Bulgarian Chemical Communications, Volume 46, Special Issue A (pp. 179 – 186) 2014

Influence of the environment on the antioxidant action of two 6-(propan-2-yl)-4-methyl-morpholine-2,5-diones

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Received May 21, 2014; Revised August 11, 2014

Dedicated to Acad. Dimiter Ivanov on the occasion of his 120th birth anniversary

Density functional theory was used to study diketo and enol structures of two cyclodidepsipeptides, 3-(2-methylpropyl)-6-(propan-2-yl)-4-methyl-morpholine-2,5-dione and 3,6-di(propan-2-yl)-4-methyl-morpholine-2,5-dione, able to form radicals and act as reducing agents. Three possible mechanisms of antioxidant action were considered: H-atom abstraction (HAT), single electron transfer (SET), and sequential proton loss electron transfer (SPLET). The influence of the environment was elucidated by calculating the respective dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE) in non polar solvent benzene, and polar solvents methanol and water. The preferred mechanism in different environment was outlined based on the obtained reaction enthalpies and showed that the reaction pathway depends on the environment polarity. HAT is the most probable mechanism in nonpolar phase, while SPLET is the preferred one in polar environment.

Key words: cyclodidepsipeptide, 6-(propan-2-yl)-3-methyl-morpholine-2,5-dione, antioxidant activity, reaction mechanism, solvent polarity

INTRODUCTION

Cyclodidepsipeptides are the simplest members of cyclodepsipeptides family, which have an ester group and an amide group in the same 6-membered ring. They contain only one residue of amino acid and one residue of lactic, α-hydroxyisovaleric or other α-hydroxy acid. The cyclodidepsipeptides exhibit antimicrobial [1,2], immunomodulating [1,3,4], anticoagulant [5], and inhibitory activity towards acyl-CoA:cholesterol acyltransferase [6], α-glucosidase [7-9] and xanthin oxidase (XO) [10]. In this way they are interesting candidates for pharmacological application. As a part of our continuing study of identification [11], synthesis [11,2] and biological activities [1,2,4,10] of cyclic didepsipeptides, recently we elucidated the antioxidant activity of the two synthesized cyclodidepsipeptides 3-(2-methylpropyl)-6-(propan-2-yl)-4-methyl-morpholine-2,5-dione (**1a**) and 3,6-di(propan-2-yl)-4-methyl-morpholine-2,5-dione (**2a**), by applying two assays, 2,2-diphenyl-1-picrylhydrazyl (DPPH)-radical scavenging capacity and total reducing power [12]. Our data indicate moderate antioxidant potentials of the two studied cyclodepsipeptides. A high correlation between DPPH-radical scavenging capacity and total reducing power were found. Diketo, enol and dienol structures of compounds **1** and **2** (Fig. 1), able to form radicals and act as reducing agents, were examined using density functional theory (DFT) calculations in gas phase. The calculated total energies indicate the diketo form "**a**" as the most stable.

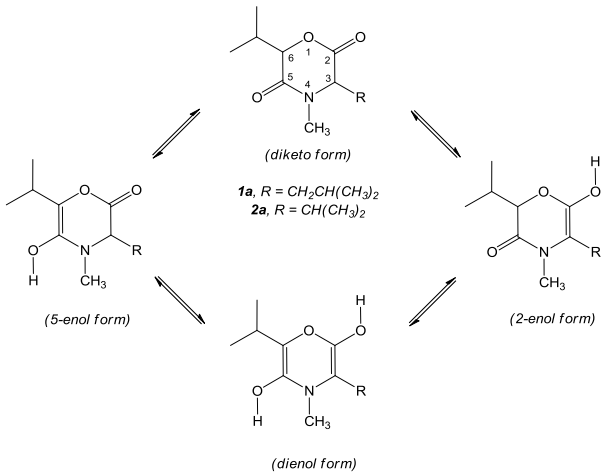

Fig. 1. Tautomeric structures of compounds **1** and **2**.

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One possible mechanism by which the antioxidants can deactivate a free radical is H-atom abstraction (HAT mechanism) [13-16]:

$$A\text{-}H \rightarrow A^{\cdot} + H^{\cdot} \text{ (HAT)}$$

The efficacy of the antioxidant to react via HAT is characterized by the bond dissociation enthalpy (BDE). Higher stability of A, i.e., lower BDE values, corresponds to good antioxidant capacity of A-H. Another possible mechanism is electron transfer (SET mechanism), in which the radical cation is first formed followed by deprotonation [16-19]:

$$A\text{-}H \rightarrow A^{+\cdot} + e^{-} \text{ (SET)}$$
$$A^{+\cdot} \rightarrow A^{\cdot} + H^{+}$$

For evaluation of reactivity via SET, the ionization potential (IP) is used. A lower IP implies an easier electron release. More recently a third mechanism has been discussed – sequential proton loss electron transfer (SPLET) [13, 20]:

$$A\text{-}H \rightarrow A^{-} + H^{+} \text{ (SPLET)}$$
$$A^{-} \rightarrow A^{\cdot} + e^{-}$$

In the first step of this mechanism an anion is formed by initial proton transfer, followed by an electron transfer. The proton affinity (PA) of the formed anion is used as a measure for reactivity via SPLET. Higher stability of A^{-}, i.e., lower PA values, indicates an easier extraction of the proton.

The net result of the three antioxidant action mechanisms is the same. SET and SPLET mechanisms are favoured in polar environment because the generated charged species are stabilized by the solvent. Based on calculation of the reaction enthalpies for each of the mechanisms, it is possible to suggest the most probable mechanism of action of a particular group of compounds [13].

In the case of the two cyclodidepsipeptides **1** and **2** studied by us, hydrogen atom abstraction from the activated C-H group at 3-position in the diketo form was found to be the most probable mechanism of antioxidant action in gas phase. However, these calculations do not account for the influence of the polarity of the surrounding medium. For this reason, the main goal of the present contribution is to determine the preferred mechanism of antioxidant action in polar environment as a description of the processes taking place in the living organism. Calculations in benzene will be performed in order to improve the description of the antioxidant action of **1** and **2** in nonpolar environment representing the biological membranes. The polar medium is also very important as illustration of the biological liquids and therefore the relevant enthalpies will be calculated in water. Based on the obtained enthalpies it will be clarified which of the three possible mechanisms of antioxidant action (HAT, SET or SPLET) is the most probable in polar liquid environment. In this way, the expected mechanism of antioxidant action of the title compounds will be described for all potential sites in the living organism. The study will be complemented also by computations in methanol in order to take account of the conditions used in the *in vitro* radical scavenging assays [12].

COMPUTATIONAL DETAILS

All theoretical calculations were performed using the Gaussian 09 package [21] of programs. Geometry and vibrational frequencies of species studied were performed by analytical gradient technique without any symmetry constraint. All the results were obtained using the density functional theory (DFT), employing the B3LYP (Becke's three-parameter non-local exchange [22] and Lee *et al.* correlation [21] potentials). To establish the stability order for the neutral, radical and ionic species in solvent we used the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM) [23] at the same level of theory.

The geometries of all possible isomers of the studied compounds, radicals, radical cations were fully optimized by application of the UB3LYP functional in conjunction with the 6-311++G** basis set. The optimized structures were further characterized by analytical computations of harmonic vibrational frequencies at the same level. Dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE) were calculated according the equations given by Klein *et al.* [13].

$$BDE = H(A^{\cdot}) + H(H^{\cdot}) - H(A\text{-}H)$$
$$IP = H(A^{+\cdot}) + H(e^{-}) - H(A\text{-}H)$$
$$PDE = H(A^{\cdot}) + H(H^{+}) - H(A^{+\cdot})$$
$$PA = H(A^{-}) + H(H^{+}) - H(A\text{-}H)$$
$$ETE = H(A^{\cdot}) + H(e^{-}) - H(A^{-})$$

The enthalpy of hydrogen atom, $H(H^{\cdot})$, for each solvent was obtained by the same method and basis set. All reaction enthalpies were calculated for 298 K. Solvation enthalpies of proton $H(H^{+})$, electron,

H(e^-), in organic solvents, determined using IEF-PCM DFT/B3LYP/6-311++G** calculations, were taken from the literature [24].

Natural bond orbitals (NBO) analysis [25-27] has been performed to characterize the delocalization of electron density within the molecule.

RESULTS AND DISCUSSION

In order to determine the preferred geometry of the compounds studied, a large number of probable geometries should be constructed taking into account the flexibility of the ring system and the change-over to chair- and boat-conformations. For each boat or chair ring conformation, all relevant combinations of axial and equatorial positions of the 3- and 6-alkyl groups should also be considered. In previous studies [2,11,28], it was demonstrated that in all cases the morpholine-2,5-dione ring adopts boat conformation and the most favourable orientation of the larger 3- and 6-substituents is equatorial/axial and axial/equatorial.

The title compounds, **1a** and **2a**, are synthesized in a condensation reaction of 2-bromo-3-methylbutanoyl chloride with *(L)*-N-methylleucine or *(L)*-N-methylvaline, respectively, followed by intramolecular cyclization [11]. The mechanism of the amide group formation does not involve conversion of the stereo configuration of the amino acid residues, therefore only the *(3S)* diastereo-isomers could be considered in the structure optimizations. In gas phase the most stable among them is the *(3S,6R)* form [11]. It was also found that the higher polarity of the environment (in solvents such as water and DMSO) does not influence the stability order of diastereoisomers of a related com-pound 6-(propan-2-yl)-3-methyl-morpholine-2,5-dione [2]. For this reason, in the present study, only the most stable gas-phase diastereoisomers of **1a** and **2a** were taken for the optimization in benzene, water and methanol. The structural parameters of **1a** and **2a** in all employed solvents are similar. The morpholine-2,5-dione rings are in boat confor-mations with the sp^3 C3 and C6 atoms displaced by 25-35^o out of the plane formed by O1, C2, N4 and C5.

For the antioxidant action, the interconversion between diketo, enol and dienol structures is more important as it leads to the formation of different radicals able to act as reducing agents. In order to examine the prototropic tautomerism, the relative stability of the two most stable gas-phase structures of **1** and **2** – diketo **"a"** and 2-enol **"b"** were optimized in the different solvents. The calculated total energies are summarized in Table 1.

Table 1. Calculated total and relative energies, and dipole moments of neutral, radical and ionic species of **1** and **2**.

Species		E_{tot}, (Hartree)	ΔE, kJ/mol	μ, D		E_{tot}, (Hartree)	ΔE, kJ/mol	μ, D
				Benzene (2.271)[a]				
Molecule	**1a**	-750.593201		4.08	**2a**	-711.261514		4.27
Enol	**1b**	-750.567096	68.53[b]	3.35	**2b**	-711.239677	57.3[a]	3.28
Radical	**1c**	-749.963946		4.46	**2c**	-710.636419		4.37
	1d	-749.946488	45.83[c]	2.91	**2d**	-710.615411	55.1[b]	3.23
Radical cation	**1e**	-750.310199		3.52	**2e**	-710.981092		3.33
Anion	**1f**	-750.065192		6.80	**2f**	-710.737265		5.31
	1g	-750.047205	47.2[d]	6.56	**2g**	-710.719960	45.4[c]	4.33
				Methanol (32.613)[a]				
Molecule	**1a**	-750.600900		5.00	**2a**	-711.269287		5.13
Enol	**1b**	-750.573064	73.1[b]	4.23	**2b**	-711.245598	62.2[a]	4.18
Radical	**1c**	-749.971607		5.40	**2c**	-710.643888		5.38
	1d	-749.952652	49.7[c]	3.51	**2d**	-710.621738	58.1[b]	3.84
Radical cation	**1e**	-750.345624		4.81	**2e**	-711.015835		4.16
Anion	**1f**	-750.103919		8.67	**2f**	-710.775302		6.95
	1g	-750.083373	53.9[d]	4.97	**2g**	-710.757432	46.9[c]	3.28
				Water (78.355)[a]				
Molecule	**1a**	-750.601392		5.07	**2a**	-711.269769		5.19
Enol	**1b**	-750.573430	73.4[b]	4.29	**2b**	-711.245968	62.5[a]	4.24
Radical	**1c**	-749.972081		5.47	**2c**	-710.644359		5.45
	1d	-749.953045	50.0[c]	3.56	**2d**	-710.622133	58.3[b]	3.88
Radical cation	**1e**	-750.347428		4.91	**2e**	-711.017557		4.21
Anion	**1f**	-750.105869		8.80	**2f**	-710.777227		7.07
	1g	-750.085170	54.3[d]	4.93	**2g**	-710.759315	47.1[c]	3.25

[a] Relative dielectric permittivity [35 and references therein]; [b] $\Delta E = E_{(enol)} - E_{(keto)}$; [c] $\Delta E = E_{(radical\ 1c)} - E_{(radical\ 1d)}$; [d] $\Delta E = E_{(anion\ 1f)} - E_{(anion\ 1g)}$.

In all cases the energy differences between diketo and enol forms are much higher than 50 kJ/mol; therefore prototropic conversion is not expected to occur. The values in water are higher than the corresponding in benzene (Table 1) showing in this way that the diketo structures of **1** and **2** are further stabilized by the polar environment. This result is in accordance with the experimental NMR and IR data for **1** and **2** showing that both compounds are present in diketo form in solid state and chloroform. The possibility of prototropic tautomerism of a related compound, 6-(propan-2-yl)-3-methyl-morpholine-2,5-dione, was recently studied in solution and in this case again no evidence of enol formation was found neither in polar nor in nonpolar environment [2]. So further only diketo forms will be taken into account for evaluation of their capability to form radicals and act as reducing agents via HAT, SET and SPLET mechanisms in different environment.

The calculated reaction enthalpies, involved in the three mechanisms of antiradical activity of **1** and **2**, are presented in Table 2. Two possible sites for hydrogen atom abstraction were estimated – C3 (radicals **"c"**) and C6 (radicals **"d"**, respectively) as well as for generation of anion species – deprotonation at C3 (anions **"f"**) and C6 (anions **"g"**, respectively).

Table 2. DFT bond dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE) values of **1a** and **2a** in kJ/mol.

Species	BDE	IP	PDE	PA	ETE
		Gas phase[a]			
1a	306	824	782	1439	167
2a	294	818	776	1427	167
		Benzene (2.271)[b]			
1a	312	733	-7	459	267
2a	301	727	-12	449	266
		Methanol (32.613)[b]			
1a	311	583	-78	235	269
2a	300	578	-85	226	267
		Water (78.355)[b]			
1a	302	559	-59	246	254
2a	291	555	-65	238	252

[a] According to [12]; [b] Relative dielectric permittivity [35 and references therein].

Site C3 is more reactive both via HAT and SPLET as demonstrated by the relative stability of the radicals produced by proton transfer from C3 and C6 (HAT) and the anions produced by deprotonation at C3 and C6 (SPLET). The energy differences between the more stable radicals of **1c** and **2c** and the less stable **1d** and **2d** in benzene is smaller than in water. The same trend is observed also with the stability of anions **1f** and **2f** versus **1g** and **2g**.

Important information for the radical stability could be derived also from atomic spin population analysis. The energy of a free radical can be efficiently decreased if the odd electrons are delocalized through the conjugated system. Fig. 2 illustrates the spin density distribution over the fragments in **1c**, **1d**, **2c** and **2d** in benzene and water obtained by NBO population analysis. Approximately 0.5 of the spin density in **1c** and **2c** is localized on C3 and the rest is distributed equally between the ester and the amide moiety. The spin density in the radicals generated by abstraction of a hydrogen atom from C6 is less effectively delocalized indicating lower stability of the respective radicals. Comparing the values in benzene and water, it could be concluded the in polar environment **1c** and **2c** show slightly higher stability which would be favourable for their radical scavenging efficiency.

In order to rationalize the solvent polarity significance for the stabilization of the molecules and their derivatives (enols, radicals, and ions), data for their dipole moments are presented in Table 1. As could be seen there, the polarity of the anionic derivatives is considerably higher than those of the radical species. Therefore, the polarity of the environment is expected to have a bigger impact on the processes involving anionic species. In accordance with this, when analysing the reaction enthalpies for the HAT, SET and SPLET mechanisms in gas phase [12] and in different solvents presented in Table 2, it can be noted the C-H bond dissociation enthalpies (BDEs) are similar in all solvents i.e. the energy requirements for HAT do not change much with the environment polarity. On the other hand, the solvation of the electron and the positively charged radical species of **1a** and **2a** exerted even by nonpolar solvents such as benzene lowers the IP values in liquid phase. As a result of the greater stabilisation in polar environment (water) the corresponding IPs are significantly lower than in benzene. As the SPLET mechanism is also involving charged species, the respective reaction enthalpies are affected by the solvation and the medium polarity. Mainly due to the large enthalpy of H^+ solvation, the PAs in benzene differ dramatically from those in gas-phase. They are further lowered in aqueous environment.

The comparison of the respective BDE, IP and PA values outlines clearly the most probable mechanism of antioxidant activity of **1a** and **2a** in

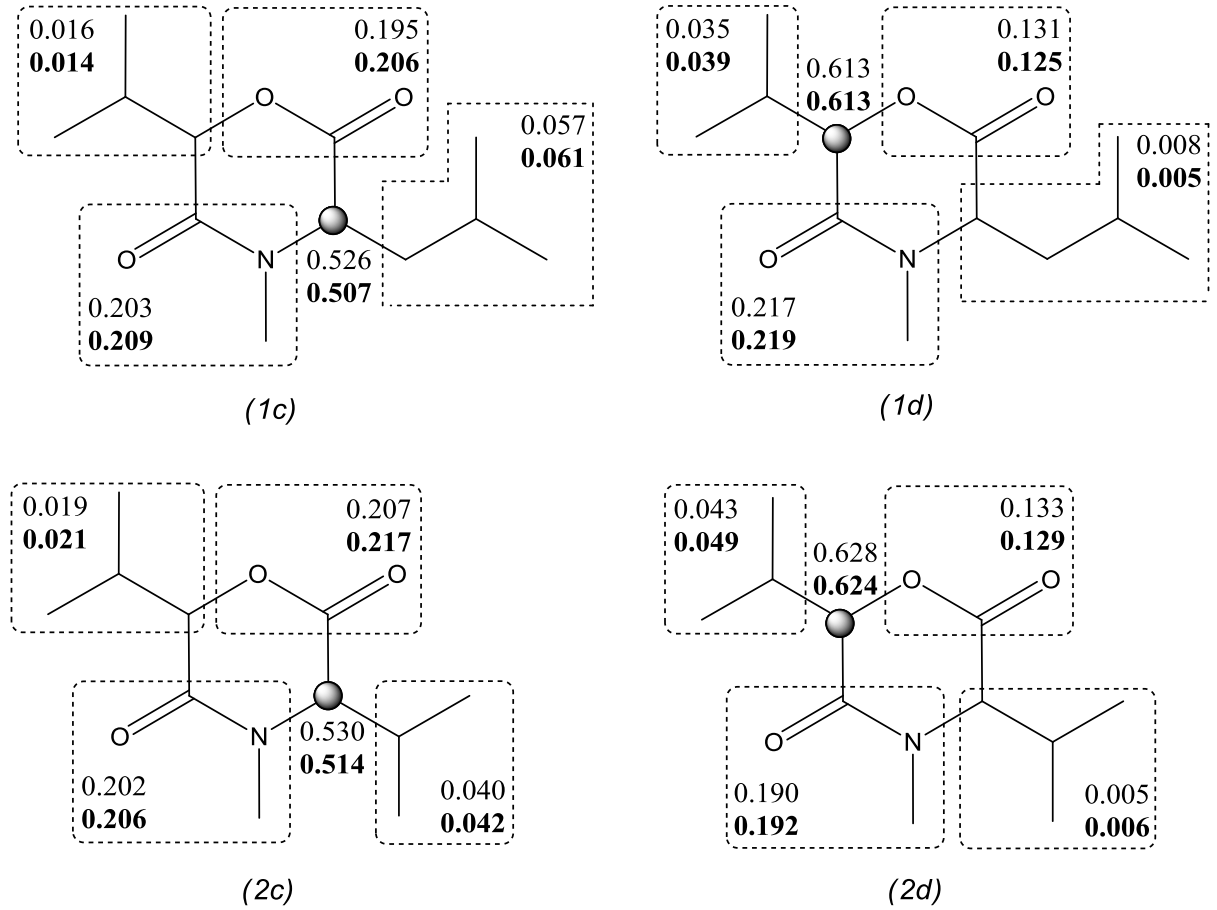

Fig. 2. Calculated NBO spin density over fragments of radicals **1c**, **1d**, **2c** and **2d** in benzene and water (in bold).

the polar and nonpolar environment. Similarly to the gas phase, in benzene the BDE values of **1a** and **2a** are lower than the IPs and PAs which supports the assumption of HAT as the most probable mechanism in nonpolar environment. Taking into account the interactions with the surrounding nonpolar molecules is necessary to conclude accurately on the preferred mechanism in nonpolar environment. These interactions change dramatically the thermodynamic requirements of the SPLET reaction and examination of the gas-phase reaction enthalpies alone might not lead to the right conclusions.

Clarification of the possible mechanism of antioxidant action of **1a** and **2a** in nonpolar environment is very important in relation to the lipophilic nature of both compounds and their favourable physico-chemical properties for efficient blood penetration and intestinal absorption [28]. This would allow their transportation to different possible sites of action. Their partition into lipid bilayers would provide increased local concentration and thus antiradical activity. Free lipid-peroxyl radicals of the type LOO˙typically display a BDE of about 367 kJ/mol [29]. Thus, an effective chain-breaking antioxidant that could prevent lipid peroxidation should have a lower BDE value. A well-known antioxidant that reacts via HAT is α-tocopherol, for which a BDE values of 327 kJ/mol was calculated in gas-phase and 293 kJ/mol in water using the same computational scheme [13]. In the present case, the calculated BDE values are also within this range and suggest good potential of **1a** and **2a** to prevent lipid peroxidation. Compounds **1a** and **2a** exhibit antimicrobial [1] and antioxidant [12] activity. Furthermore, they were excellent inhibitors of XO and significantly suppressed the activation of the nuclear factor κB (NF-κB) [10]. NF-κB is a redox-associated transcription factor that is required for maximal transcription of a wide array of pro-inflammatory mediators. It is well known that Reactive Oxygen Species (ROS) stimulate the NF-κB pathway in the cytoplasm through IκB (inhibitor of kappa B) degradation. Overexpression of the antioxidant proteins was shown to inhibit NF-κB activation [28]. Xu *et al.* [30] have found NF-κB binding site on human xanthine dehydrogenase (XDH) gene, and it is

known that XDH conversion to XO may represent a feed-forward mechanism for stimulation of ROS production [31]. It can be concluded that NF-κB may directly affect the XO activity and ROS production. **1a** and **2a** were confirmed as non-toxic in thymocites [1] and therefore may give a promise to be used in the treatment of gout and other excessive uric acid production or inflammatory conditions [10].

The feasibility of the three mechanisms of antioxidant action in polar environment will give us a clue to the processes in physiological liquids whose main constituent is water. The BDE values in the three polar solvents are similar to those in nonpolar environment, so the preferred reaction pathway depends on the changes in the IP and PA induced by the polar solvent. The reactivity of **1a** and **2a** via SET was estimated according to the principle defined by Wright *et al.* [16], i.e., when IPs drop to *ca*. 167 kJ/mol below phenol, the SET mechanism gains importance in solution. The IP value of phenol in water is calculated at the same theoretical level as 346 kJ/mol [13]. In all studied polar solvents, the IPs of **1a** and **2a** are higher than 500 kJ/mol. It implies that the SET mechanism is not preferred for this type of compounds in any kind of environment. SET mechanism is typical mainly for electron-donating compounds containing a conjugated system of double bonds. Such example are the pyrrolopyrimidines, which were described as effective *in vitro* and *in vivo* antioxidants possessing neuroprotective activity in brain injury and ischemia models [32]. Another class of compounds reported recently to act as lipid peroxidation inhibitors presumably via SET mechanism are the 2-amino-5-alkylidenethiazol-4-ones [33].

As can be seen in Table 2, the first step of SPLET has lower energy requirements than HAT and SET in water. This indicates the SPLET as the most probable mechanism in polar environment in general. In some cases, the HAT mechanism could be competitive to the SPLET one, because in spite of the low values of PA, the second step of the SPLET mechanism, i.e., electron transfer might require higher energy than the corresponding hydrogen atom abstraction [34]. However, in the present case not only the PAs, but also the ETE values are lower than the BDEs which confirms that the SPLET mechanism is the most probable mechanism of antioxidant action in polar environment.

The PAs in methanol are slightly lower than in water due to the greater solvation enthalpy of the proton [24]. Similarly to water solution, the expected mechanism of antioxidant action is SPLET.

CONCLUSION

Density functional theory (DFT) calculations in benzene, methanol and water were used to study diketo and enol structures of compounds **1** and **2**, able to form radicals and act as reducing agents. The calculated energy differences between diketo and enol forms are much higher than 50 kJ/mol and therefore prototropic conversion is not expected to occur. The ability of compounds **1** and **2** to be oxidized according to HAT, SET and SPLET mechanisms was estimated in the above-mentioned solvents. The environment polarity hardly affects the BDEs of the C-H bond, while the IPs and PAs are significantly lowered in the polar environment. The dramatic change of the reaction enthalpy of SPLET (three time less compared to the gas phase) results in a reversal of the antioxidant mechanism of **1** and **2** in polar solvents. Hence, HAT is the most probable mechanism in nonpolar phase, while SPLET is expected to be the preferred one in polar environment. Hydrogen atom abstraction and deprotonation might occur at two possible sites (C3 and C6), but C3 is found to be more reactive both via HAT and SPLET in all media.

Acknowledgments: *The financial support of this work by the National Science Fund of Bulgaria (Contracts: DMU-03/66 and RNF01/0110) and the Ministry of Education and Science of the Republic of Serbia (Grant No.172044) is gratefully acknowledged.*

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ВЛИЯНИЕ НА ОБКРЪЖАВАЩАТА СРЕДА ВЪРХУ АНТИОКСИДАНТНОТО ДЕЙСТВИЕ НА ДВА 6-(ПРОПАН-2-ИЛ)-4-МЕТИЛ-МОРФОЛИН-2,5-ДИОНА

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Постъпила на 21 май 2014 г.; Коригирана на 11 август 2014 г.

(Резюме)

Теорията на плътностния фукционал беше използвана за изследване на дикето и енолни форми на два циклодидепсипептида, 3-(2-метилпропил)-6-(пропан-2-ил)-4-метил-морфолин-2,5-дион и 3,6-ди(пропан-2-ил)-4-метил-морфолин-2,5-дион, способни да образуват радикали и да действат като редуктори. Бяха разгледани три възможни механизма на антиоксидантно действие: откъсване на водороден атом (HAT), пренос на електрон (SET) и отделяне на протон, последвано от пренос на електрон (SPLET). Влиянието на полярността на средата беше изследвано чрез определяне на съответните енталпии на дисоциация (BDE), йонизационни потенциали (IP), енталпии на дисоциация на протона (PDE), протонни афинитети (PA) и енталпии на електронния пренос (ETE) в неполярен разтворител бензен и полярни разтворители вода и метанол. Предпочетеният механизъм в различните обкръжения беше изяснен на базата на получените енталпии. Резултатът показва, че реакционният път зависи от полярността на средата. Откъсването на водороден атом е най-вероятният процес в неполярна среда, докато в полярна среда предпочетен механизъм е отделянето на протон, последвано от пренос на електрон.