

Theoretical Investigation on Radical-Coupling Reactivity of Indolinonic Aminoxyls

Hong Yu ZHANG^{1*}, Lan Fen WANG²

¹Laboratory for Computational Biology, Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Shandong University of Technology, Zibo 255049

²Department of Chemistry, Shandong Teachers' University, Jinan 250014

Abstract: Indolinonic aminoxyls can effectively scavenge various radicals by directly coupling with them or by imitating superoxide dismutase. To better understand the radical-coupling reactions, DFT method B3LYP/6-31G(d,p) was employed to calculate variations of free energy for the coupling reactions and other physico-chemical parameters. The radical-coupling activity difference between aminoxyls was elucidated to a large extent in terms of electronic properties of substituents.

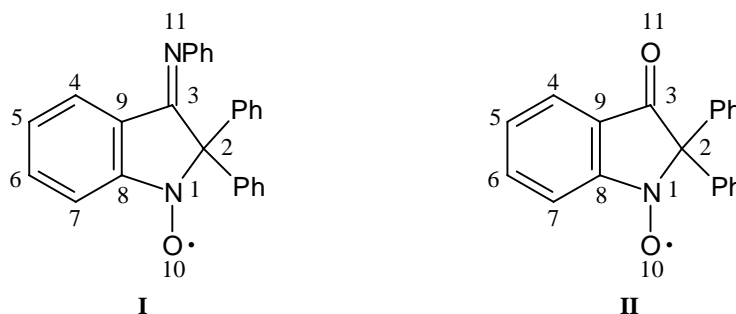
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Antioxidants are beneficial to prevent biological and chemical molecules from oxidation. Hence, antioxidants have been widely used in pharmaceutical industry, food industry and chemical industry. Recently, apart from the traditionally used phenolic antioxidants, aminoxyls, such as 1, 2-dihydro-2, 2-diphenyl-3H-indole-3-phenylimino-1-oxyl (**I**) and 1, 2-dihydro-2, 2-diphenyl-3H-indole-3-one-1-oxyl (**II**), also showed good antioxidative activities^{1,2}. They can effectively scavenge carbon-, nitrogen-, and oxygen-centered radicals ($R\cdot$, $R_2N\cdot$, $RO\cdot$, $ROO\cdot$, $O_2\cdot^-$) by directly coupling with them or by imitating superoxide dismutase (SOD)³. Although **I** and **II** are similar in structure, they showed different radical-scavenging activities, *i.e.*, **I** was more efficient than **II** to prevent methyl linoleate or linolenic acid from $ROO\cdot$ induced peroxidation^{1,2}. To better understand the antioxidant activity difference of aminoxyls, we will have to investigate the radical-coupling reactivity of **I** and **II** by theoretical calculations.

In the calculations, phenyl groups at position 2 were substituted by hydrogen atoms, and phenyl group at position 11 was substituted by methyl group.

Owing to the accuracy and the convenience of density functional theory (DFT), B3LYP function on basis set of 6-31G(d,p) was used to do calculations in this letter. The calculation procedures can be found elsewhere^{4,5}.

*E-mail: zhang630@mail.zbu.net.cn

Scheme 1 Structures of two indolinonic aminoxylys

Results and Discussion

It has been found by previous experiments that nucleophilic carbon-centered radicals were mainly trapped by N-O \cdot group, while electrophilic oxygen-centered radicals were mainly trapped by the carbons of the conjugated benzene ring, specially C5 or C7³. Accordingly, the coupling reactions occurred between O10, C5, C7 and various radicals were studied. The variations of free energy (ΔG) for the coupling reactions between aminoxylys and model radicals, *i.e.*, H₃C \cdot , H₃CO \cdot and H₃COO \cdot , were calculated (**Table 1**) and used as a theoretical index to characterize the coupling activity. In the viewpoint of thermodynamics, the lower the ΔG is, the more the reaction is facilitated.

As indicated from ΔG (**Table 1**), carbon-centered radicals really preferentially attack N-O \cdot group in aminoxylys, while oxygen-centered radicals preferentially react with carbons of the benzene ring, suggesting the theoretical calculations are reliable and applicable. ΔG also indicates that aminoxylyl **II** has more potential than **I** to couple with carbon-centered radical, which can be understood from the difference in spin density on O10. As shown in **Table 2**, oxygen-centered radicals in aminoxylys **I** and **II** are efficiently stabilized by the adjacent N1, so aminoxylyl radicals are rather stable. However, due to the distinct substituents, the stability of the aminoxylyl radical gets different. According to the physico-organic chemistry theory^{6,7}, electron-donating groups are beneficial to stabilize the oxygen-centered radical, whereas electron-withdrawing groups have an opposite effect. Since =O is a stronger electron-withdrawing group than =NR, the spin density on O10 of **II** is higher than that on O10 of **I** (**Table 2**).

On the other hand, the calculated ΔG suggests that aminoxylyl **I** is indeed more efficient than **II** to scavenge oxygen-centered radicals (**Table 1**), which also can be elucidated from the higher spin densities on C5 and C7 in **I** than those in **II** (**Table 2**). Thus, it seems the radical-coupling potential for aminoxylys is mainly determined by the spin density of the target atom. In fact, C5 and C7 have the highest spin density in the carbon atoms, consistent with the fact that C5 and C7 are radical-coupling positions. In addition, it seems =O is more efficient than =NR to lower the spin density on carbon atoms, which is different from the substituent effect on oxygen-centered radicals.

Table 1 Thermodynamic parameters for indolinonic aminoxyls (**I** and **II**) and the products derived from coupling reactions at different positions (in parentheses) (T = 298.15 K)

	TE ^a	TCE ^b	H ^c	S ^d	G ^e	ΔG ^f
I	-533.036076	0.175732	-532.8628303	99.769	-532.8154268	
I-CH ₃ (10)	-572.950354	0.217224	-572.7364263	107.494	-572.6853524	-52.76
I-CH ₃ (5)	-572.934666	0.217218	-572.7207433	106.320	-572.6702272	-43.27
I-CH ₃ (7)	-572.934886	0.217289	-572.7208940	105.988	-572.6705357	-43.46
I-OCH ₃ (10)	-648.102713	0.221292	-647.8847961	116.291	-647.8259425	-16.54
I-OCH ₃ (5)	-648.132160	0.222739	-647.9128247	113.524	-647.8588858	-34.95
I-OCH ₃ (7)	-648.131279	0.222868	-647.9127572	112.925	-647.8591029	-35.09
I-OOCH ₃ (10)	-723.247733	0.226066	-723.0251349	123.459	-722.9664755	-5.84
I-OOCH ₃ (5)	-723.270027	0.227153	-723.0463637	121.174	-722.9887900	-19.84
I-OOCH ₃ (7)	-723.268403	0.227142	-723.0447502	120.320	-722.9875823	-19.09
II	-513.601948	0.133953	-513.4696668	90.577	-513.4266307	
II-CH ₃ (10)	-553.524280	0.175631	-553.3511333	98.824	-553.3041788	-57.54
II-CH ₃ (5)	-553.499095	0.175311	-553.3262622	97.656	-553.2798627	-42.28
II-CH ₃ (7)	-553.499709	0.175437	-553.3267526	97.195	-553.2805721	-42.73
II-OCH ₃ (10)	-628.670016	0.179530	-628.4930465	107.133	-628.4421442	-17.42
II-OCH ₃ (5)	-628.696246	0.180824	-628.5180079	104.980	-628.4681285	-33.72
II-OCH ₃ (7)	-628.696271	0.181014	-628.5178470	104.518	-628.4681871	-33.76
II-OOCH ₃ (10)	-703.813365	0.184217	-703.6317997	114.087	-703.5775933	-5.79
II-OOCH ₃ (5)	-703.833537	0.185239	-703.6509698	113.027	-703.5972670	-18.13
II-OOCH ₃ (7)	-703.833118	0.185279	-703.6505118	111.470	-703.5975488	-18.31
H ₃ C·	-39.842880	0.032867	-39.8097137	50.232	-39.7858469	
H ₃ CO·	-115.054595	0.039832	-115.0145999	56.499	-114.9877554	
H ₃ COO·	-190.219211	0.046907	-190.1722782	64.275	-190.1417391	

^a Total electronic energy (in hartree) ^b Thermal correction to energy (in hartree), including zero-point energy, vibrational contribution, translational and rotational terms ^c Enthalpy (in hartree) ^d Entropy (in cal/mol K) ^e Free energy (in hartree) ^f Variation of free energy for coupling reaction (in kcal/mol)

However, this is in agreement with previous findings that both electron-withdrawing and electron-donating groups are favorable to stabilize carbon-centered radicals, and the stronger the electronic effect the substituent has, the more stable the radical is⁸.

Table 2 Spin densities on atoms of aminoxyls **I** and **II**

	C4	C5	C6	C7	C8	C9	O10	N(O)11
I	-0.07881	0.14463	-0.07927	0.14439	-0.11174	0.13514	0.49252	0.05304
II	-0.07373	0.13720	-0.07458	0.13657	-0.10207	0.12752	0.50856	0.04153

In summary, the calculation results support the previous conclusion that aminoxyl **I** is more efficient than **II** to scavenge oxygen-centered radicals. Considering the fact that aminoxyl **I** has a weaker prooxidant activity than **II**², **I** is better than **II** to be used as an antioxidant in practice.

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