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Molecular Properties of Monoaminergic Catecholamines in Water

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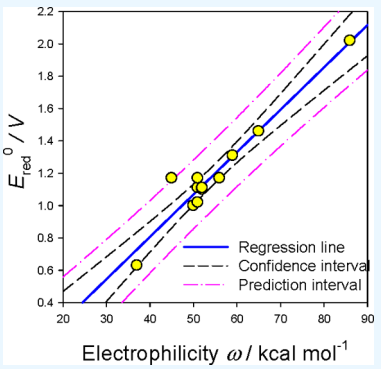
ABSTRACT: Three neurotransmitters belonging to catecholamines (dopamine, noradrenaline, adrenaline) and related α-amino acids (DOPA and tyrosine) were studied by quantum-chemical *ab initio* and DFT calculations using B3LYP and DLPNO−CCSD(T) methods in water. In addition to the three canonical forms, zwitterionic forms were also investigated, each in three oxidation states (molecular cation L^+, electroneutral molecule L^0, and molecular anion L^-). Each species was subjected to geometry optimization followed by vibrational analysis. Electronic properties (adiabatic ionization energy, electron affinity, chemical hardness, molecular electronegativity, electrophilicity index, dipole moment, electric polarizability, and quadrupole moment) and standard thermodynamic quantities (inner energy, entropy, enthalpy, and Gibbs energy) were evaluated, which allows the absolute oxidation and reduction potentials to be calculated. The absolute reduction potential (ARP) was found to correlate with the electrophilicity index ω along a straight line. Moreover, in addition to the standard expression for the absolute redox potential using reaction Gibbs energy, an approximation based on ionization energy and/or electron affinity was also tested. The main finding is that dopamine is a much weaker oxidizing agent with the ARP = 0.99 V relative to tyrosine with ARP = 1.38 V for canonical structures in water. This is also true for the zwitterionic structures in water: for dopamine ARP = 0.63 V is much lower relative to tyrosine with ARP = 1.31 V. The protonated form ($DOPAH^+$) has the highest ARP = 2.02 V. Prediction of the redox potentials is an important factor influencing antioxidant (EC_{50}) and/or antireductant activity. Based on 16 molecular properties for 20 molecules (320 entries), advanced statistical methods (cluster analysis, principal component analysis, pair-correlation) reveal that several groups of similarity exist: {dopamine-noradrenaline}, different from {adrenaline-DOPA-(tyrosine)} and zwitterionic forms of {dopamine-noradrenaline-adrenaline}.



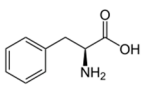
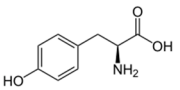
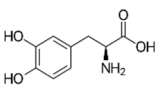
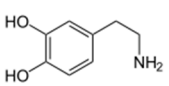
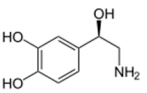
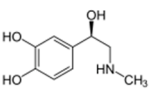
1. INTRODUCTION

Of the monoaminergic neurotransmitters, catecholamines—dopamine, noradrenaline (norepinephrine), and adrenaline (epinephrine)— play an important role and are structurally related and similar to the amino acids *l*-DOPA and *l*-tyrosine. The chemical formulas of these species are shown in Table 1. Several enzymes assist in the complex metabolic pathway that includes biosynthesis of dopamine and its degradation: *l*-phenylalanine → *l*-tyrosine → *l*-DOPA → dopamine → noradrenaline → adrenaline with parallel pathways.[1]

In the canonical form, catecholamines contain a benzene-1,2-diol group with an attached aliphatic chain terminated by an amine group $-NH_2$ or $-NH-CH_3$. However, these species crystallize as zwitterions with $-NH_3^+$ or $-NH_2^+-CH_3$ terminal groups. DOPA belongs to the α-amino acids forming a five-membered ring HO−C−C−N−H_2 for the amino acid form and O^-−C−C−N−NH_3^+ for the zwitterionic form.[2]

Due to *N* rotatable C−C and C-NH_2 bonds, 3^N rotamers can exists, and the number of conformers is increased due to different hydrogen atom attachments. For example, the structure of the zwitterionic isomer of dopamine in the solid state possesses the diol moiety {(H)O−C−C−O-H}, where the hydrogen atom is oriented inward with the torsion angle $C^3(O^1)-C^4-O^2-H^2 \sim 0$ deg (Z). There are three isomers in the canonical structure: both hydrogen atoms are oriented outward $(H^1O^1)C^3-C^4-O^2-H^2 \sim 180$ deg and $C^2-C^3-O^1-H^1 \sim 0$ deg (isomer A1), and/or one is inward and the other is outward (isomer A2 or A3); A2 forms an intramolecular hydrogen bond 3-OH with 4-O whereas A3 forms a hydrogen

Table 1. Monoaminergic Species and Related Compounds

l-phenylalanine	*l*-tyrosine	*l*-DOPA
		
Dopamine	Noradrenaline	Adrenaline
		

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bond 4-OH with 3-O (Figure 1). The total number of conformers for dopamine is 27 × 3.

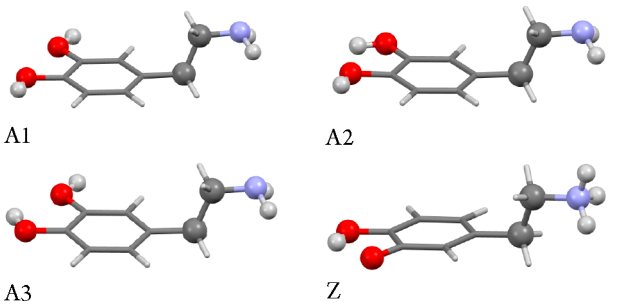

Figure 1. Three canonical (A1, A2, A3) and one zwitterionic (Z) structure of dopamine. Color code: black − C, blue − N, red − O, white − H.

Catecholamines are white or colorless solids with little solubility in water; some of their physicochemical properties are listed in Table 2. Small negative values of octanol−water partition coefficients confirm that the studied species are hydrophilic: log$P$ < 0. The low solubility of dopamine in lipids prevents its penetration throughout the brain-blood barrier (BBB). The rate of catecholamines uptake by the brain correlates with the molar-mass weighted partition coefficient $\log(P{\cdot}M_r^{-1/2})$; the exception is *l*-DOPA, which easily crosses the BBB.[8]

Electrochemical studies of dopamine and related compounds are quite numerous; especially massive cyclic voltammetric data are available.[9−12] Dopamine (DA) in neutral solutions exists in the protonated (dopaminium) form DAH^+, which upon two-electron oxidation ($-2e^-$, $-2H^+$) transforms into the dopaminequinone DQH^+. The reaction depends on pH (stabilized by a puffer) and temperature, so there are numerous tabulations and graphs about peak values.[13,14] The reaction continues with the formation of a cyclic product−leucoaminochrome (LAC) − which is further oxidized to form a bicyclic quinone−dopaminochrome (DC). To this end, dopamine oxidation products provide a number of neurotoxic species that contribute to excessive oxidative stress. The redox properties of dopaminomergic catecholamines with iron sources were also studied.[15,16] Along with experimental studies, theoretical calculations also brought important information about the molecular structure, electronic structure and thermodynamic properties of catecholamines.[17,18]

This communication focuses on the relationships between the structure, electronic structure and molecular properties of five related species−dopamine, noradrenaline, adrenaline, DOPA and tyrosine−in water as a solvent. The ambition is to obtain a huge data set on the molecular properties of neutral, cationic and anionic species using the same methodology and basis set. This worksheet will be processed with advanced statistical methods to obtain latent intercorrelations between variables and samples.

Solved tasks include: (i) comparison of the structure and stability of the three canonical amino forms with respect to the zwitterionic forms; (ii) intercomparison of the electronic properties of electroneutral substances, such as adiabatic ionization energy, electron affinity, chemical hardness, molecular electronegativity, electrophilicity index, dipole moment, electric polarizability and quadrupole moment; (iii)

Table 2. Review of Physicochemical Properties of the Studied Catecholamines and Related Amino Acids[a]

Species	Dopamine, DA	Noradrenaline, NA	Adrenaline, AD	*l*-DOPA DO	*l*-tyrosine, Tyr, Y
Name	4-(2-aminoethyl) benzene-1,2-diol	norepinephrine, 4-[(1*R*)-2-amino-1-hydroxyethyl] benzene-1,2-diol	epinephrine, 4-[(1*R*)-1-hydroxy-2-(methylamino) ethyl]benzene-1,2-diol	(2*S*)-2-amino-3-(3,4-dihydroxy phenyl) propanoic acid	*l*-2-amino-3-(4-hydroxyphenyl) propanoic acid
Formula	$C_8H_{11}NO_2$	$C_8H_{11}NO_3$	$C_9H_{13}NO_3$	$C_9H_{11}NO_4$	$C_9H_{11}NO_3$
Molar mass M_r	153.18	169.18	183.20	197.19	181.19
Rotatable C−C bonds	2	2	3	3	3
Consistency	White solid	Colorless microcrystals	Light brown or nearly white crystalline powder	Colorless solid	White solid
Solubility in water	0.600 g/cm^3	0.849 g/cm^3	0.180 g/cm^3	5.0 mg/cm^3	0.479 mg/cm^3
Octanol−water partition coefficient log$P$	−0.98	−1.24	−1.37, − 1.2	−2.39	−2.26
Acidity constants pK_a	8.71 (phenol)	8.55 (phenol)	9.49 (phenol)	2.32 (carboxyl)	2.20 (carboxyl)
	10.90 (amine)	10.32 (amine)	11.28 (amine)		9.11 (amine)
	13.68 (phenol)	13.49 (phenol)	13.07 (phenol)		10.07 (phenol
Class	Neuro-transmitter	Neuro-transmitter	Neuro-transmitter	Precursor	Precursor
Transfer through BBB	Does not cross	Does not cross	Does not cross	Crosses	Crosses
PubChem CID[3]	681	439260	5816	6047	6057
CCDC code[4−7]	942079	1215820	1101358	1204457	1208550

[a]According to the databases PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Dopamine, CCDC https://www.ccdc.cam.ac.uk/structures/, and Drugbank https://go.drugbank.com/drugs/DB00988.

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comparison of electronic properties during one-electron oxidation and reduction; (iv) comparison of standard thermodynamic properties for neutral and ionized molecules, such as zero-point vibration energy, entropy and Gibbs energy; and (v) analysis of absolute oxidation and reduction potentials as predispositions for one-electron redox processes.

To obtain this information, B3PYP calculations were performed for 60 species, including full geometry optimization and complete vibrational analysis. In addition, more sophisticated DLPNO−CCSD(T) calculations were performed for 42 selected species.

2. METHODS

Ab initio calculations of molecular properties and electronic structure were performed using ORCA software.[19−21]

The B3LYP hybrid variant of Density-Functional Theory was chosen as a good starting point for comparison with other references;[22] this method includes part of the correlation energy and is therefore preferred for geometry optimization and vibrational analysis. The second method, DLPNO−CCSD(T) method (Domain Localized Pair Natural Orbitals − Coupled Cluster Singlets + Doublets + Triplets) is a post-Hartre-Fock method that includes a substantial part of the correlation energy; CCSD(T) is considered the gold standard in current quantum chemistry although geometry optimization using numerical gradients is not a realistic task.[20,21] This method is applied using geometries preoptimized with B3LYP.

Several basis sets of different extent have been tested. The results are presented mostly for the basis set def2-TZVPD (Triple-Zeta-Valence with Polarization and Diffuse functions) for the B3LYP method.[23] For the DLPNO−CCSD(T) method, aug-cc-pVTZ (Dunning Correlation Consistent with Polarization Valence Triple-Zeta, augmented by diffuse functions) with the auxiliary set aug-cc-pVTZ/C was used, as recommended for a highly correlated wave function.[24,25]

The solvent effect was considered in terms of the Conductor-like Polarizable Continuum Model (CPCM) in water.[26] Using the B3PYP method, a complete vibrational analysis was performed after the full geometry optimization, so that no imaginary frequencies were detected. This allows the evaluation of thermodynamic quantities, namely inner energy, entropy, enthalpy and Gibbs energy, along with their rotational, vibrational, electronic, and translational contributions.

The molecular structures of the studied systems were retrieved from the PubChem and CCDC database.[3,27] They enter full geometry optimization until the gradient criteria indicated a global energy minimum. Molecular properties are characterized by HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energies, the permanent dipole moment, the isotropic value of dipole polarizability, and the isotropic value of the quadrupole moment. Molecular ions, as open-shell systems, were calculated in the unrestricted version (UKS) with reoptimized geometry. This procedure enables determination of the adiabatic ionization energy $E_i = E^+ - E^0$, electron affinity $E_{eg} = E^- - E^0$, Mulliken's molecular electronegativity (minus the chemical potential) $-\mu = \chi = (E_i - E_{eg})/2$, Pearson's chemical hardness $\eta = (E_i + E_{eg})/2$ and Parr's electrophilicity index $\omega = \chi^2/2\eta$.[28−30] Molecular electronegativity represents a driving process of electron transfer; chemical hardness acts as an electronic force constant representing resistivity. The electron flow can be written as $\Delta N = \chi/\eta$ (analogous to Ohm's Law $I = V/R$); the electrophilicity index (electrophilic power) is formally analogous to the electric power $W = V^2/R$. After geometry optimization and vibrational analysis for the respective molecular cation L^+ and anion L^-, the reaction Gibbs energy on oxidation $\Delta_r G^o(L^0/L^+)$ and reduction $\Delta_r G^o(L^0/L^-)$ is evaluated; they enter the formula for the absolute redox potential $E_{abs}{}^o(L^0/L^q)$ [V] $= -\Delta_r G^o$[J mol^{-1}]$/F$ with the Faraday constant F = 96485 A s mol^{-1} (previous studies on tyrosine using def2-TZVP have been remade using a larger basis set def2-TZVPD, which includes diffuse functions).[31]

3. RESULTS AND DISCUSSION

3.1. Effect of the Basis Set. According to Table S1, the results obtained using several basis sets were compared: 6-31G**, 6-311G**, TZVP, and def2-TZVPD. It can be seen that HOMO and ionization energies E_i are little sensitive to the basis set extension, in contrast to LUMO and electron affinities E_{eg}. The most reliable is the def2-TZVPD basis set, which contains the diffuse functions essential for the molecular anions. The MP2 correction to the Hartree−Fock SCF method increases the molecular electronegativity χ and also the chemical hardness η. The inclusion of the solvent effect causes a dramatic decrease in the LUMO energy, which in turn decreases the negative value of the electron affinity.

3.2. Structure and Stability. Dopamine conformers have been studied elsewhere by B3LYP calculations in the 6-31++G(d,p) basis set (264 functions) using the CPCM hydration model.[32] Three isomers resulting from different arrangements of hydrogen atoms in the catechol (3,4-dihydroxyphenyl) moiety were considered. The lowest Gibbs energy (after full geometry optimization and complete vibrational analysis) refers to conformer **b** (A2) with an intramolecular hydrogen bond between the 3-OH and 4-O groups. Conformer **c** (A3) forming a hydrogen bond between 4-OH and 3-O groups has an energy above conformer **b** only $\Delta_{cb}G$ = 0.12 kcal mol^{-1}; conformer **a** (A1), without hydrogen bonds, lies above **b** by $\Delta_{ab}G$ = 1.98 kcal mol^{-1}. These data were reproduced (Table 3) using a more extended basis set (def2-TZVPD, 512 functions): $\Delta_{cb}G$ = 0.15 kcal mol^{-1} and $\Delta_{ab}G$ = 1.34 kcal mol^{-1}. For this purpose, A2 is the most stable conformer for dopamine. Note that the calculated total energies and Gibbs energies are the results of a full geometry optimization, where the ethylamine residue can relax slightly, so the energy difference between structures A2 and A3 is not solely due to

Table 3. Calculated Gibbs Energies and Related Quantities in Optimized Geometries for Three Conformers of Dopamine and Its Cation by the B3PYP Method[a]

Item	Property	(a)=A1	(b)=A2	(c)=A3
	Neutral molecule DA^0			
1	ΔE^0/kcal mol^{-1}	0.996	reference	0.017
2	ZPE/kcal mol^{-1}	114.13	113.98	113.98
3	ΔG^0/kcal mol^{-1}	1.335	reference	0.149
	Molecular cation DA^+			
4	E_i /kcal mol^{-1}	125.02	125.91	125.57
5	ZPE/kcal mol^{-1}	114.72	114.52	114.53
6	$\Delta_{ox}G^o$ /kcal mol^{-1}	125.34	126.36	125.89
5	$E^o{}_{ox}$ /V	−5.44	−5.48	−5.46

[a]Ionization energy $E_i = E^+ - E^0$; standard Gibbs energy on oxidation $\Delta_{ox}G^o = G^+ - G^0$; standard oxidation potential $E^o{}_{ox} = -\Delta_{ox}G^o/F$.

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Table 4. Electronic Energy and Standard Gibbs Energy Relative to the Reference State for Catecholamines and Related Amino Acids in Water Calculated by the B3LYP Method Using the def2-TZVPD Basis Set[a]

		Electronic energy E^q			Gibbs energy $G^{o,q}$		
		$\Delta_{ox}E$		$\Delta_{red}E$	$\Delta_{ox}G^o$		$\Delta_{red}G^o$
Conformer		L^+	L^0	L^-	L^+	L^0	L^-
				(A) Dopamine DA			
DA1	A1	126.02	0.99	−17.87	126.67	1.34	−21.42
DA2	A2	125.91	ref	−19.99	126.36	ref	−23.10
DA3	A3	126.58	0.02	−20.01	126.04	0.15	−23.40
DAZ	Z	104.02	5.57	−9.12	106.35	7.30	−7.20
				(B) Noradrenaline NA			
NA1	A1	127.88	0.99	−19.58	128.40	1.26	−24.36
NA2	A2	127.76	ref	−20.25	128.17	0.11	−23.58
NA3	A3	127.57	0.04	−20.31	127.72	ref	−23.59
NAZ	Z	105.25	5.57	−14.58	107.18	7.21	−19.62
				(C) Adrenaline AD			
AD1	A1	128.89	0.98	−19.67	129.52	1.23	−24.43
AD2	A2	128.78	ref	−21.17	129.16	ref	−25.51
AD3	A3	128.68	0.00	−25.67	129.19	0.13	−29.26
ADZ	Z	103.17	3.52	−19.75	105.70	5.39	−21.49
				(D) DOPA DO			
DO1	A1	128.88	1.93	−19.75	128.35	0.96	−24.59
DO2	A2	133.28	4.78	−16.52	133.20	3.61	−21.75
DO3	A3	132.98	4.77	−16.86	131.40	3.62	−22.22
DO1h	Z	127.91	ref	−24.83	128.23	ref	−29.06
				(E) DOPA A1h[b]			
DO1h	A1	133.22	5.76	−15.29	132.24	4.74	−20.70
				(F) Tyrosine Tyr			
Tyr2h	A2	136.9	1.9	−27.1	135.4	0.8	−31.0
TyrZ	Z	136.9	ref	−25.3	136.5	ref	−30.1
				(G) $DOPAH^+$			
		Z^{2+}	Z^+	Z^0	Z^{2+}	Z^+	Z^0
DOH+	Z	131.1	ref	−43.2	131.7	ref	−46.6

[a]Electronic energies E^q and standard Gibbs energies $G^{o,q}$ in optimized geometry are given in kcal mol^{-1} relative to the most stable conformer (ref). [b]Energies are relative to DOPA (Z0) as a reference.

the geometry of the −OH groups. The relative energies (item 3) were inserted into the Boltzmann distribution, and the weights of the individual conformers A1 to A3 at standard temperature are w = 0.055, 0.532, and 0.413. At room temperature, the A2 and A3 isomers have approximately the same Boltzmann weights, so the ensemble average of molecular properties is simple their arithmetic mean. The dopamine cation was investigated in all three conformers, and calculations confirm minor differences in ionization energy, reaction Gibbs energy for oxidation and absolute oxidation potential.

After the geometry optimization, the calculated relative energies with respect to the most stable neutral isomer are collected in Table 4; the subsequent vibrational analysis gave the relative Gibbs energies (data from Table S3 were used). They include the total electronic energies in their minima and the standard Gibbs energies (harmonic vibrations are assumed). Since absolute values of energies depend on the method and basis set used, the relative energies are presented with the E^0 reference point for either canonical or zwitterionic forms (bold typed).

For dopamine, noradrenaline, adrenaline, and DOPA, the canonical forms A2 and A3 have almost the same total electronic energy, and the Gibbs energies differ only in 0.1 kcal mol^{-1}. For dopamine, noradrenaline and adrenaline, the A1 and Z forms are higher in electronic energy and/or Gibbs energy with respect to A2/A3. For amino acid DOPA, the situation is different: the most stable is the zwitterionic form, then A1 followed by A2/A3.

For dopamine, the standard Gibbs energies determine the relative stability of conformers: A2 (reference), A3 (0.15), A1 (1.34) and Z (7.30) kcal mol^{-1} above the reference. For noradrenaline: A3 (reference), A2 (0.11), A1 (1.26) and Z (7.21) kcal mol^{-1}. For adrenaline: A2 (reference), A3 (0.13), A1 (1.23), and Z (5.39). For DOPA: Z (reference), A1 (0.96), A2 (3.61), A3 (3.62), and the conformer with the intramolecular hydrogen bond DOPA-A1h is 4.74 kcal mol^{-1} above the reference.

The optimized geometries for neutral species are shown in Figure 2. These involve three conformers of the canonical forms (A1, A2, A3) and one conformer (Z) of the zwitterionic form. In three cases, intramolecular hydrogen bonds forming five membered rings are recognized: O···H = 1.955 Å in DOPA(Z), O···H = 1.955 Å in tyrosine(Z) and N···H = 1.829 Å in DOPA(A1h). For neutral species and molecular cations, both (catechol)−OH groups lie in the aromatic plane; however, for molecular anions of A1 conformers, the electron attachment causes a change of the SP^2 hybridization on one of the oxygen atoms, so the attached hydrogen atom points out of the aromatic plane (see the SI).

3.3. Electronic Properties. The molecular properties of catecholamines and related amino acids in water calculated by

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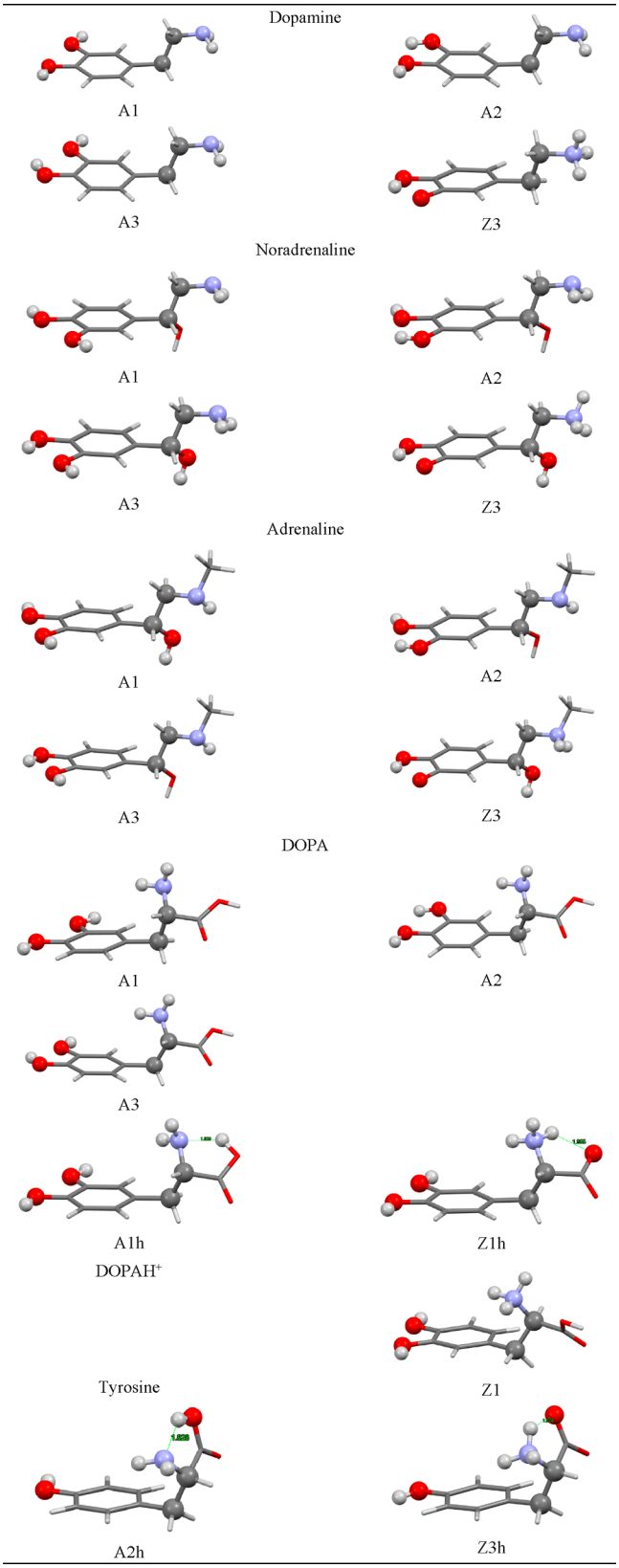

Figure 2. Optimized geometries of the studied neutral molecules. Color code: black − C, blue − N, red − O, white − H. Torsion angles in deg. Initial structures according to the PubChem database and CCDC database..

B3LYP are listed in Table 5 for canonical as well as zwitterionic forms. The calculated molecular properties can be divided into two groups: (i) properties that increase with molar mass, and (ii) independent of molar mass. The first group is represented by the solvated surface S, the solvated volume V, the isotropic quadrupole moment $|Q|$, the isotropic polarizability α, the zero-point vibration energy E_{zpe}, and the total entropic term $S{\cdot}T^{\circ}$. The dipole moment is a different task, because it depends on the spatial separation of the barycenters of negative and positive charges. The dipole moments of the zwitterionic forms are an order of magnitude higher compared to the canonical forms.

In canonical structures, the collective electronic properties in water show the following trends. (i) The HOMO energies are almost the same in the series, about −136 kcal mol^{-1}, and the adiabatic ionization energies are about 125−129 kcal mol^{-1} (tyrosine shows a slightly lower HOMO and a slightlyt higher E_i). (ii) The LUMO energies are negative and vary noticeably from −6.5 (dopamine) to −13.2 (tyrosine) kcal mol^{-1}. This causes negative electron affinities E_{eg} ranging from −19 (dopamine) to −30 (tyrosine) kcal mol^{-1}. (iii) Other molecules, except tyrosine, show analogous molecular electronegativity of $\chi \sim 74$, chemical hardness of $\eta \sim 53$ and the electrophilicity index of $\omega \sim 51$ kcal mol^{-1}. For the tyrosine molecule, the lowest electron affinity causes a lower electrophilicity index of $\omega = 65$ kcal mol^{-1}. This electronic predisposition is manifested in the reaction Gibbs energy for the reduction process, and consequently in the most positive absolute reduction potential of $E_{red}^{\circ} = 1.46$ V. Dopaminergic molecules have an $E_{red}^{\circ} = 0.99$ (dopamine) to 1.12 V.

The zwitterionic forms existing in neutral aqueous solutions show the following trends. (i) Catecholamines form their own group (I), distinct from the α-amino acids (DOPA and tyrosine), which belong to group II. (ii) HOMO(I) energies approximately −108 are less negative compared to canonical forms approximately −136 kcal mol^{-1}. This causes a decrease in the ionization energy $E_i \sim 99$, a decrease in molecular electronegativity χ, and a decrease in chemical hardness η. This group of electronic properties also depends on the electron affinity, which varies less systematically. The lowest electrophilicity index of $\omega = 37$ kcal mol^{-1} is shown by dopamine(Z), and this correlates with the lowest reduction potential of $E_{red}^{\circ} = 0.63$ V. Conversely, the highest $\omega = 86$ kcal mol^{-1} corresponds to the highest $E_{red}^{\circ} = 2.02$ V for DOPAH$^+$(Z).

3.4. Redox Properties. Correlation of calculated absolute oxidation potential with ionization energy and/or molecular electronegativity is shown in Figure 3; other panels show the correlation of the absolute reduction potential with the electron affinity and/or electrophilicity index. In all cases, correlations along straight lines are proven (correlation coefficients $r^2 = 0.999$, 0.861, 0.950, and 0.922). Note that the molecular electronegativity and electrophilicity index are derived from the electronic energies only, while the redox potentials are thermodynamic quantities derived from the reaction Gibbs energies under standard conditions (see Table 6 for dopamine).

Remember that the Gibbs energy G includes: (i) the inner energy U consisting of electronic energy as the dominating part, correction for zero-point vibration and correction for residual vibrations at standard temperature; (ii) the enthalpic term, which for one isolated molecule is simply $H = U + k_B T^{\circ}$; and (iii) the entropic term $S^{\circ}T^{\circ}$, which includes translational, rotational, vibrational and electronic contributions. Since all corrections $G^{\circ} - E^{el}$ are less than 150 kcal mol^{-1}, and $E^{el} \sim$ 300,000 to 400,000 kcal mol^{-1}, then the reaction Gibbs energy

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Table 5. Molecular Descriptors Calculated by the B3LYP Method Using Adiabatic Ionization/Affinity Processes in Water[a]

def2-TZVPD basis set		Adiabatic redox properties									Properties of neutral molecules							
Abbrev.	Molecule	E_i	E_{eg}	χ	η	ω	E_{ox}^{o}	E_{red}^{o}	p	$-Q$	α	S	V	E_{zpe}	S^oT^o	−HOMO	LUMO	weight
								Canonical forms										
DA1	Dopamine A1	125.0	−18.9	71.9	53.1	48.8	−5.44	+0.99	2.547	49.28	165.5	726	1283	114.1	29.88	134	−6.8	0.055
DA2	Dopamine A2	125.9	−20.0	72.9	53.0	50.2	−5.48	+1.00	3.716	47.99	165.0	724	1281	114.0	30.13	134	−6.5	0.532
DA3	Dopamine A3	125.6	−20.0	72.8	52.8	50.2	−5.46	+1.02	3.580	49.84	165.0	724	1282	114.0	30.00	134	−6.9	0.413
NA1	Noradrenaline A1	126.9	−20.6	73.7	53.2	51.1	−5.51	+1.11	2.458	54.39	171.8	758	1365	116.8	31.35	135	−7.9	0.061
NA2	Noradrenaline A2	127.8	−20.2	74.0	53.8	50.9	−5.55	+1.03	3.892	52.77	171.3	755	1369	116.7	31.44	136	−7.9	0.426
NA3	Noradrenaline A3	127.5	−20.3	73.9	53.6	51.0	−5.54	+1.02	5.448	54.58	171.3	754	1358	116.7	31.52	136	−8.0	0.513
AD1	Adrenaline A1	127.9	−20.6	74.3	53.6	51.4	−5.56	+1.11	0.826	57.48	188.5	831	1493	134.3	33.35	136	−7.9	0.065
AD2	Adrenaline A2	128.8	−21.2	75.0	53.8	52.2	−5.60	+1.11	4.136	55.30	188.0	829	1493	134.1	33.52	137	−8.0	0.519
AD3	Adrenaline A3	128.7	−25.7	77.2	51.5	57.8	−5.60	+1.27	3.018	57.59	188.0	826	1485	134.2	33.43	137	−8.0	0.416
DO1	DOPA A1	126.9	−21.0	74.3	52.6	52.5	−5.52	+1.10	1.597	60.87	189.3	834	1523	123.3	33.58	136	−10.3	0.069
DO2	DOPA A2	128.5	−21.3	74.9	53.6	52.3	−5.62	+1.10	4.194	58.15	188.8	838	1532	123.2	33.81	137	−10.2	0.466
DO3	DOPA A3	128.1	−21.6	74.9	53.3	52.7	−5.54	+1.12	3.714	61.12	188.9	839	1534	123.2	33.81	137	−10.3	0.465
DO1h	DOPA A1h	127.5	−21.0	74.3	53.2	51.8	−5.52	+1.11	5.687	68.30	188.0	843	1536	123.3	33.72	136	−10.3	
Tyr2h	Tyrosine A2h	135.1	−29.0	82.0	53.0	63.4	−5.84	+1.38	5.482	57.68	178.6	781	1444	120.9	31.57	143	−13.2	
								Zwitterionic forms										
DAz	Dopamine	98.4	−14.7	56	42	38.2	−4.29	+0.63	29.48	35.92	174.1	715	1274	115.6	29.72	107	−0.87	
NAz	Noradrenaline	99.7	−20.1	60	40	45.1	−4.33	+1.16	27.86	44.54	181.1	753	1363	118.2	31.06	109	−0.17	
ADz	Adrenaline	99.6	−23.3	62	38	49.5	−4.35	+1.17	28.35	53.36	196.8	826	1495	135.9	33.14	108	−2.7	
DOz	DOPA	127.9	−24.8	76	52	56.5	−5.56	+1.26	12.21	74.74	190.3	856	1537	124.3	33.67	137	−0.63	
DOH+	$DOPAH^+$	131.1	−43.2	87	44	86.4	−5.71	+2.02	(12.85)	(48.2)	(180.5)	848	1540	132.8	33.65	140	−20.2	
Tyrz	Tyrosine	136.9	−25.3	81	56	59.0	−5.92	+1.31	15.35	57.90	180.4	782	1447	122.0	31.56	145	−14.1	
Abbreviation for properties		I	A	X	H	O	Eo	Er	p	Q	al	S	V	Z	ST	Ho	Lu	

[a]All energies are in units of kcal mol^{-1}; conversion (IUPAC recommendation): 1 hartree = 627.5095 kcal mol^{-1}; 1 eV = 23.06054 kcal mol^{-1}; 1 kcal mol^{-1} = 4.184 kJ mol^{-1}. Redox properties: ionization energy $E_i = E^+ - E^0$; electron affinity $E_{eg} = E^- - E^0$; chemical hardness $\eta = (E_i + E_{eg})/2$; molecular electronegativity $\chi = (E_i - E_{eg})/2$; electrophilicity index $\omega = \chi^2/2\eta$; absolute oxidation potential $E_{ox}^{o} = -\Delta_{ox}E(L^0/L^+)/F$ in V; absolute reduction potential $E_{red}^{o} = -\Delta_{red}E(L^0/L^+)/F$ in V; Faraday constant 96485 A s mol^{-1}. Solvated surface area S/a_0^2 (bohr, $a_0 = 5.292 \times 10^{-11}$ m); solvated volume V/a_0^3; dipole moment p/D (debye, $D = 3.336 \times 10^{-30}$ A m s); isotropic quadrupole moment Q/ea_0^2; isotropic dipole polarizability α/a_0^3. Standard temperature T^o = 298.15 K. Weight − Boltzmann population of A1, A,2 and A3 conformers.

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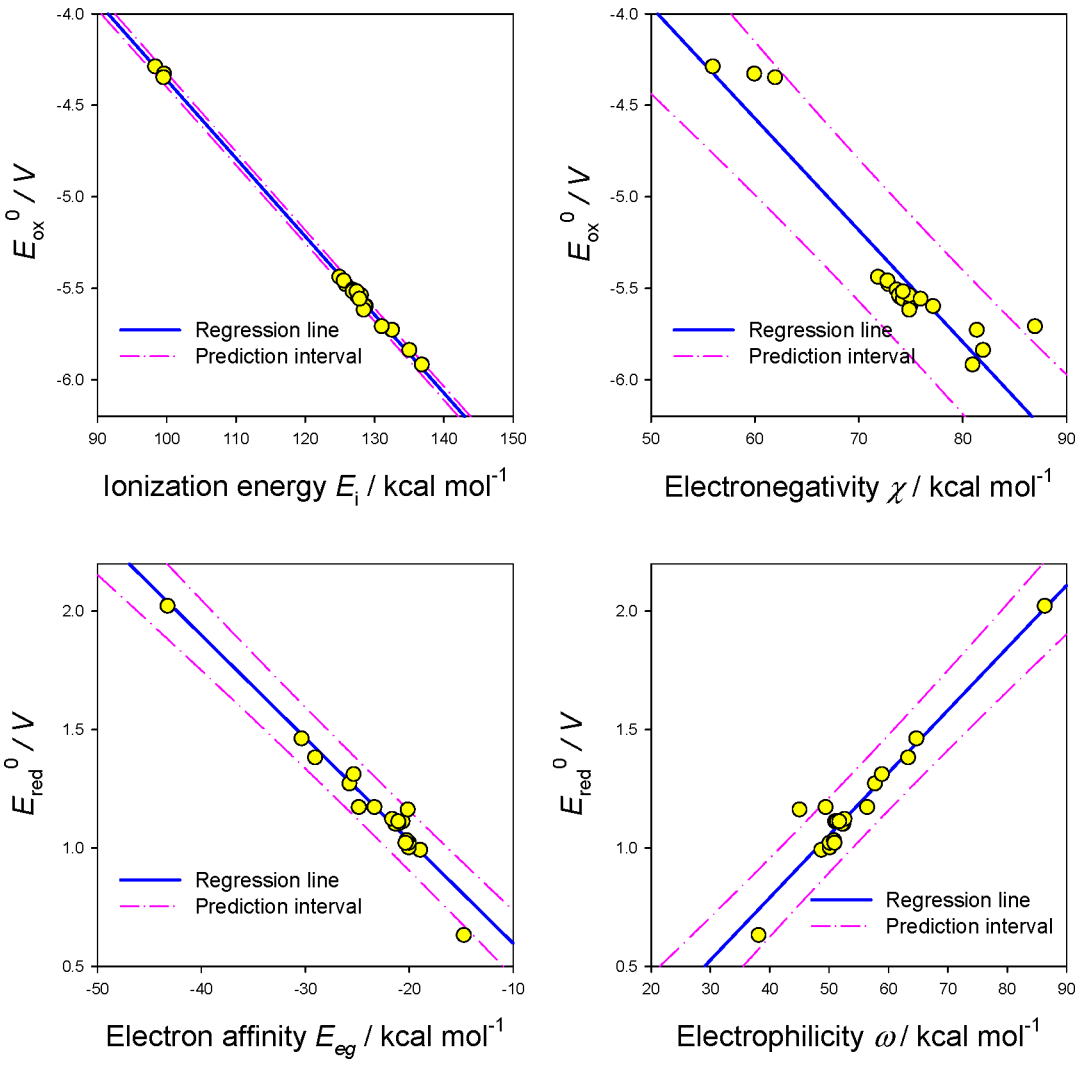

Figure 3. Correlations of absolute redox potentials with adiabatic ionization energy, electron affinity, molecular electronegativity, and electrophilicity index. Data from Table 5.

$\Delta_r G^\circ = \Delta_r E^{el} + \Delta_r E^{vib} + \Delta_r(S^\circ T^\circ)$ can be approximated by the reaction electronic $\Delta_r E^{el}$, which is either the ionization energy E_i or the electron affinity E_{eg}. For the studied molecules, the relative difference $(\Delta_r G^\circ - \Delta_r E^{el})/\Delta_r G^\circ$ is less than 0.4% for oxidation. Therefore, the absolute oxidation potential $E_{ox}^* = -E_i/F$ can work as a good approximation (Figure 4). With the absolute reduction potential, the situation is more complicated, since the calculated electronegativities are less accurate. However, one again can try the approximation $E_{red}^* = -E_{eg}/F$. The main contribution to the difference $G^\circ - E_{el}$ (0.45 and −3.11 kcal mol^{-1} for the oxidation and reduction, respectively) arises from the zero-point vibration correction (0.54 and −2.76 kcal mol^{-1}): the molecular anion is softer (lower ZPE) and cation harder (higher ZPE) relative to the neutral molecule.

Redox potentials are key factors that control the redox properties of molecular agents in living systems. The oxidation potential influences antioxidant activity, a well-known property of dopaminergic molecules.[33] The existence of the above correlations allows the approximation of absolute redox potentials by means of electronic energies, omitting the tedious vibrational analysis. For complex molecules, when the vibrational analysis is difficult to handle (e.g., using the DLPNO−CCSD(T) method), the reduction potential can be approximated by the adiabatic electron affinity (not LUMO) or electrophilicity index, and the oxidation potential by the adiabatic ionization energy (not HOMO) or molecular electronegativity.

3.5. Highly Correlated Method. The calculations obtained by the DLPNO−CCSD(T) method are compiled in Tables 7 and 8. The total electronic energies are listed in Table S4. The data calculated by the DLPNO−CCSD(T) method agree qualitatively with that from B3LYP, but some exceptions are evident, as follows (Table 8). (i) The vertical ionization energies by DLPNO−CCSD(T) are always higher by 5 to +10 kcal mol^{-1} relative to the adiabatic values by B3PYP; this means an increase of up to 7%. (ii) The electron affinities are always less negative from 1 to +9 kcal mol^{-1}, which for small values represents a considerable deviation from 2 to 45%. The main finding is that dopamine is a much weaker oxidizing agent (E_{ox}^* = 0.87 V) relative to tyrosine (E_{ox}^* = 1.31 V) for canonical structures. This holds true also for the zwitterionic structures (that are more stable in water). The protonated form DOPAH$^+$ (supplied as the hydrochloride salt) has the highest absolute reduction potential of E_{red}^* = 1.87 V.

The approximate redox potentials calculated by the DLPNO−CCSD(T) method were correlated with the

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Table 6. Comparison of Electronic and Thermodynamic Properties for Dopamine an Its Ions Calculated by B3LYP Method[a]

Item	Property	$\Delta_{ox}(L^+ - L^0)$	L^+	L^0	L^-	$\Delta_{red}(L^- - L^0)$
1	ΔE_{el}	125.91		ref		−19.99
2	Zero-point energy	0.54	114.52	113.98	111.22	−2.76
3	*U*-vib	−0.21	4.94	5.15	5.17	0.02
4	*U*-rot	0.00	0.89	0.89	0.89	0.00
5	*U*-trans	0.00	0.89	0.89	0.89	0.00
6	ΔU	126.24		ref		−22.72
7	ΔH	126.24		ref		−22.72
8	S^oT-el	0.41	0.41	0.00	0.41	0.41
9	S^oT-vib	−0.52	8.28	8.80	8.76	−0.04
10	S^oT-rot	−0.01	9.10	9.11	9.11	0.00
11	S^oT-trans	0.00	12.22	12.22	12.22	0.00
12	Total entropic term S^oT	0.88	31.01	30.13	30.51	0.38
13	ΔG	126.36		ref		−23.10
14	$G^o - E_{el}$	0.45	91.82	91.37	88.26	−3.11
15	E^o/V	−5.48				+1.00
16	E^*/V	−5.46				+0.87

[a]All energy data in kcal mol^{-1}.

Table 7. Electronic Energy Relative to the Reference State for Catecholamines and Related Amino Acids in Water Calculated by the DLPNO−CCSD(T) Method

	Molecule/ion	L^+	L^0	L^-
aug-cc-pVTZ basis set		$\Delta_{ox}E_{ref}$		$\Delta_{red}E_{ref}$
DA1	Dopamine A1	135.0	1.1	−11.6
DA2	Dopamine A2	135.0	ref	−10.9
DAz	Dopamine Z	110.3	6.5	−13.8
NA1	Noradrenaline A1	136.8	1.1	−18.1
NA3	Noradrenaline A3	136.2	ref	−11.6
NAz	Noradrenaline Z	111.2	6.3	−13.4
AD1	Adrenaline A1	136.8	1.1	−18.2
AD2	Adrenaline A2	136.6	ref	−19.0
ADz	Adrenaline Z	107.9	3.0	−10.8
DO1	DOPA A1	139.8	4.4	−15.1
DOz	DOPA Z	136.3	ref	−24.2
DO1h	DOPA A1h	135.3	ref	−20.5
Tyr2h	Tyrosine A2h	144.3	1.0	−25.1
TyrZ	Tyrosine Z	144.6	ref	−25.1
		Z^{2+}	Z^+	Z^0
DOH+	$DOPAH^+$ Z	138.7	ref	−40.55

potentials obtained using B3LYP calculations (Figure 5). The match is obvious. This makes it possible to avoid tedious vibrational analysis (with numerical gradients) when DLPNO−CCSD(T) method is used and to calculate redox potentials in good approximation using the vertical ionization energies and/or electron affinities.

3.6. Statistical Analysis. The molecular descriptors calculated by the B3LYP method were subsequently analyzed using advanced statistical methods.[34] These methods work with a huge data set containing 16 molecular properties for 20 molecules, i.e. 320 entries (Table 5). Cluster Analysis (CA) is a kind of classification method that classifies similar objects or observables into groups according to their "distance". A squared Euclidean distance metric was used along with the Wards method. The results are shown in Figure 6 for objects (molecules) and observables (molecular properties). It is clear that 20 species can be classified into four groups: (i) dopamine and noradrenaline in canonical forms; (ii) dopamine, noradrenaline and adrenaline in zwitterionic forms; (iii) adrenaline and DOPA molecules, where the subgroup consists of two tyrosine forms; (iv) own group forms $DOPAH^+$. Of the observables: (i) bulk properties form their own group (polarizability al, solvated surface S and volume V, total entropic term ST, zero-point vibration energy Z, and quadrupole moment Q); (ii) collective electronic properties are classified together (ionization energy I, energy of HOMO, electronegativity X and hardness H), (iii) reduction parameters electrophilicity O and the reduction potential Er; (iv) the remaining properties (A, Lu, Eo, and p) form the last group.

Principal Component Analysis (PCA) is a type of multivariate statistical method that creates *principal components* based on a linear combination of variables that contain the most variance. A PCA biplot is drawn in Figure 7 to show which molecular properties are correlated (close lying rays)/anticorrelated (opposite rays)/noncorrelated (perpendicular rays). In accordance with CA, variables located in adjacent rays are correlated with each other: {I, Ho, X, H}, {O, Er, Q}, {al, Z, S, V, ST}, and {A, Lu, Eo, p}. This analysis also confirms a tight correlation of the reduction potential (Er) with the

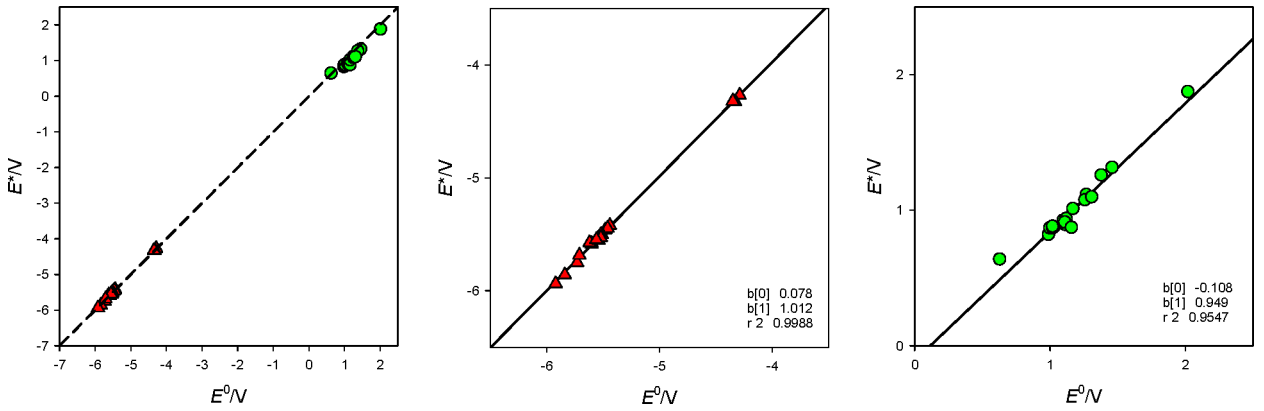

Figure 4. Correlation of the standard redox potential E^o derived from the reaction Gibbs energy and the approximate expression E^* based on the electronic energy (ionization energy/electron affinity): $E_{ox}^* = -E_i/F$, $E_{red}^* = -E_{eg}/F$. Green circles−electron affinity, red triangles−ionization energy. Dashed line−ideal correlation. Solid lines−least-square fit.

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Table 8. Molecular Descriptors Calculated by the DLPNO−CCSD(T) Method Using Ionization/Affinity Processes in Water[a]

aug-cc-pVTZ basis		Redox properties				Approximate			Properties of neutral molecules at SCF level					
Molecule (conformer)		E_i	E_{eg}	χ	η	ω	E_{ox}*	E_{red}*	p	−Q	S	V	−HOMO	LUMO
Canonical forms (A)														
DA1	Dopamine A1	133.9	−12.7	73.3	60.6	44.3	−5.81	0.55	2.972	49.38	726	1283	189.3	19.4
DA2	Dopamine A2	135.0	−10.9	73.0	62.1	42.9	−5.86	0.47	3.885	48.04	724	1281	190.0	19.2
NA1	Noradrenaline A1	135.7	−19.2	77.5	58.2	51.6	−5.88	0.83	2.476	54.57	758	1365	191.5	18.9
NA3	Noradrenaline A3	136.2	−11.6	73.9	62.3	43.9	−5.91	0.50	5.495	54.76	753	1358	192.1	18.7
AD1	Adrenaline A1	135.8	−19.3	77.5	58.3	51.6	−5.89	0.84	1.161	57.63	831	1493	192.1	18.6
AD2	Adrenaline A2	136.7	−19.0	77.8	58.8	51.5	−5.93	0.83	4.149	55.36	829	1493	192.8	18.4
DO1	DOPA A1	135.3	−19.6	77.4	57.9	51.8	−5.87	0.85	1.802	61.43	843	1536	191.4	18.9
DO1h	DOPA A1h	135.3	−20.5	77.9	57.4	52.9	−5.87	0.89	5.536	69.09	834	1523	191.7	18.9
Tyr2h	Tyrosine A2h	143.3	−26.0	84.6	58.6	61.1	−6.21	1.13	5.781	57.99	781	1444	197.9	18.8
Zwitterionic forms (Z)														
DAz	Dopamine	103.8	−20.4	62.1	41.7	46.2	−4.50	0.88	30.18	38.88	517	1274	160.5	18.9
NAz	Noradrenaline	104.9	−19.7	62.3	42.6	45.6	−4.55	0.85	28.62	44.61	753	1363	161.3	18.4
ADz	Adrenaline	104.9	−13.8	59.3	45.6	38.6	−4.55	0.60	29.15	53.55	826	1495	161.2	18.6
DOz	DOPA	136.3	−24.2	80.2	56.0	57.5	−5.91	1.05	12.25	75.75	837	1537	192.9	18.7
DO+	DOPAH$^+$	138.7	−40.6	89.6	49.1	81.8	−6.01	1.76	(13.2)	(49.0)	848	1540	195.2	17.4
Tyrz	Tyrosine	144.6	−25.1	84.8	59.7	60.2	−6.27	1.09	15.99	58.14	782	1447	198.8	18.6

[a]See footnote to Table 5, E_{ox}* = $-E_i/F$, E_{red}* = $-E_{eg}/F$.

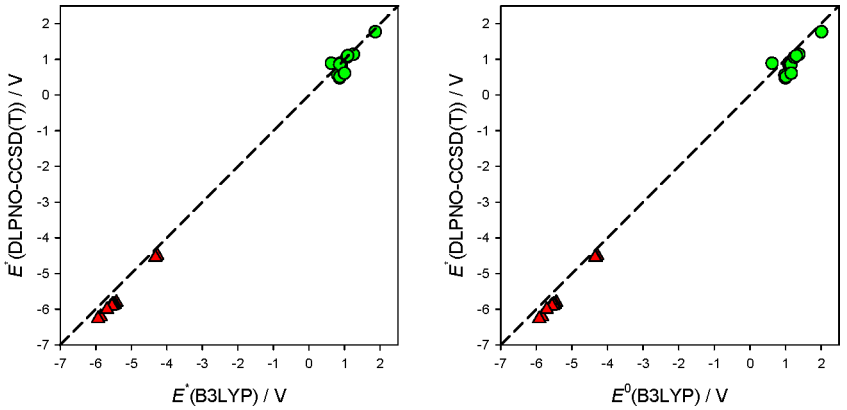

Figure 5. Correlation of the approximate redox potentials E* calculated by B3LYP and DLPNO−CCSD(T) methods.

electrophilicity (O), and the oxidation potential (Eo) with the energy of -HOMO (Ho).

Observables were subjected to Pearson's pairwise correlation: high correlation coefficients show I−X = 0.93, I−Ho = 1.00, I−Eo = −1.00, A−O = −0.98, A−Er = −0.98, X−Eo = −0.93, X−Ho = 0.93, O−Er = 0.96, Eo−Ho = −1.00, S−V = 0.99, S−ST = 0.99, and V−ST = 0.97 (Table S7). The matrix plot of observables is given in Table S8. One can monitor visually the (linear) correlation of molecular properties. Molecular electrostatic potential is plotted on isosurface contours and displayed in Figure S1. This brings information about spatial localization of electrophilic/nucleophilic domains.

3.7. Reproduction of Experimental Data. Available experimental data for catecholamines ion water are rather scarse; they cover mostly the vibrational spectra, ionization energies *in vacuo*, and voltammetry in solutions; some data are collected in Table 2. As already mentioned, the voltammetric data involve two electron transfer accompanied by protonation and a geometry rearrangement to dopaminequinone;[9−16,35−38] therefore the one-electron transfer studied here cannot be counter-studied by voltammetry. Moreover, the voltammetric studies in diluted solutions are influenced by pH, temperature, scan rate, supporting electrolyte of unknown electric permittivity, etc. When the solvated molecule approaches electrode, its solvation shell is no longer spherical: it resembles a comet with tail. Thus, the elementary electron transfers proceed from a partly desolvated species of unknown constitution. The calculated absolute redox potentials refer to one-electron processes and they are free of the above complications.

There are several publications on the vertical ionization energy of dopamine studied using DFT and HF family of calculations;[39−44] these are collected in Table S9. The experimental value of the adiabatic ionization energy is 7.67 eV, so the vertical ionization energies are higher.[40] Net Hartree−Fock calculations in various basis sets yield values that are severely underestimated but correction for correlation energy by the MP2 method significantly increases the calculated E_i. B3LYP calculations in the largest basis sets give E_i(vertical) ∼ 7.6−7.8 eV.

Experimental data provide evidence that dopamine and the members of its family (noradrenaline, adrenaline, DOPA, abbr. Ar(OH)$_2$) are effective antioxidants trapping radicals in aqueous solutions.[45,46] One of the mechanism is SPLET (Sequential Proton Loss Electron Transfer) which accelerates

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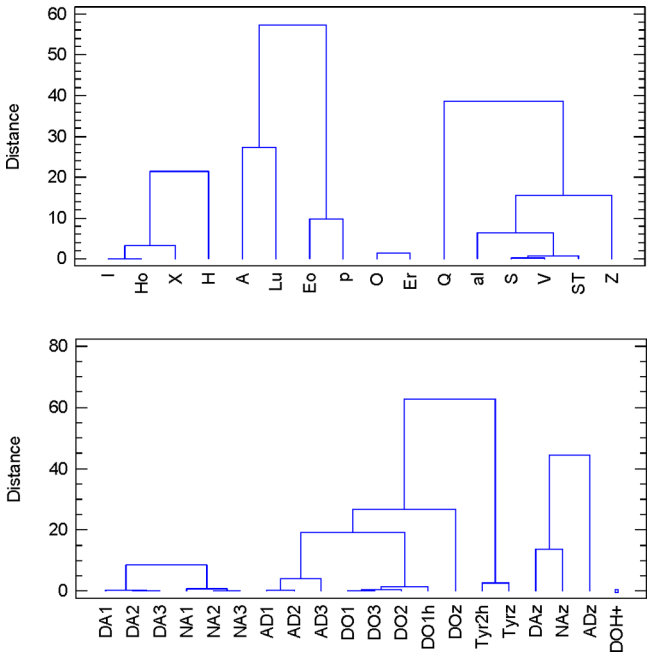

Figure 6. Results of cluster analysis. Top—observables, bottom—objects. Abbreviations according to Table 5.

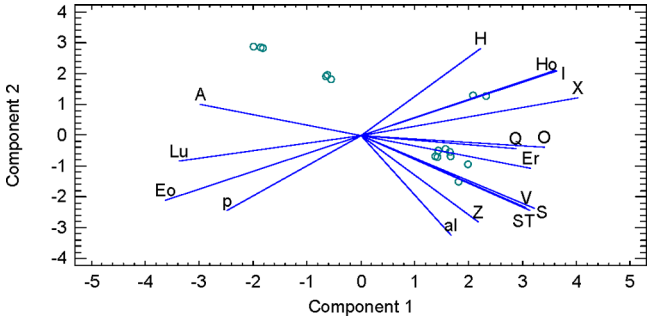

Figure 7. Biplot of principal component analysis for properties (rays) and molecules (points). Abbreviations according to Table 5.

the reaction rate 140 times as the pH varies from 5.5 to 7.4. Deprotonation of the hydroxyl group $Ar(OH)_2 + H_2O \rightarrow Ar(OH)O^- + H_3O^+$ is followed by rapid electron transfer from the phenolate anion (as dpph•) to the electron deficient radical $Ar(OH)O^- + dpph^{\cdot} \rightarrow Ar(OH)O^{\cdot} + dpph^-$. This process was correlated with the calculated HOMO energies (*in vacuo*). Some data on the HOMO energies are given in Table S10. Note that Koopmans theorem $E_i \sim -E(\text{HOMO})$ is not satisfied in general. In addition, the values of HOMO *in vacuo* are significantly reduced when switching to water as a solvent. Ionization energy is connected with the antioxidant capacity of catecholamines, because this quantity is directly related to one of the mechanism that drives the oxidation process—electron transfer.

The calculated absolute oxidation potentials for dopaminergic molecules in water are very similar: −5.48, −5.54, −5.60, −5.52, and −5.56 V for the most stable dopamine (DA2), noradrenaline (NA3), adrenaline (AD2) and DOPA (DO1 and DOz) conformers. This corresponds to a slight variation in the EC_{50} antioxidant index (half maximal effective concentration in the DPPH · assay): 10.5, 10.6, 10.5, and 6.9 μM.[33] On the other hand, reduction potentials correlate with the antireduction activity (exemplified by carotenoids, phenols and flavonoids).[47] Some compounds have been identified as both antioxidands and antireductands (quercetin, caffeic acid, fumarate), and such ambiguity is quite common within biomolecules.

The infrared spectra of dopamine have been collected using the IR and Raman techniques;[48−50] these are presented in Table S11 and Figure S2, along with calculated (unscaled) spectra using solvent-free and solvated molecules in the canonical and zwitterionic forms, respectively. It is seen that the solvent effect to the vibrational frequencies of the canonical structure is moderate: only 5 vibrational frequencies of a total of 60 differ by more than 20 cm^{-1}. For the zwitterionic form the situation is different: 18 frequencies differ on solvation by more than 20 cm^{-1}.

4. CONCLUSIONS

The present work has certain advantages over the fragmentary quantum-chemical studies found in the literature. The novelty of the present communication is that dopamine, noradrenaline, adrenaline, DOPA and tyrosine were considered in three forms (conformers A1, A2, A3) for canonical structures and one zwitterionic form (Z). In total, 20 species were studied in three oxidation states: as a neutral molecule, molecular cation and molecular anion, so 60 structures were subjected to full geometry optimization and complete vibrational analysis using B3LYP method in def2-TZVPD basis set.

(i) The studied objects (tyrosine, dopamine, noradrenaline, adrenaline and DOPA) are members of a series having similar molecular structure. The question is how such a similarity translates into a similarity of electronic and thermodynamic properties when studied by consistent theoretical methodologies: B3LYP as a hybrid variant of DFT methods, and the DLPNO−CCSD(T) method with a controlled contribution to the correlation energy. (ii) All studies were done in water as a solvent, where experimental data are greatly lacking. (iii) The ability to reproduce experimental data in a vacuum was tested by calculating the vertical and adiabatic ionization energies and vibrational spectra; the agreement is satisfactory. (iv) The calculated molecular properties include two classes: (A) energetic and electric properties of neutral species, such as dipole moment p (measure of polarity, or charge separation), quadrupole moment Q (measure of eccentricity of the charge cloud), dipole polarizability α (the ability of the electron cloud to be distorted in an electric field), solvated surface S and solvated volume V, zero-point vibrational energy E_{zpe}, and total entropic term $S^{\circ}\cdot T^{\circ}$; and (B) properties that characterize the redox processes forming ionized forms, such as adiabatic ionization energy E_i (for electron withdrawal), electron affinity E_{eg} (for electron attachment), chemical hardness η (electronic force constant, resistance to change in electron density), molecular electronegativity χ (electronic gradient, driving force of electron transfer), electrophilicity index ω (electrophilic power), and absolute oxidation E_{ox}° and reduction E_{red}° potentials (thermodynamic driving forces for oxidation/reduction).

1. The stability of structural forms (A1, A2, A3, and Z) was assessed using the standard Gibbs energy. B3LYP calculations confirm that catecholamines (dopamine, noradrenaline, and adrenaline) are more stable in their canonical forms A2 (by 3−6 kcal mol^{-1}), while related α-amino acids (DOPA and tyrosine) are more stable in

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their zwitterionic forms Z (by 2−6 kcal mol^{-1}) in water as a solvent.

2. Koopmans' theorem approximating the ionization energies violates by ca. 9 kcal mol^{-1}. The dipole moment for the canonical forms varies unsystematically (between p = 1.6 and 5.7 D); it is an order of magnitude higher for the zwitterionic forms (between p = 12 and 29 D).
3. The absolute redox potentials (evaluated from the reaction Gibbs energies) correlates with the electronic properties, such as adiabatic ionization energies, electron affinities, molecular electronegativities and electrophilicity indexes along a straight line. In a good approximation, the redox potential can be expressed using the difference in electronic energies, i.e. adiabatic ionization energy and/or adiabatic electron affinity *via* $E^* = -\Delta E/F$.
4. The lowest standard absolute reduction potential is identified for dopamine (Z form) E_{red}° = 0.63 V, and 1.00 V for dopamine (A2); the highest one E_{red}° = 1.31 V for tyrosine (Z) and 1.38 V for tyrosine (A2h). A very high value of E_{red}° = 2.02 V was found in DOPAH$^+$ (Z), indicating that this moiety can act as an efficient oxidizing agent (antireductant). The calculated absolute oxidation potentials for dopaminergic molecules is very similar: E_{ox}° = −5.48, to −5.56 V; this agrees with only a small variation in the antioxidant activity index IC_{50}.
5. The quantum-chemical calculations gave a huge data set containing 16 molecular properties for 20 molecules, i.e. 320 entries. This massive worksheet has been processed by advanced statistical methods: cluster analysis, principal component analysis, and Pearson's pair-correlation. They allow determining latent correlations among molecular properties and among objects (molecules). It is observed that canonical structures (A1, A2, A3) of dopamine and noradrenaline form a first group (I) of the mutual similarity; adrenaline and DOPA form the second distinct group (II); tyrosine spans the group (III); and zwitterionic forms of dopamine, noradrenaline and adrenaline form a separate class (IV). When comparing the most stable canonical conformers for group I{DA2, NA3/2}, II{AD2, DO1}, and III(Tyr2), the similarity/dissimilarity is given mostly by (i) electrophilicity index I{50−51}, II{52}, III{63} kcal mol^{-1}; (ii) absolute reduction potential I{1.0}, II{1.1}, III{1.4} V; (iii) dipole polarizability I{165, 171}, II{188, 189}, III{179} a_0^3; (iv) entropic term I{30}, II{34}, III{32} kcal mol^{-1}; and zero-point vibration energy I{114−117}, II{123−134}, III{121} kcal mol^{-1}.

The same qualitative conclusions are obtained using the DLPNO−CCSD(T) method. Ionization energies and electron affinities are higher when compared to B3LYP calculations. The redox potentials were lowered when studied by the DLPNO−CCSD(T) method using an approximation based on ionization energies and electron affinities. The highest reduction potential for DOPAH$^+$ (Z) relaxes to E_r^* = 1.87 V, still confirming an efficiency as an oxidizing agent (antireductant).

The approximate redox potentials calculated by the DLPNO−CCSD(T) method were correlated with the potentials obtained using B3LYP calculations. This makes it possible to avoid tedious vibrational analysis (with numerical gradients) when DLPNO−CCSD(T) method is used and to calculate redox potentials in good approximation using the vertical ionization energies and/or electron affinities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c10227.

Detailed tables of calculated molecular properties (Tables S1−S11), molecular electrostatic potential and vibrational transitions (Figures S1−S3) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. R.B. was responsible for the conceptualization and calculations, C.R. for the core of calculations, J.S. and I.R. for the medicinal aspects, A.M. for the literature search and driving figures.

Notes

The authors declare no competing financial interest.

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