



Through-bond instability in polyphenol tautomers

Masashi Hatanaka

Department of Green & Sustainable Chemistry, School of Engineering, Tokyo Denki University, 5 Senju-Asahi-cho, Adachi-ku, Tokyo 120-8551, Japan

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ABSTRACT

Unusual instability of keto tautomers in polyphenols is theoretically analyzed. Apart from ordinary resonance energy and bond energy, it is shown that there should be additional keto instability originated from through-bond interactions between the true and pseudo π orbitals. The interactions are characteristic of non-bonding like amplitude pattern in the frontier π orbitals. The magnitude of instability is estimated to be 4 kcal/mol per carbonyl group by modern DFT calculations and experimental results.

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Polyphenols often exhibit tautomerism between the enol and keto forms. Figure 1 shows typical three (poly)phenols and their tautomers. Phenol (**1**) prefers the enol form, and the keto forms **2** and **3** have not been observed due to large resonance energy of the aromatic enol. However, apart from the resonance energy, the keto skeleton itself is generally more stable than the enol structure due to large bond energy of the C=O group. So, when the number of the functional groups in polyphenols increases, we can expect keto preference. Indeed, resorcinol (**4**) sometimes reacts as the diketo form **5** to afford secondary aryl amines.¹ Phloroglucinol (**6**) also behaves as the triketo form **7** to afford similar compounds.¹ Oxime synthesis through phloroglucinol also suggests us the triketo intermediate.² With increase in the number of the functional groups, the equilibrium inclines toward the right-hand sides.

Wheland predicted a stability series of polyphenols considering the change of resonance energy ΔR and bond energy ΔB , which are based on experimental results such as heats of hydrogenation or combustion.³ While the resonance stability is considerably lost through the transformation from enol to keto, bond energy stability is gained with increase in C=O moieties. Table 1 shows Wheland's prediction of keto–enol energy gaps ($\Delta H_W = E_{\text{keto}} - E_{\text{enol}} = \Delta R + \Delta B$) for phenol, resorcinol, and phloroglucinol. For phenol, keto forms **2** and **3** cannot be distinguished by Wheland's method, because they have approximately same parameters.³ We here solely deal with **2** as the keto form of phenol, because **3** is not so important for our purpose, as seen later. Wheland's energy gaps ΔH_W are regarded as change of enthalpy of the systems due to invariance of molecularity. We note that the positive sign

represents keto instability. We see that the keto structures are preferred when the number of functional groups increases, and phloroglucinol is predicted to be keto as the stable tautomer. Judging from the magnitude of ΔH_W , phloroglucinol lies in the border line in this series. Indeed, the stability problem of phloroglucinol has attracted many chemists. However, scrutiny of the energy contribution is still a controversial problem related to experimental results. According to Wheland, the keto instability is predicted to be -3 kcal/mol, having minus sign. However, experimentally, keto/enol ratio is 10^{-6} in water.⁴ This is corresponding to the change of Gibbs energy ΔG by ca. $+8.2$ kcal/mol, as noted in Table 1. NMR studies show proton exchange between the enol and keto forms, though the keto structures have not been observed directly due to the too small concentration.⁵ In solid states, only the enol form has been known, in which crystal waters are often clathrated. So, we wonder why Wheland's prediction and the experimental Gibbs energy gap are so much different. Apart from the side effects such as the entropy term or solvation energy, the difference ($+8.2 - (-3) = +11.2$ kcal/mol) seems to be beyond the theoretical and/or experimental errors. In this Letter, the hidden instability is analyzed in view of through-bond orbital interactions between the true and pseudo π orbitals.

Until now, enol stability of phloroglucinol itself has been qualitatively reproduced by several workers. However, energy contribution to the enol stability has not been well analyzed due to lack of basis set quality. The energy gap between the keto and enol forms is highly sensitive to approximation levels. For example, early Hartree–Fock calculations predicted enol stability by $+34.9$ kcal/mol.⁵ On the contrary, PM3 semi-empirical calculations predicted keto stability by $+1.7$ kcal/mol.⁶ Some DFT (density-functional theory) or single-point MP2 (second-order Møller–Plesset

E-mail address: mhatanaka@xug.biglobe.ne.jp

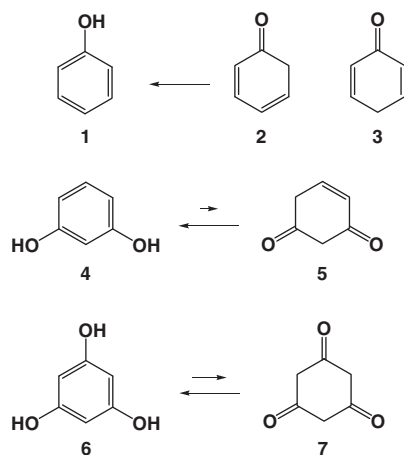


Figure 1. Keto–enol tautomerism of phenol, resorcinol, and phloroglucinol.

perturbation) calculations also gave keto stability with the same order.⁶ At present, MP2 calculations with full optimization of geometries are difficult. Instead, B3LYP calculations^{7a–c} with enough large basis sets are probably most suitable for the scrutiny of the keto–enol energetics. The accuracy of calculations depends on polarization functions rather than diffuse functions, as shown later. To eliminate the basis-set impact for phenol, resorcinol, and phloroglucinol, we first recalculated the keto–enol energy gap with full optimized geometries at B3LYP/6-311+G(d,p) level, followed by single-point calculations by Dunning's augmented-correlation-consistent-pVQZ (so-called aug-cc-pVQZ or ACCQ) basis set under the same geometries. All the calculations were done by GAMESS program.^{7d} Making thermodynamic corrections at 298 K, change of enthalpy ΔH_{calcd} and Gibbs free energy ΔG_{calcd}

are summarized in Table 1. We see that the calculated enthalpy change for phenol is very consistent with that of Wheland's result. For resorcinol, the change of enthalpy is slightly overestimated with respect to Wheland's result, and for phloroglucinol, the overestimation is relatively large. This indicates that some additional keto instabilities that are approximately proportional to the number of C=O groups are induced in polyphenols. We note that the entropy term is small, and contribution to the change of Gibbs energy is at most -1 kcal/mol.⁸ We can easily imagine that solvation energy for the enol form also contributes to the additional keto instability (enol stability) through the hydrogen bonds. However, by performing PCM (polarizable continuum model) calculations, we can show that solvation effects are also small. In water, the resultant keto–enol energy gap was predicted to be $+3.1$ kcal/mol, which does not show significant solvation effect. This is due to cancellation of solvation effects between enol and keto forms, or triviality of the solvation energy itself. It has been shown by Onsager model that solvation energy toward the enol form of phloroglucinol is enough negligible^{9a} due to molecular symmetry, even if conformational effects are included. It has also been shown that energy deviations by orientation of the hydroxyl groups are very small, which are at most 1 kcal/mol.⁹ So, in these systems, we can grasp the energetics only by analyzing the electronic terms without thermal or solvent correction.

Table 2 shows basis-set impact on the keto–enol energy gap for phloroglucinol at B3LYP optimized calculations up to 6-311+G(d,p) basis set, and single point calculations by aug-cc-pVnZ (ACCn, $n = D, T, \text{ and } Q$) basis sets. While the enol form has a C_{3h} geometry, the keto form has a C_{3v} geometry due to relaxation of torsional energy. Evidently, the small deviation from planarity does not affect the qualitative keto instability. The PCM data are also shown for references. Under B3LYP levels, the 6-31G basis set coincidentally gives enol stability. However, the 6-31G(d) and 6-31+G(d) basis sets afford energy gaps with opposite signs. It is not until we use

Table 1
Summary of keto–enol energy gaps for phenol, resorcinol, and phloroglucinol

		Wheland's predictions			B3LYP		B3LYP	
		ΔR^a	ΔB^a	ΔH_W^a	$\Delta H_{\text{calcd}}^b$		$\Delta G_{\text{calcd}}^c$	ΔG_{obs}^d
		(kcal/mol)	(kcal/mol)	(kcal/mol)	6-311+G(d,p)	ACCQ (kcal/mol)	6-311+G(d,p)	In water (kcal/mol)
Phenol	(1→2)	+31	−13	+18	+17.4 (+18.1)	(+19.6)	+16.7	−
Resorcinol	(4→5)	+31	−26	+5	+9.9 (+10.5)	(+13.3)	+9.5	−
Phloroglucinol	(6→7)	+36	−39	−3	+3.8 (+4.8)	(+8.9)	+2.8	+8.2

ΔR =change of resonance energy, ΔB =change of bond energy, ΔH =change of enthalpy, ΔG =change of Gibbs energy.

^a Based on heats of hydrogenation and combustion.³

^b Data with no parenthesis are based on thermodynamic calculations at 298 K under B3LYP/6-311+G(d,p) level of theory. Data in parenthesis are based on pure electronic terms without zero-point energies. ACCQ data are based on B3LYP/ACCQ/B3LYP/6-311+G(d,p) calculations.

^c Based on thermodynamic calculations at 298 K under B3LYP/6-311+G(d,p) level.

^d Based on experimental keto–enol ratio (10^{-6}) determined by relaxation methods.⁴

Table 2
Summary of basis-set impact on the keto–enol energy gaps of phloroglucinol

B3LYP full optimized calculations							
	6-31G	6-31G(d)	6-31+G(d)	6-31G(d,p)	6-31+G(d,p)	6-311+G(d,p)	6-311+G(d,p) ^b (in water)
Triol (C_{3h}) (hartree) ^a	−457.523166	−457.653510	−457.679491	−457.675092	−457.701428	−457.814587	−457.830702
Triketone (C_{3v}) (hartree) ^a	−457.515986	−457.661354	−457.684971	−457.670059	−457.693319	−457.806899	−457.825732
Keto–enol gap (kcal/mol)	+4.506	−4.922	−3.439	+3.158	+5.089	+4.824	+3.119
B3LYP/ACCn/B3LYP/6-311+G(d,p) single-point calculations							
	ACCD			ACCT			ACQ
Triol (C_{3h}) (hartree) ^a	−457.748551			−457.864658			−457.893290
Triketone (C_{3v}) (hartree) ^a	−457.736918			−457.850210			−457.879167
Keto–enol gap (kcal/mol)	+7.300			+9.066			+8.862

^a Electronic terms without zero-point energy and/or thermal corrections.

^b PCM calculations corresponding to water.

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