303RTm(\mathrm{pH}) \quad (7)$$

This equation shows that as the pH increases, so does the thermochemical viability of the CDCM reactions. On the other hand, for the DCM pathways $\Delta G' = \Delta G^\circ$, since the corresponding equilibria do not explicitly involve H^+ and, consequently, the DCM Gibbs energies are not affected by pH. The Gibbs energies of the chelation reactions are reported in Tables 6 and 7 for adrenaline and noradrenaline, respectively. The ΔG° values for the CDCM reactions were calculated using $\Delta G_{gas}(H^+) = -4.39$ kcal/mol and $\Delta G_{solvation}(H^+) = -265.89$ kcal/mol, based on the recommendation of Camaioni and Schwerdtfeger,[140] which in aqueous solution leads to $\Delta G_s(H^+) = -270.28$ kcal/mol.

For each chelation site the ΔG° and $\Delta G'$ values are similar for both catecholamines and also for the protonated and neutral forms. The only difference is that, when protonated, site N9 cannot bind to Cu, as expected. Regarding the chelation mechanism, it was found that in general the thermochemical viability is higher for the CDCM (at physiological pH) than for DCM. This is particularly important for the chelation reactions involving phenolic sites (3a and 4a) which are exergonic via CDCM, at pH = 7.4, while they are endergonic via DCM. Accordingly, it is proposed that under physiological conditions, CDCM is the main reaction mechanism involved in the copper chelation of adrenaline and noradrenaline. In addition, the most thermochemically favored reactions systematically correspond to the formation of bidentate complexes. Thus, they are expected to be the most abundant chelation products, albeit others can be produced to a lower extent. This is supported by the populations of the thermochemically viable complexes, predicted from Maxwell−Boltzman distribution calculations, which are reported in Tables 5S and 6S (Supporting Information).

According to the gathered data it can be concluded that both adrenaline and noradrenaline are capable of chelating Cu(II), under physiological conditions, yielding several complexes. The next step in this investigation was quantifying the effects of the copper sequestering ability of the studied catecholamines on oxidative stress, in particular on the $^\bullet$OH production. To that purpose, the thermochemical viability of the Cu(II) reduction by the anion superoxide radical ($O_2^{\bullet-}$) was examined (Tables 8 and 9). This reaction was chosen because it represents the starting point for the $^\bullet$OH production, catalyzed by copper (first step of the Haber−Weiss reaction). In addition, since it was proposed that in biological systems Cu(II) can also be reduced to Cu(I) by the ascorbate ion (Asc^-), this reaction was also investigated. Only the stable complexes, i.e., those produced from exergonic reactions, were included in these analyses since they would be the significant ones in actual biological systems. The Gibbs free energies of the reduction reactions of free copper were compared with those involving copper chelated by adrenaline and noradrenaline, for both reducing agents ($O_2^{\bullet-}$ and Asc^-), to elucidate the role of the Cu(II) sequestering ability of these catecholamines on the $^\bullet$OH production. This strategy is based on the fact that Cu(II) is the most abundant and stable of the copper ions, while Cu(I) is the one involved in the Fenton reaction. Consequently, if the formation of Cu(I) from Cu(II) is inhibited, so is the $^\bullet$OH production, and consequently the oxidative damage caused by this very reactive radical. Therefore, any chelating agent that decreases the viability of Cu(II) reduction is expected to be effective for preventing $^\bullet$OH-induced oxidative stress.

Table 8. Gibbs Free Energies of Reaction (kcal/mol, at 298.15 K) for the Reduction of Noradrenaline−Copper(II) Complexes, by $O_2^{\bullet-}$ and Asc^-

	H_2NA		H_3NA^+	
	Asc^-	$O_2^{\bullet-}$	Asc^-	$O_2^{\bullet-}$
free Cu(II)	−2.24	−28.59		
		DCM[a]		
N9	−3.58	−29.93		
O7a, N9	2.17	−24.18		
		CDCM[b]		
O4a	4.34	−22.01	4.61	−21.74
O3a	5.58	−20.77	3.24	−23.11
O4a, (O3a)	9.24	−17.10	9.03	−17.32
(O4a), O3a	7.66	−18.69	7.99	−18.36
(O4a), (O3a)	24.37	−1.98	24.25	−2.10
(O7a), N9	21.30	−5.05		

[a]DCM = formed via direct-chelation mechanism. [b]CDCM = formed via coupled-deprotonation-chelation mechanism (deprotonation site in CDCM pathways involving more than one acid site).

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Table 9. Gibbs Free Energies of Reaction (kcal/mol, at 298.15 K) for the Reduction of Adrenaline–Copper(II) Complexes, by $O_2^{\bullet-}$ and Asc^-

	H_2A		H_3A^+	
	Asc^-	$O_2^{\bullet-}$	Asc^-	$O_2^{\bullet-}$
free Cu(II)	−2.24	−28.59		
		DCM[a]		
N9	−1.29	−27.64		
O7a, N9	5.66	−20.69		
		CDCM[b]		
O4a	4.37	−21.98	1.96	−24.39
O3a	5.95	−20.40	3.56	−22.79
O4a, (O3a)	7.19	−19.16	8.07	−18.27
(O4a), O3a	8.45	−17.90	6.24	−20.11
(O4a), (O3a)	23.58	−2.77	24.01	−2.34
(O7a), N9	19.20	−7.15		

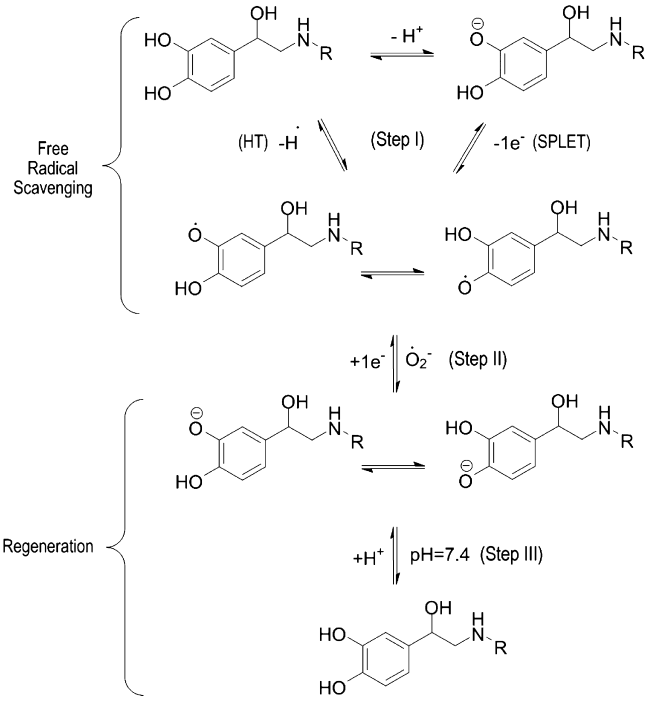
[a]DCM = formed via direct-chelation mechanism. [b]CDCM = formed via coupled-deprotonation-chelation mechanism (deprotonation site in CDCM pathways involving more than one acid site).

Several of the complexes identified as thermochemically viable were found to decrease the feasibility of Cu(II) reduction reactions, compared to those involving free copper (Tables 8 and 9). It was found that the Cu(II) reduction by Asc^- is turned off by all of the complexes involving both catecholamines, yielded to a significant extent. The most radical effect arises from the bidentate complexes, which are also predicted to be the most abundant ones. Accordingly, adrenaline and noradrenaline are both expected to prevent the oxidative stress induced by copper(II)–ascorbate mixtures. On the other hand, the Cu(II) reduction by $O_2^{\bullet-}$ is inhibited to some extent, but not fully prevented, by the adrenaline and noradrenaline sequestering ability. The exergonicity of these reduction reactions are significantly diminished, by up to 26 kcal/mol, which is a large effect but not enough for them to become endergonic. Accordingly, it is proposed that the formation of Cu(I) decreases to a considerable extent as a consequence of the Cu(II) complexation by adrenaline and noradrenaline, albeit it is not completely turned off. In this case, the most significant effects on inhibiting Cu(II) reduction also arise from the formation of the most stable complexes, i.e., the bidentate ones involving the phenolic sites (O3a and O4a). This seems to be a relevant finding, since the most abundant complexes are also expected to be the most efficient for counteracting the oxidative effects of copper arising from the $^{\bullet}OH$ production. Taking all of this into consideration, it can be safely concluded that the studied catecholamines are capable of efficiently inhibiting the oxidative stress induced by copper(II)–ascorbate mixtures, and the $^{\bullet}OH$ production via Haber–Weiss reaction, albeit the effects on the later are only partial.

Antioxidant Protection vs Oxidative Degradation. As previously discussed, adrenaline and noradrenaline may play a protective role against oxidative stress by both scavenging free radicals and sequestering metal ions that promote $^{\bullet}OH$ production via the Fenton reaction. Even though this might seem to be a positive effect, it is actually a double-edged sword because after these catecholamines react with free radicals or metal ions, they may lose their functions as a consequence of the associated structural modifications. This eventually may lead to the same effects that appear as a consequence of adrenaline and noradrenaline depletion. Therefore, it seems important to analyze the possible further fate of the products yielded by the reactions of these catecholamines with free radicals and metal ions, and possible regeneration routes that might restore their original structures and functions.

It has been previously proposed that radical scavengers with the catechol moiety can be regenerated in aqueous solution, at physiological pH. After the first peroxyl radical is scavenged, and in the presence of good electron donors, such as the superoxide radical anion ($O_2^{\bullet-}$), as the latter is consumed, the catechol group is restored. Since catecholamines present this structural feature, such a possibility has been explored (Scheme 3). Step I in this scheme corresponds to the direct free radical

Scheme 3. Mechanism of the Free Radical Scavenging Activity and Regeneration of Adrenaline (R = CH_3) and Noradrenaline (R = H)



scavenging activity discussed in a previous section, the second step is the electron transfer reaction from $O_2^{\bullet-}$ to the radical produced in step I, yielding the corresponding anion, and the last step is the protonation of this anion from the environment.

Step I was already proven to be thermochemically viable, and fast enough to guarantee the efficiency of adrenaline and noradrenaline as peroxyl radical scavengers, and logically of any other radical more reactive than $^{\bullet}OOH$. The second step was found to be exergonic (Table 10) and very fast with rate constants within the diffusion limit regime. Consequently, it is predicted that this step can easily take place under physiological conditions.

Since step III involves protonation, it depends on the $[H^+]$ in the environment, which makes its analysis less straightforward. It actually corresponds to a base–acid equilibrium that does not involve a reaction barrier but, instead, is controlled by the pH of the media. As a result, the Gibbs energy of reaction at each particular buffered pH can be calculated using the expression:

$$\Delta G'_{III} = \Delta G^{\circ}_{III} + 2.303RT(\mathrm{pH}) \quad (8)$$

It is derived from the corresponding equilibrium constant in the same way as eq 7. However, in this case, as the pH increases,

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Table 10. Gibbs Energies of Reaction (kcal/mol), at 298.15 K, for Steps II and III in the Regeneration Route of Noradrenaline and Adrenaline

		noradrenaline		adrenaline	
		step II	step III	step II	step III
O3a					
	pH = 0	−15.88	−16.08	−17.04	−14.69
	pH = 7.4		−5.99		−4.59
O4a					
	pH = 0	−16.92	−16.27	−16.32	−14.89
	pH = 7.4		−6.17		−4.79

the thermochemical viability decreases, because step III corresponds to a protonation process (while eq 7 corresponds to a depronation reaction). The Gibbs energies are negative for both standard conditions and pH = 7.4 (Table 10); i.e., under physiological conditions step III is a spontaneous reaction. These data support the viability of the regeneration process, which is expected to take place very fast, in a cascade way, under such conditions. According to this route, it is predicted that the catechol moiety in both adrenaline and noradrenaline can be efficiently regenerated at the same time that two free radicals (one $HOO^{\bullet}$ and one $O_2^{\bullet-}$) are scavenged. However, it seems worthwhile to note that this process may be prevented if some of the intermediates are consumed by reacting with other species in the environment. This regeneration ability is an unusual, and desirable, feature contributing to increase the protection effects of antioxidants when they are at relatively low concentrations, which is the most common case in the regions where free radicals are generated, within biological systems. Moreover, the regeneration of catecholamines should contribute to restoring their concentration and making them available for exerting their classical functions. This also means that adrenaline and noradrenaline can act as free radical scavengers without a serious risk of diminishing their concentrations under physiological conditions.

Regarding metal chelation, the situation may become more complicated because to restore the studied catecholamines to their original forms, i.e., as free neurotransmitters not bonded to metal ions, it is necessary that other ligands replace them from the formed complexes. One possibility is melatonin, and its metabolites, which had already be proven to form particularly strong complexes with Cu(II).[141] They may be found in the same environments as adrenaline and noradrenaline, and their concentrations can be increased through the intake of melatonin dietary supplements.

To analyze the possibility that melatonin and its metabolites replace adrenaline and noradrenaline from the Cu(II) complexes, the most stable ones are those analyzed, i.e., the bidentate complexes involving the catechol moiety (O3a, O4a) and the O7a, N9 sites. In the same way, the complexes reported as the most stable ones for melatonin and its metabolites[141] are the ones considered for the substitution reactions. For all of these compounds the most stable complexes were produced via CDCM. It was found that only the melatonin metabolite cyclic 3-hydroxymelatonin (3OHM) is capable of replacing adrenaline and noradrenaline from their Cu(II) complexes (Table 11), and it is expected to be very efficient for that purpose since the associated reactions are exergonic by more than 10 kcal/mol in all of the analyzed cases. Accordingly it can be stated that, in the presence of 3OHM, or other potential chelating agents stronger than adrenaline, and noradrenaline, these neurotransmitters can be released from their Cu(II) complexes and be available for exerting their original functions.

Table 11. Gibbs Energies of Reaction (kcal/mol), at 298.15 K, for Ligand Substitution Reactions between 3OHM and the Noradrenaline− and Adrenaline−Copper(II) Complexes

	complex (O3a), (O4a)	complex (O7a), N9
H_2NA	−13.28	−11.32
H_3NA^+	−11−19	
H_2A	−12.89	−10.52
H_3A^+	−11.17	

[a]Deprotonation site in CDCM pathways involving more than one acid site.

Taking into account the previously discussed data, adrenaline and noradrenaline can be efficient for reducing oxidative stress, but at the same time they might lose their functions in the process. Accordingly, these catecholamines are both protectors and targets of oxidative stress. Under the proper conditions, both catecholamines can be regenerated to their original form after scavenging free radicals or sequestering metal ions. However, under high oxidative conditions, their availability may be seriously affected.

CONCLUSION

The potential role of neurotransmitters adrenaline and noradrenaline on oxidative stress related processes were investigated considering different aspects of their reactivity, including their peroxyl radical scavenging activity, their Cu(II) sequestering ability, and their possible regeneration.

It was found that in lipid media HT from site 4a is responsible for most of the peroxyl radical scavenging activity of both catecholamines, while in aqueous solution at physiological pH SPLET is the reaction mechanism contributing the most to the overall peroxyl scavenging activity of these compounds.

Compared to the reference antioxidant Trolox, in nonpolar media adrenaline and noradrenaline react with $^{\bullet}OOH$ about 49 and 38 times faster, respectively, while in aqueous solution these ratios become 17 and 24. Therefore, it was concluded that the studied catecholamine neurotransmitters are better peroxyl radical scavengers than Trolox.

Adrenaline and noradrenaline were also found to be capable of inhibiting the oxidative stress induced by copper(II)−ascorbate mixtures, and the $^{\bullet}OH$ production via Haber−Weiss reaction, albeit the effects on the later are only partial. They exert such beneficial effects by sequestering Cu(II) ions. It is proposed that, under physiological conditions, CDCM would be the main chelation route and the most stable complexes would be the bidentate ones involving the catechol moiety and the O7a and N9 sites.

Accordingly, these catecholamines can be efficient for reducing oxidative stress, but at the same time they might lose their functions in the process. Consequently, regarding oxidative stress they can be both protectors and molecular targets. This means that, under high oxidative conditions, their availability may be seriously affected. Fortunately, under the proper conditions, both catecholamines can be regenerated to their original form so their functions are restored.

ASSOCIATED CONTENT

Supporting Information

Tables listing Gibbs free energies of reaction for successive deprotonations in aqueous solution, imaginary frequencies of

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the TS, Gibbs free energies of activation, tunneling corrections used in the HT kinetic calculations, and relative product population at equilibrium conditions and figures showing optimized geometries of the transition states and the Cu(II) complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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