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Antiradical activity in the series of novel 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones: experimental study and quantum chemical prediction

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Abstract.
The antiradical activity of novel 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones: was predicted by means of quantum chemical calculations, by calculating the stability of radicals formed as a result of interaction of the test substances with diphenylpicrylhydrazyl (DPPH). The results of quantum chemical calculations are largely consistent with experimental data of antiradical activity, the regularities between antiradical activity and substituents in the aryl fragments of the test compounds were revealed.
Keywords: antiquantum chemical prediction, antioxidant, antiradical, DPPH, pyrrol-2-ones.

INTRODUCTION

Antioxidants are compounds possessing multiple biological and physiological activities: anti-inflammatory, antimicrobial and antitumor [1–8]. Previously, we have synthesized various heterocyclic compounds with antioxidant [9–12], antimicrobial, antimycotic, antitumor and other types of activity [13–19].

One of the main mechanisms specific to antioxidants is the antiradical mechanism, which has been studied in a series of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones that are the standards of antiradical activity (tocopherol, as well as its water-soluble analogue – Trolox). [20].

To reduce the number of synthesized compounds and their subsequent tests, we made an attempt to model antiradical activity using quantum chemical calculations. Simulation of antiradical activity consisted in predicting the stability of radicals formed as a result of binding of typical diphenylpicrylhydrazyl (DPPH) radicals. Earlier, we studied the radical-binding mechanism in mono- [21], bi- [22, 23] and tricyclic heterocycles [24].

Widely applied direct methods of estimation of antioxidant activity are developed on the basis of studying of influence of antioxidants on kinetics of model reactions of oxidation of biological materials. In practice, indirect methods are often used, according to which the parameters correlated with antioxidant activity of antiradical antioxidants are studied [25]. These methods include the method used by us and based on the interaction of potential antioxidants (PA) with stable radicals of 1,1-diphenyl-2-picrylhydrazyl (DPPH) **(fig. 1)**.

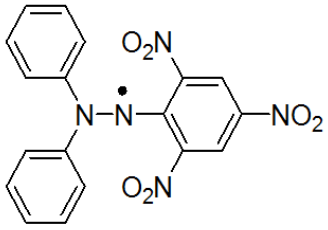

Fig. 1.

The reaction of DPPH with potential radical antioxidants occurs under the mechanism [26], according to which in the first stage, which is limiting, the PA molecule donates DPPH the most mobile hydrogen atom.

Since 1,1-diphenyl-2-picrylhydrazyl participates in all similar reactions, the ease of their occurrence and, consequently, the antiradical activity can also depend on the stability of the formed particle A• **(fig. 2)**.

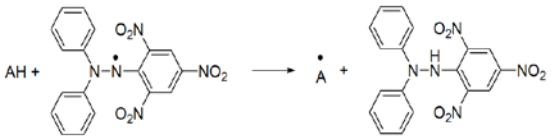

Fig. 2

Presumably, the antiradical activity of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones can be related to their ability to interact with a radical particle according to the scheme **(fig 3).**

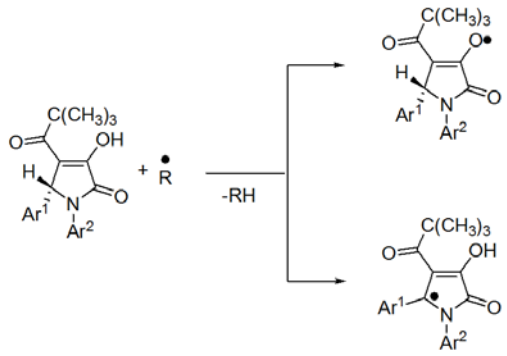

Fig 3.

The radical R• tears a hydrogen atom away from a fragment of pyrrol-2-one, converting it into another radical. Depending on the position of the teared-away hydrogen atom, the O-radical (upon tearing-away of the hydroxyl group hydrogen atom) or the C-radical (in case of tearing of hydrogen atom away from the carbon atom C^5) can form in this reaction.

MATERIALS AND METHODS

In order to predict the parameters of antiradical activity, we calculated the total energies of their molecules, as well as the corresponding O- and C-radicals, using the Firefly software package and the B3LYP/6-31(d) methodology [27]. As objects of study, we selected a series of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones **(fig. 4)** synthesized by us earlier [28].

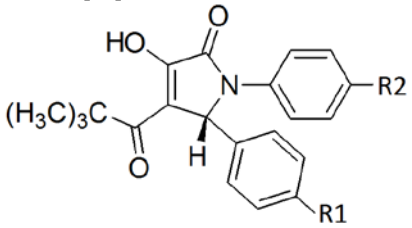

Fig. 4

Table 1 shows the values of total energies ($E_{tot.}$) in atomic units (AU) and the difference of their energies and energies of molecules (Δ, AU). From our point of view, the smaller the difference between the energies of a molecule and the radical formed from it, the more stable is the radical and the more antiradical activity of the parent molecule. Calculations show that C-radicals are more stable than O-radicals, which follows from a comparison of the values of their total energies. The experimental indices of antiradical activity are given in **Table 1.**

Table 1. Total energy of compounds (1–12) and radicals formed on their basis.

№	R1	R2	$E_{tot.}$, AU	$E_{1tot.}$ (o-radical)	Δ_{E1}	$E_{2tot.}$, AU (c-radical)	Δ_{E2}
1	H	H	-1093,3169	-1092,6716	**0,6453**	-1092,6858	**0,6311**
2	4-CH_3	H	-1132,6352	-1131,9901	**0,6451**	-1132,0044	**0,6308**
3	4-CH_3	4-CH_3	-1171,9532	-1171,3084	**0,6448**	-1171,3225	**0,6307**
4	4-NO_2	4-NO_2	-1502,3186	-1501,6707	**0,6479**	-1501,6855	**0,6455**
5	4-CH_3	4-OCH_3	-1247,1572	-1246,5132	**0,6440**	-1246,5271	**0,6301**
6	4-Br	4-CH_3	-3703,7793	-3703,1336	**0,6457**	-3703,1484	**0,6309**
7	4-Br	4-NO_2	-3868,9626	-3868,3161	**0,6465**	-3868,3302	**0,6324**
8	4-NO_2	H	-1297,8181	-1297,1707	**0,6474**	-1297,1866	**0,6315**
9	4-NO_2	4-OC_2H_5	-1451,6600	-1451,0137	**0,6463**	-1451,0289	**0,6311**
10	4-F	4-CH_3	-1231,8683	-1231,2228	**0,6455**	-1231,2376	**0,6307**
11	4-OCH_3	4-CH_3	-1247,1579	-1246,5138	**0,6441**	-1246,5279	**0,6300**
12	4-Cl	4-CH_3	-1592,2310	-1591,5851	**0,6459**	-1591,6000	**0,6310**

Table 2. Antiradical activity of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones (1–12) according to the experiment and to quantum chemical calculations.

Compound	Loss of radicals (Q), %	Place* in a series of antiradical activity according to the experiment	Place* in a series of antiradical activities according to calculations
1	20,11 ± 1,07	12	8
2	35,65 ± 0,93	8	5
3	72,86 ± 3,24	1	3
4	19,10 ± 0,94	13	14
5	68,49 ± 3,78	2	2
6	46,18 ± 2,29	6	6
7	23,90 ± 2,71	11	11
8	7,28 ± 0,62	14	10
9	24,19 ± 1,35	10	9
10	36,53 ± 1,93	7	4
11	65,94 ± 2,31	3	1
12	52,80 ± 1,15	5	7

*****Note:* 1 – the highest radical-binding activity, 14 – the lowest radical-binding activity.

The C-radical of compound **11** (0.6300 AU) is characterized by the lowest difference in energies, therefore, if our assumptions are correct, 4-(2,2-dimethylpropanoyl)-3-hydroxy-5-(4-metoxyphenyl)-1-(4-methylphenyl)-1,5-dihydro-2*H*-pyrrol-2-one (**11**) should have the largest, and compound **4** – the lowest antiradical activity in the test series. Thus, a series of decrease in antiradical activity should have the following form:

11(Δ=0,6300 a.e)>**5**(Δ=0,6301 a.e)>**3**(Δ=0,6307 a.e)≈**10** (Δ=0,6307 a.e)>**2**(Δ=0,6308 a.e)>**6**(Δ=0,6309 a.e)>**12**(Δ=0,6310 a.e)>**1** (Δ=0,6311 a.e)≈**9**(Δ=0,6311 a.e)>**8**(Δ=0,6315 a.e)>**7**(Δ=0, 6324 a.e)> **4**(Δ=0,6455 a.e).

It is noteworthy that radicals with an electron donating substituent in the aryl ring bonded to the carbon atom C^5 (CH_3O, CH_3) are the most stable, and the electron acceptors (F, Cl, NO_2) in any of the aryl rings, on the contrary, destabilize the radicals. The most significant differences between the calculated and experimental values of antiradical activity were found in compounds with nitro groups.

The results of comparison of the antiradical activity indices of the 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones obtained during calculations and experiments are given in **Table 2**.

The calculations were performed on the PGU-Tesla supercomputer of the Parallel and Distributed Computing Center at the Perm State National Research University.

CONCLUSION

To a large extent, the predicted results of the manifestation of the radical-binding ability in the series of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones (**1–12**) are consistent with the results obtained experimentally. The highest activity was observed in compounds **3**, **5**, **11**, having aryl fragments substituted by methyl and methoxy groups. Earlier, we published data on the effect of the nature of substituents on radical-binding activity in a number of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones [29], as well as in a number of other heterocycles [30].

Due to the fact that a number of compounds possessing antiradical activity exhibits pronounced cytotoxic properties [31, 32], the study of such compounds allows to expand the search for potential antitumoral drugs.

Thus, the quantum chemical prediction of antiradical activity using the Firefly software package allows to successfully predict the level of anti-radical activity of new compounds in a series of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones, which will significantly reduce the number of synthesized compounds and increase the effectiveness of their biological screening.

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