

## Theoretical investigation on the antioxidant activity of p-cresol and its derivatives: Effects of propenyl group and solvents

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**Abstract.** The effect of propenyl group on the antioxidant activity of p-cresol and its derivatives were investigated in gas and solvent phases by using density functional theory (DFT) method. Three accepted antioxidant mechanisms, including hydrogen atom transfer (HAT), single-electron transfer followed by proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET), were considered to explore which mechanism p-cresol and its derivatives preferred to in different environments. The bond dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA) and electron transfer enthalpy (ETE), closely related to the above three antioxidant mechanisms, were calculated systematically. The obtained results indicate that the antioxidant process of studied compounds prefers to the SET-PT and SPLET mechanism in gas phase and polar solvents, respectively. Meaningfully, the introduction of the propenyl group into the molecular structure can reduce the PA values and then improve the antioxidant activity of the studied compounds, which can provide theoretical guidance for the synthesis of novel antioxidants in the experiment.

**Keywords:** Proton transfer; Substituent group; Solvent effects; Density functional theory

### 1. Introduction

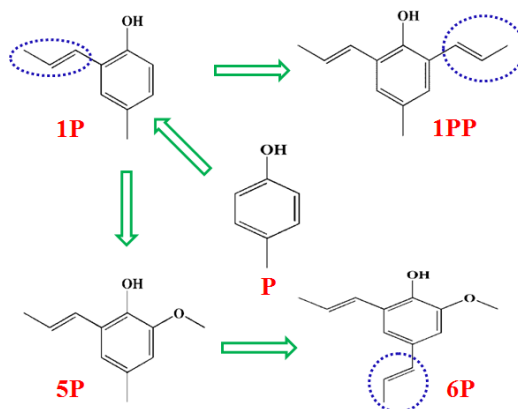
Too much free radicals in vivo can cause damage to DNA, unsaturated fatty acids in biomembrane, protein and other biological macromolecules, thereby resulting in many diseases [1,2]. To mitigate the harm of free radicals to the human body, more and more researchers are devoting themselves to find and synthesize novel antioxidants with the advantages of efficient, cheap, low toxic or even non-toxic [3-5].

Cresols have three isomers, which are named o-cresol, m-cresol and p-cresol, respectively. Each monomer of cresol is an important intermediate to synthesize antioxidants, preservatives, disinfectants and so on [6,7]. P-cresol is an important organic chemical raw material. A series of derivatives can be obtained by further processing with p-cresol as starting material, in which an extensive family of antioxidants can be derived through coupling reaction based on p-cresol, such as butylated hydroxytoluene (BHT), and these antioxidants receive a great deal of attention because of their relatively low toxicity [8,9]. Recently, Marteau et al. [10] designed and synthesized a series of novel antioxidants by introducing the propenyl group into the structure of p-cresol and its derivatives. The chemical structures of p-cresol and its derivatives, named as P, 1P, 1PP, 5P and 6P respectively, are shown in **Figure 1**. The results indicated the antioxidant activities of p-cresol and its derivatives were gradually enhanced along with the increased number of propenyl group in p-cresol. Why did the introduction of propenyl group can enhance the antioxidant activities of p-cresol and its

derivatives?

In this work, the relationship between the structures and antioxidant activities of p-cresol and its derivatives were investigated by using DFT method. Besides the influence of structure, the surrounding environment will also affect the parameters containing bond dissociation enthalpy (BDE), ionization potential (IP) and proton affinity (PA), which are connected with the antioxidant activities of phenolic compounds [11-13]. So the gas and three solvents including toluene, methanol and water were taken into accounts in this work. The parameters related to three antioxidant mechanisms, including hydroxyl BDE, IP, PDE, PA and ETE, were calculated to evaluate the antioxidant activities of p-cresol and its derivatives.

All the calculations in this work were completed by using Gaussian program suite [14]. The geometric configurations of the investigated compounds were optimized in the framework



**Figure 1:** Chemical structures of the investigated compounds.

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of DFT [15-17], with B3LYP [18-23] functional at 6-31G(d,p) basis set. For the sake of the following discussion, we have numbered the atoms in the compound 1PP. Three solvents, containing toluene, methanol and water with the dielectric constants of 2.38, 32.63 and 78.39, respectively, were considered to investigate the effect of solvent polarity on the antioxidant activities of p-cresol and its derivatives. The calculations in the solvent phases were adopted the integral equation formalism polarized continuum model (IEFPCM) [24-26]. The radical and ionic structures for the investigated compounds were optimized using DFT method with UB3LYP functional at 6-311++G(d,p). The BDE, IP, PDE, PA and ETE, which closely related to the above three antioxidant mechanisms, were calculated according to the equations in the literatures [11,27,28]. The enthalpies of hydrogen atom ( $H^{\cdot}$ ), proton ( $H^+$ ) and electron ( $e^-$ ) in gas and solvent phases at the same method employed the values in the work of Rimarčík et al. [29].

As one of the theoretical parameters to characterize the rate of hydrogen abstraction reaction, the BDE value represents the order of difficulty of hydrogen abstraction from phenolic hydroxyl. The smaller the BDE value is, the easier hydrogen abstraction reaction occurs [30]. In view of this, the BDE values of p-cresol and its derivatives in gas and solvent phases were calculated and summarized in **Table 1**. As listed in **Table 1**, the BDE values of P, 1P and 1PP show the common tendency in the same environment:  $1PP < 1P < P$ , implying that the antioxidant activity gradually increases from P to 1P and 1PP, in agreement with the experimental results [10]. For

instance, the BDE values of P, 1P and 1PP in gas phase are 392.9 kcal/mol, 389.9 kcal/mol and 385.7 kcal/mol, respectively. When a methoxyl group is introduced into the structure of 1P forming the compound 5P, the BDE values of 5P in the different environments are all greater than that of 1P, which is due to the formation of intramolecular hydrogen bond between the hydrogen atom of phenolic hydroxyl and the oxygen atom of methoxyl group. Compared the BDE values of 5P with that of 6P in the different environments, we can find the BDE values of 6P are all lower than that of 5P. Those results indicate that increasing number of propenyl group in p-cresol is beneficial to enhancing the antioxidant activity of p-cresol in theory.

Moreover, with the increasing polarity of solvent (from toluene to water), the BDE values of the studied compounds decrease gradually except for that of 1PP showing the trend of first increase and then decrease. By comparing the BDE values of p-cresol and its derivatives in the investigated environments, we can find that the lowest BDE values for p-cresol and its derivatives all are in the water phase, which suggests that the antioxidant ability of p-cresol and its derivatives are the strongest in water phase.

The SET-PT and SPLET mechanisms are of importance in solvent media, so we have taken the two mechanisms into account in this work [31]. The calculated IP and PDE values of p-cresol and its derivatives in gas and solvent phases are listed in **Table 2**. As listed in **Table 2**, it can be found that the IP values of P, 1P and 1PP all are following the same order in the investigated environments:  $1PP < 1P < P$ , which indicates that increasing the number of propenyl group in p-cresol can improve the single electron donating ability of p-cresol. Moreover, the IP values of 5P are lower than that of 1P in the studied environments except in water phase, implying that introducing the methoxyl group into the structure of 1P can enhance the single electron donating ability of 1P. Compared the IP values of 5P with that of 6P in the studied environments, we can find that the IP values of 6P all are lower than that of

**Table 1.** Calculated bond dissociation enthalpy (BDE) values of investigated compounds in gas and solvent phases.

BDE (kcal/mol)	Gas	Toluene	Methanol	Water
P-OH	392.9	394.4	394.2	392.1
1P-OH	389.9	390.8	390.8	388.1
1PP-OH	385.7	387.3	387.4	385.2
5P-OH	390.5	391.2	389.3	389.2
6P-OH	388.7	389.3	387.3	387.2

**Table 2.** Calculated ionization potential (IP) and proton dissociation enthalpy (PDE) values of investigated compounds in gas and solvent phases.

	IP (kcal/mol)				PDE (kcal/mol)			
	Gas	Toluene	Methanol	Water	Gas	Toluene	Methanol	Water
P-OH	183.5	152.9	117.9	112.6	212.6	16.0	6.5	11.1
1P-OH	170.0	142.3	110.5	104.7	223.1	23.2	10.5	15.0
1PP-OH	165.2	140.3	109.2	104.0	223.7	21.6	8.4	12.8
5P-OH	165.0	139.5	108.3	125.1	228.7	26.2	11.2	38.7
6P-OH	158.5	134.7	104.0	120.9	233.4	29.2	13.4	40.9

**Table 3.** Calculated proton affinity (PA) and electron transfer enthalpy (ETE) values of investigated compounds in gas and solvent phases.

	PA (kcal/mol)				ETE (kcal/mol)			
	Gas	Toluene	Methanol	Water	Gas	Toluene	Methanol	Water
P-OH	347.9	95.1	46.1	48.8	48.2	73.8	78.3	74.8
1P-OH	343.7	93.5	46.3	47.9	49.4	71.9	74.7	71.8
1PP-OH	338.9	91.3	43.7	46.5	50.0	70.7	73.9	70.3
5P-OH	344.8	96.4	48.9	74.9	48.9	69.4	70.5	88.9
6P-OH	340.1	93.2	46.6	72.6	51.8	70.8	70.9	89.2

5P. This result again shows the introduction of propenyl group can improve the single electron donating ability of compound. Furthermore, the IP values of the investigated compounds in the toluene solvent follow the order of 6P (134.7 kcal/mol)<5P (139.5 kcal/mol)<1PP (140.3 kcal/mol)<1P (142.3 kcal/mol)<P (152.9 kcal/mol), which is according with the order of their antioxidant activity [10]. In addition, the IP values of p-cresol and its derivatives decrease by degrees along with the increasing polarity of the environments except for 5P and 6P in the water phase, which may be due to the cation radicals of p-cresol and its derivatives are more stable in the polar environment [11].

Besides, it can be seen from **Table 2** that the PDE values of p-cresol and its derivatives in gas show the significant differences with that in solvent phases, in which the PDE values of p-cresol and its derivatives in gas are obviously greater than that in solvent phases. In the investigated solvent phases, the PDEs of P, 1P and 1PP in methanol show the lowest values, while present the largest values in toluene. For 5P and 6P, their PDEs have the lowest and largest values in methanol and water phases, respectively.

The obtained proton affinity (PA) and electron transfer enthalpy (ETE) values of p-cresol and its derivatives in gas and solvent phases are summarized in **Table 3**. As listed in **Table 3**, the PAs of p-cresol and its derivatives in gas are greater than that in the solvents. For instance, the PAs of compound P in gas, toluene, methanol and water phases are 347.9 kcal/mol, 95.1 kcal/mol, 46.1 kcal/mol and 48.8 kcal/mol, respectively. Those results indicate that the proton affinities of p-cresol and its derivatives are susceptible to the effect of solvent. Compared the PAs of P, 1P and 1PP in the different environments, we can find that the PAs are following the order of 1PP<1P<P except for that abiding by the order of 1PP<P<1P in methanol solvent. In addition, the PA values of 1P, 5P and 6P show the trend of first increase and then decrease, which implies that introducing the methoxyl group into the structure of 1P can inhibit the antioxidant activity of 1P, and introducing the propenyl group into 5P can improve the antioxidant activity of 5P from the point SPLET mechanism. For p-cresol and its derivatives, those PAs in methanol solvent exhibit the lowest values, while have the largest values in gas phase.

Moreover, it can be found from **Table 3** that the ETE values of P, 1P and 1PP decrease gradually in the studied environments except in gas phase. For 1P, 5P and 6P, the ETE values show the trend of decrease first and then increase in the studied environments except in the water solvent, in which the ETE values of 1P, 5P and 6P exhibit the increasing trend. Furthermore, all the ETEs of p-cresol and its derivatives have the lowest values in gas compared with that in the other solvents.

According to the relevant literatures [11,32], the antioxidant process of compounds tends to which mechanism mainly depends on the three values: BDE, IP and PA, because of the IP and PA values being related to the first step of SET-PT and SPLET mechanisms, respectively. It can be found from the obtained results that in gas phase, the IP values of the investigated compounds are lower than their BDE and PA values, implying that the antioxidant process of compounds in

gas phase prefers to the SET-PT mechanism. As far as the solvent is concerned, the PAs of the investigated compounds show the lowest value compared with their BDE and IP values in the three studied solvent phases. This result suggests that the antioxidant process of studied compounds in solvent phases is in favor of the SPLET mechanism. Especially in polar solvents, the studied compounds present the relatively lower PA values in methanol and water phases by comparison with that in toluene phase, which indicates the antioxidant process of studied compounds in polar solvent phases is more inclined to the SPLET mechanism.

The influences of unsaturated substituent propenyl group on the antioxidant activity of p-cresol and its derivatives in gas and solvent phases were studied by using DFT method. The key parameters including BDE, IP, PDE, PA and ETE, related to the HAT, SET-PT and SPLET antioxidant mechanisms, were calculated to explore which mechanism p-cresol and its derivatives preferred to in different environments. The obtained results indicate that the antioxidant process of studied compounds in gas phase prefers to the SET-PT mechanism, and that of studied compounds is more inclined to the SPLET mechanism in polar solvent phases. Moreover, introducing the propenyl group into the molecular structure can reduce the PA values and then improve the antioxidant activity of compounds, which can provide valuable reference for the synthesis of new antioxidants in the experiment.

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