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Scavenging effect of chinonin on free radicals studied with quantum chemistry[1]

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KEY WORDS chinonin; antioxidants; computer-aided design

ABSTRACT

AIM: To study whether the xanthonoid structure can enhance the ability of chinonin to scavenge free radicals and to understand the sequence of activity of chinonin hydroxyls. **METHODS**: Semiempirical quantum chemistry method AM1 was employed to calculate △HOF values, the differences between heat of formations of mother molecule and its free radicals, and spin density distribution of different states of chinonin. △HOF values were used as theoretical indices to measure scavenging activity of chinonin on free radicals and effects of structure on △HOF values were investigated. **RESULTS**: △HOF values of different phenolics were calculated to be 139.09 kJ·mol^{-1} (O5 – H6), 141.46 kJ·mol^{-1} (O4 – H5), 185.14 kJ·mol^{-1} (O2 – H2) and 195.71 kJ·mol^{-1} (O1 – H1). Spin density distribution of free radicals were obtained as well. **CONCLUSION**: Xanthonoid structure of chinonin made ring C to display high passive effect on ring B, which reduced scavenging activity of phenolics of ring B on free radicals. The sequence of activities of chinonin hydroxyls was O5 – H6 > O4 – H5 > O2 – H2 > O1 – H1.

INTRODUCTION

Chinonin is an active principle of *Anemarrhena asphodeloides* Bunge, a traditional Chinese drug and a new type of xanthonoid antioxidant proved by experimental and theoretical study[1-3]. In a broad sense, xanthonoids belong to well-known flavonoids[4]. But they show much difference in the structures, as ring B and ring C of xanthonoids are in better conjugation.

Judging from structure, chinonin is similar to other phenolic antioxidants that they are all through H-abstruction reaction of hydroxyls and generating resonance-stabilized semiquinonoid free radicals to break the chain reaction and display antioxidant activity. Inferred from well-known stabilization-rule of free radicals, semiquinonoid free radicals of xanthonoids will be more stabilized owing to better conjugation between ring A, B, and C. So, scavenging activity of chinonin on free radicals will be higher than that of other flavonoids. However, structure-activity relationships (SAR) of tocopherolic antioxidants indicated that electron-withdrawing groups would enhance the bond strength of O – H, and reduce its scavenging activity on free radicals[5]. Obviously, ring C of xanthonoids possesses fairly strong electron-withdrawing ability, which apparently results in that whether conjugation between ring B and C is good to enhance chinonin antioxidant activity can not be determined simply by the well-known rule of free radical stabilization. But this is very important in investigating chinonin pharmacological mechanism and evaluating its medical potential. Hence, semiempirical quantum chemistry method AM1 was employed to calculate and investigate the influence of xanthonoid structure on chinonin activity of scavenging free radicals, and the sequence of activity of hydroxyls was revealed as well.

METHODS

Determination of theoretical parameter

The difference of heat of formation between mother

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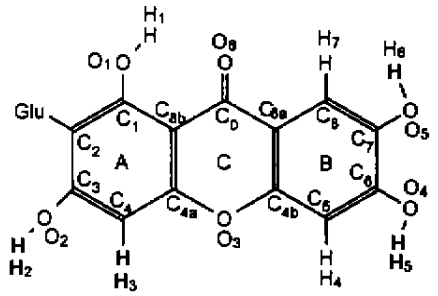
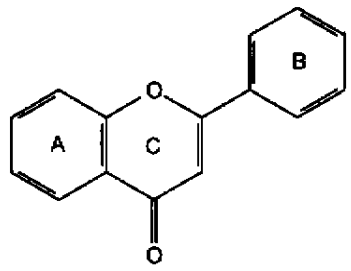


Chinonin



Center of favonoids

molecule and its free radical, △HOF, was the best theoretical index to measure the scavenging ability[5]. Low △HOF indicates weaker strength of O – H and more stabilized semiquinonoid free radical, correspondingly, the antioxidants are more active. After comparison of many indices representing bond strength, such as bond order, bond length, charge difference between oxygen and hydrogen, and △HOF value, we found that △HOF was indeed the best theoretical index to measure bond strength of O – H. Although △HOF was only a thermodynamic parameter and kinetic process was out of consideration, calculation on △HOF of 13 antioxidants indicated that there was a very good correlationship between △HOF and logarithm of their relative rate constant of scavenging free radicals[6]: $\lg k_3/k_1 = 14.6491 - 0.0955\triangle HOF$, $r = 0.949$. k_3 is rate constant of antioxidant to scavenge lipo-oxygenic free radical of methyl linoleate, and k_1 is rate constant of the radical reacting with lipid[7]. △HOF was used as theoretical parameter measuring scavenging activity of chinonin.

Selection of calculation method AM1 method was employed to calculate △HOF values, as it was better than other semiempirical methods, such as MNDO and PM3[6]. The procedure was as follows. First, molecular mechanic method MMX[8] in program PCMODEL was used to optimize the molecular structures and then AM1[9] in MOPAC7 was employed to calculate the theoretical parameter. Heat of formation of mother molecule and the state of removing phenolic H were obtained to calculate △HOF. To compare with each other mother molecules and free radicals were all calculated using RHF(restricted Hartree Fock). △HOF values obtained by this method were almost equal to that firstly calculated by UHF (unrestricted Hartree Fock) and then calculated by a 1SCF restricted Open Shell (ROHF)[5]. But this method was easier to be self consistent. As the glucose substituted in position C_2 is hardly conjugated with ring A, B, and C, and glucose only possesses very weak electron-donating effect, it has little influence on scavenging activity of chinonin and is omitted in calculation.

RESULTS AND DISCUSSION

Influence of xanthonoid structure on free radical scavenging activity of chinonin △HOF values of 4 hydroxyls of chinonin were calculated and listed in Tab 1. It can be found that △HOF values of OHs in ring A were approximately 190 kJ · mol^{-1}, similar to the values of other flavonoids. But △HOF values of OHs in ring B were about 140 kJ · mol^{-1}, when intramolecular hydrogen bond (IHB) is formed. Considering the corresponding values of flavonoids were about 133 kJ · mol^{-1} and the values of catecholic phenol was 132 kJ · mol^{-1}[10], we found that electron-withdrawing property of ring C of chinonin approximately made △HOF values of OHs in ring B 8 kJ · mol^{-1} higher, which indicated that ring C indeed reduced the scavenging activity of OHs in ring B. According to the linear equation between △HOF and $\lg k_3/k_1$, k_3/k_1 of OHs in ring B could be calculated to be 19.02. However, k_3/k_1 of flavonoids with △HOF 133 kJ · mol^{-1} was 88.63 and k_3/k_1 of typical flavonoids were about 50 – 100[7]. So, scavenging activity of chinonin was fairly low compared with other flavonoids (Tab 1).

Sequence of activity of chinonin hydroxyls The sequence of activity of chinonin 4 hydroxyls was O5 – H6 > O4 – H5 > O2 – H2 > O1 – H1 (Tab 1). In the scavenging process, two OHs of ring B can be stabilized by forming IHB after H-abstraction reaction (Fig 1 – 1), so they were more active than OHs in

Tab 1. HOF and △HOF values (kJ · mol^{-1}) of chinonin.

		HOF	△HOF
Chinonin		-767.97	
-H1		-572.26	195.71
-H2		-582.83	185.14
	HB	-626.51	141.46
-H5			
	NHB	-608.21	159.76
	HB	-628.88	139.09
-H6			
	NHB	-612.04	155.93

HOF - Heat of formation; HB - Hydrogen bond is formed; NHB - Hydrogen bond is not formed.

ring A. However, calculations on OHs of ring B that no hydrogen bond was formed (Fig 1 - III) indicated that although IHB indeed had a stabilizing effect on semiquinonoid free radicals, and hydrogen bond energy could be estimated as 17 kJ · mol^{-1} from difference between △HOF values of the two states, OHs of ring B were still more active than OHs of ring A even though hydrogen bond was not formed. The △HOF values of ring B without IHB were still 30 - 40 kJ · mol^{-1} lower than that of ring A. The reason was that semiquinonoid free radical of the former state could form *ortho* bezoquinone structure through resonance (Fig 1 - II, IV) and made unpaired electron well-distributed, especially on neighbor oxygen, which reduced the internal energy and made the free radical stabilized. Obviously, semiquinonoid free radical of ring A had no similar mechanism. Tab 2 indicated that when semiquinonoid free radical of ring A was formed, spin density distributed on another oxygen was about only 0.0005, but the corresponding data of ring B were 0.09 and 0.05, much higher than the former. Meanwhile, it could be found that whether IHB was formed or not had little influence on spin density distribution, which suggested that there were 2 factors in stabilizing semiquinonoid free radicals of ring B. First, IHB was formed. Second, bezoquinone structure was formed, and spin density was well-distributed. In addition, the two factors were almost independent of each other (Fig 1, Tab 2).

REFERENCES

1 Zhang HY, Wang FY, Li M, Zhang ZY, Li MF. Studies of scavenging effects on active oxygens of chinonin. J Radiat Res Radiat Proc 1997; 15: 224.
2 Zhang HY, Wang FY, Li M, Yan DY, Zhang ZY. Quantum chemistry calculation studies on chinonin. J Radiat Res Radiat Proc 1997; 15: 139.
3 Qiu QF, Mei NY, Zhang JH, Li MF, Li M. The study of electron spin transfer from γ-irradiation DNA to chinonin. J Radiat Res Radiat Proc 1995; 13: 249.
4 Wang XK. Medicinal chemistry of natural products. 1st ed. Beijing: The People's Medical Publishing House; 1993. p 272.
5 van Acker SA, Koymans LM, Bast A. Molecular pharmacology of vitamin E: structural aspects of antioxidant activity. Free Radic Biol Med 1993; 15: 311 - 28.

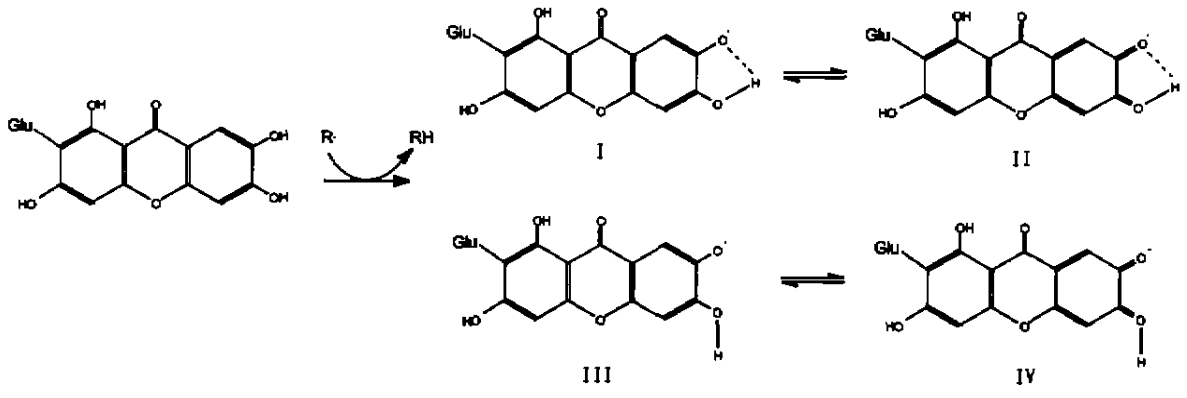


Fig 1. Scanvenging effects of chinonin on free radicals.

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Tab 2. Spin density distribution of free radicals of chinonin.

Atom number	– H1	– H2	– H5		– H6	
			HB	NHB	HB	NHB
CU	0.0035	0.0095	0.0098	0.0118	0.0027	0.0025
C1	0.0176	0.0011	0.0029	0.0032	0.0010	0.0009
C2	0.2081	0.2268	0.0001	0.0000	0.0044	0.0049
C3	0.0005	0.0211	0.0026	0.0029	0.0014	0.0014
C4	0.3578	0.2144	0.0021	0.0017	0.0091	0.0094
C4a	0.0078	0.0001	0.0025	0.0029	0.0038	0.0038
C4b	0.0029	0.0042	0.0154	0.0086	0.2376	0.2539
C5	0.0003	0.0000	0.1006	0.1317	0.0002	0.0003
C6	0.0023	0.0035	0.0408	0.0281	0.1834	0.1716
C7	0.0023	0.0015	0.2753	0.2524	0.0601	0.0441
C8	0.0006	0.0017	0.0231	0.0225	0.1968	0.2225
C8a	0.0045	0.0043	0.2533	0.2752	0.0278	0.0206
C8b	0.2216	0.3121	0.0020	0.0027	0.0024	0.0032
O1	0.1390	0.0004	0.0011	0.0012	0.0003	0.0003
O2	0.0005	0.1608	0.0007	0.0008	0.0004	0.0004
O3	0.0060	0.0012	0.0016	0.0005	0.0411	0.0419
O4	0.0006	0.0011	0.1398	0.1360	0.0558	0.0509
05	0.0005	0.0003	0.0937	0.0819	0.1643	0.1545
06	0.0235	0.0358	0.0325	0.0359	0.0075	0.0067

HB-Hydrogen bond is formed; NHB – Hydrogen bond is not formed.

6 Zhang HY. Selection of theoretical parameter characterizing scavenging activity of antioxidants on free radicals. J Am Oil Chem Soc 1998; 75: 1705 – 9.
7 Roginsky VA, Barsukova TK, Remorova AA, Bors W. Moderate antioxidative efficiencies of flavonoids during peroxidation of methyl linoleate in homogeneous and micellar solutions. J Am Oil Chem Soc 1996; 73: 777 – 86.
8 Gajewski JJ, Gillbert KE, Mckelvey J. MMX, an enhanced version of MM2. Adv Mol Model 1990; 2: 65 – 92.
9 Dewar MJS, Zoebisch EG, Healy EF, Stewart JJP. AM1: a new general purpose quantum mechanical molecular model. J Am Oil Chem Soc 1985; 107: 3902 – 9
10 Zhang HY. Theoretical elucidation of structure-activity relationships of flavonoid antioxidants. Sci Sin (B) 1999; 42: 106 – 12.

知母宁清除自由基作用的量子化学研究[1]

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关键词 知母宁; 抗氧化剂; 计算机辅助设计

目的: 研究知母宁的吡酮结构是否有利于提高其清除自由基活性并探讨知母宁酚羟基活性的顺序. **方法**: 用半经验量子化学方法 AM1 计算出知母宁不同状态的△HOF 值(母体化合物与其自由基生成热之差)和电子自旋密度分布, 以△HOF 值作为衡量知母宁清除自由基活性的理论指标, 观察结构因素对△HOF 值的影响. **结果**: 计算得出不同酚羟基的△HOF 值为 O5 – H6: 139.09 kJ·mol^{-1}; O4 – H5: 141.46 kJ·mol^{-1}; O2 – H2: 185.14 kJ·mol^{-1}; O1 – H1: 195.71 kJ·mol^{-1}, 同时得到自由基的自旋密度分布. **结论**: 知母宁的吡酮结构使 C 环对 B 环有较强的钝化作用, 降低了 B 环酚羟基清除自由基的活性. 知母宁酚羟基活性的顺序为 O5 – H6 > O4 – H5 > O2 – H2 > O1 – H1.

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