

COMMENTS

Comment on “Temperature and Solvent Effects on Radical Scavenging Ability of Phenols”

Grzegorz Litwinienko^{†,§} and Peter Mulder^{*,‡}

Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland, and Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

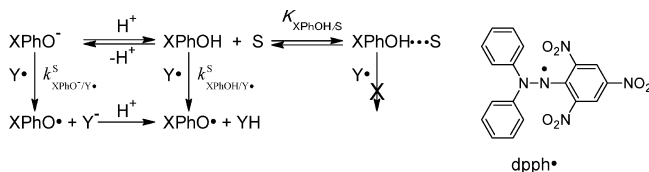
Received: September 7, 2009; Revised Manuscript Received: October 22, 2009

Solvent/solute interactions play an essential role in the magnitude of the rates for the removal of the hydroxylic hydrogen from phenolic compounds, a process of great chemical and biological importance. This results in the phenomenon that the apparent reaction rate for PhOH in heptane or in THF, for example, differs by at least a factor of 300.¹ Recently, a paper by Thavasi et al. entitled, “Temperature and Solvent Effects on Radical Scavenging Ability of Phenols” has been published in this journal.² Our comment aims to highlight a few essential shortcomings in that paper.

The radical scavenging ability of isomeric di- and trihydroxyphenols leads to the conclusion in ref 2 that “phenols with OH groups in the ortho positions have the largest rate coefficient compared to those with OH groups in meta and para position at all temperatures and in all solvent media”. An appropriate literature survey should have shown that the same conclusion has already been reached in highly cited papers published in *J. Am. Chem. Soc.*, *J. Org. Chem.*, *J. Phys. Chem. A*, and *Free Radical Biol. Med.* and authored by, for example, Barclay, Burton, Bors, Ingold, Lucarini, Neta, Pedulli, Rice-Evans, Steenken, and Wright.³ For example, a paper by Wright and co-workers entitled, “Predicting the activity of phenolic antioxidants: Theoretical method, analysis of substituent effects, and application to major families of antioxidants”,^{3b} explains why catechols are better scavengers than other dihydroxybenzenes. It was not the first study dealing with catechols; the presence of a catechol group as the main factor increasing antioxidant activity of flavonoids was identified already many years ago. In this area of research, it is almost impossible to overlook the milestone paper by Rice-Evans et al. on the structure–activity relationship in flavonoids.^{3c} There is a cornucopia of reviews dealing with catechols and other polyhydroxyphenols.⁴

The way the solvent effects are analyzed in ref 2 suggests to a casual reader that insights into these features in free radical (antioxidant) reaction kinetics are still in the infant stage. That is definitively not the case. A systematic literature search on the kinetic solvent effect, KSE (a phrase “Solvent Effect” is included in the title of ref 2), would have retrieved quite a number of papers on the KSE published during the last 15

SCHEME 1



years.^{1,5} Only four of these papers have been referenced by Thavasi et al., (refs 5c, 5d, 10a, and 18 in ref 2), supporting fuzzy and qualitative remarks that the reaction environment may influence the free radical scavenging ability of the compounds under study. The quantitative aspects of the KSE are well-documented nowadays, and this extraordinary amount of work has never been challenged in the contemporary scientific literature.

In general, at least two main mechanisms have been discerned dealing with the phenolic hydrogen atom transfer by radicals (Y•), hydrogen atom transfer (HAT) and sequential proton-loss electron-transfer (SPLET), and they are displayed in Scheme 1.

For HAT, the KSE imposed by the solvent S originates from the fact that XPhOH forms a 1:1 intermolecularly hydrogen-bonded complex with the solvent, XPhOH⋯S, which cannot undergo HAT because of steric factors. In solvents supporting ionization combined with a Y• having a high reduction potential such as dpph• SPLET becomes the ruling mechanism. Each mechanism has its own distinct kinetic characteristics. Therefore, displaying in one graph the kinetic/thermodynamic data for the processes carried out in methanol and in THF has no physical meaning (see, e.g., Figure 8 of ref 2). In methanol (but not in THF), the SPLET mechanism prevails,⁶ and the experimental activation enthalpy is not correlated with an O–H bond dissociation enthalpy (BDE) but rather with the acidity of the phenolic compound and the ionization potential of the phenolic anion. The activation barrier measured in nonionizing supporting solvents relates to the sum of the phenolic O–H BDE and the intermolecular hydrogen bond enthalpy for the association of the phenolic compound with the solvent.¹ The latter quantity varies in magnitude depending on the degree of substitution of the phenol and on the nature of the solvent. These solute/solvent interactions have been compiled and quantified by Abraham et al.⁷

With a single empirical equation (see Table 1, footnote b) quantifying the kinetic solvent effect on hydrogen atom abstractions at room temperature, we have calculated the dpph• rate constants, $k^S_{\text{XPhOH}/\text{dpph}^\bullet}$ for some phenolic compounds in various solvents, and the results are presented in Table 1. It can be inferred from Table 1 that the calculated (predicted) rate constants for PhOH, 2-HOPhOH, 4-HOPhOH, and 4-CH₃OPhOH in THF as the solvent are in satisfying agreement with those obtained experimentally, reinforcing the validity of the applied KSE equation. The agreement is less gratifying in solvents such as methanol (or acetonitrile), and the deviations can be attributed to a change in mechanism from HAT to SPLET. For 3-HOPhOH and 4-HOPhOH, the situation may be more complicated. Even in a moderate HBA solvent, one OH group is fully hydrogen bonded with the solvent (see footnote

* To whom correspondence should be addressed. E-mail: mulder_p@chem.leidenuniv.nl.

[†] University of Warsaw.

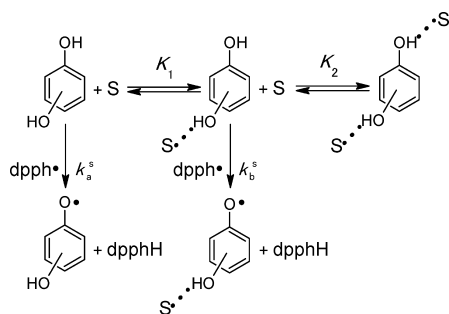
[‡] Leiden University.

[§] E-mail: litwin@chem.uw.edu.pl.

TABLE 1: Rate Constants ($M^{-1} s^{-1}$), $k_{XPhOH/dpph}^S$, for H Atom Abstraction from XPhOH by dpph• in Various Solvents: Experimental^a and Calculated According to the Kinetic Solvent Effect (KSE)^b

solvent (β_2^H)	XPhOH (α_2^H)				
	H (0.59)	2-HO (0.73)	3-HO (0.66) ^f	4-HO (0.61) ^f	4-CH ₃ O (0.57)
heptane/hexane (0.00)	0.19	1800 ^d	0.19 ^e	240 ⁱ	240
methanol (0.41)	0.038	151	1.1	65	18
	0.0037 ^c	300 ^e	0.8 ^h	80 ^h	0.99 ^e
	(0.00090)	(6.1)	(0.0010)	(2.1)	(2.7)
acetonitrile (0.44)	0.019	37.5	0.17	12	5.0
	(0.0013)	(4.0)	(0.00071)	(1.5)	(1.9)
acetone (0.50)		33	0.15	7.0	
	(0.00064)	(1.8)	(0.00033)	(0.72)	(1.0)
tetrahydrofuran (0.51)	0.00061	2.9	0.02	2.2	0.40
	(0.00057)	(1.5)	(0.00029) ^g	(0.64)	(0.90)

^a Experimental kinetic data for PhOH and 4-CH₃OPhOH (from ref 6a) are at ambient temperatures; other experimental kinetic data for 2-HO, 3-HO, and 4-HOPhOH are from ref 2 (representing average values between 20 and 25 °C), unless stated otherwise. ^b The (apparent) rate constants in hydrogen-bond-accepting solvents, $k_{XPhOH/dpph}^S$, are calculated using the KSE equation, $\log k_{XPhOH/dpph}^S = \log k_{XPhOH/dpph}^0 - 8.3\alpha_2^H\beta_2^H$ (ref 1), and they are presented in parentheses in this table. The α_2^H (ref 7a) is the descriptor for the acidity (hydrogen-bond-donating, HBD, ability) of XPhOH, and β_2^H (ref 7b) is the descriptor for the basicity (hydrogen-bond-accepting, HBA, ability) of the solvent; $k_{XPhOH/dpph}^0$ refers to the rate constant in a non-HBA solvent such as heptane with $\beta_2^H = 0.00$. Linear correlations between α_2^H and the pK_a for meta- or para-substituted phenols (ref 7a) have yielded the α_2^H values for 3-HOPhOH (0.66) and 4-HOPhOH (0.61). The α_2^H for 2-HOPhOH is taken from ref 3k. ^c In the presence of 100 mM acetic acid (ref 6a) to suppress the ionization of XPhOH. ^d From ref 3k in hexane. Only one OH group is available for H atom abstraction; the second OH (donor) is intramolecularly hydrogen-bonded with the adjacent OH (acceptor); see ref 8. ^e From ref 3m. ^f The hydrogen bond equilibrium constants, K , for HOPhOH + S \rightleftharpoons HOPhOH...S (K_1) and HOPhOH...S + S \rightleftharpoons S...HOPhOH...S (K_2) (see also Scheme 2) can be calculated from $\log K = 7.354\alpha_2^H\beta_2^H - 1.094$ (ref 7b). The α_2^H values for the two OH groups in 3-HOPhOH or 4-HOPhOH are assumed to be identical. Hence, it can be calculated that in the HBA solvents listed in this table, the concentrations of non-hydrogen-bonded 3-HOPhOH and 4-HOPhOH are negligible. Consequently, 3-HOPhOH and 4-HOPhOH behave kinetically as monosubstituted phenols, that is, XPhOH. ^g It has been demonstrated that the rate constants for hydrogen atom abstraction from phenolic compounds by dpph•, $k_{XPhOH/dpph}^S$, are proportional to the rate constants for hydrogen atom abstraction by peroxy radicals, $k_{XPhOH/ROO}^0$ (see ref 3i). From $k_{3-CH_3OPhOH/ROO}^0 \approx k_{PhOH/ROO}^0$ (ref 3i, Table S1), it follows that $k_{3-HOPhOH/dpph}^0 = k_{PhOH/dpph}^0$ and should be 0.19 M⁻¹ s⁻¹ (per OH) (ref 6a). The rate constants for 3-HOPhOH in 1,4-dioxane ($\beta_2^H = 0.41$) and in ethyl acetate ($\beta_2^H = 0.45$) are determined to be 0.053 and 0.018 M⁻¹ s⁻¹, respectively (see footnote h). According to the KSE equation, $k_{3-HOPhOH/dpph}^0$ is calculated to be 9.3 or 5.3 M⁻¹ s⁻¹ (per OH), an average of 7.3 M⁻¹ s⁻¹. We note a large discrepancy with the estimated $k_{3-HOPhOH/dpph}^0$ of 0.19 M⁻¹ s⁻¹ based on the reactivity of peroxy radicals. When $k_{3-HOPhOH/dpph}^0 = 7.3$ M⁻¹ s⁻¹ is used for the calculations, $k_{3-HOPhOH/dpph}^{THF} = 0.01$ M⁻¹ s⁻¹, which compares quite well with the experimental value of 0.02 M⁻¹ s⁻¹. ^h Measured in this work. The experimental details have been described elsewhere (refs 6a–c). ⁱ See also footnote g. With $k_{4-HOPhOH/ROO}^0 \approx k_{4-CH_3OPhOH/ROO}^0$ (per OH) (ref 3i, Table S1), it follows that $k_{4-HOPhOH/dpph}^0 = k_{4-CH_3OPhOH/dpph}^0 = 240$ M⁻¹ s⁻¹ (per OH). Recently, we have determined preliminary values (see footnote h) of $k_{4-HOPhOH/dpph}^0$ in benzene ($\beta_2^H = 0.14$) and in 1,4-dioxane ($\beta_2^H = 0.47$) of 140 and 3.6 M⁻¹ s⁻¹, respectively. With the KSE equation, see footnote b, this leads to $k_{4-HOPhOH/dpph}^0 = 360$ or 72 M⁻¹ s⁻¹ (per OH), an average of 216 M⁻¹ s⁻¹, in reasonable agreement with the predicted 240 M⁻¹ s⁻¹.

SCHEME 2

f of Table 1), and the reactivity of the free OH is governed by a OH...S substituent rather than a OH substituent (Scheme 2). This is illustrated by the fact that $k_{2,5-R_2-4-HOPhOH/dpph}^S$ [R = (CH₃)₂CHCH₂CH₂] for 2,5-di-*tert*-amylhydroquinone first increases, that is, $k_b^S > k_a^S$, with the HBA solvent concentration (acetonitrile or DMSO in CCl₄). Subsequently, the rate constant decreases due to further hydrogen bonding of the second OH group with the solvent (see Scheme 2).⁵¹

In conclusion, the radical scavenging ability of, for example, phenolic compounds and the influence imposed by the solvent medium is nowadays quite well-understood. New experimental results should be meticulously interpreted and confronted with the accessible literature on the structure–activity relationship as well as on the kinetic solvent effect in free radical chemistry.

References and Notes

- (1) Snelgrove, D. W.; Luszyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 469–477.
- (2) Thavasi, V.; Bettens, R. P. A.; Leong, L. A. *J. Phys. Chem. A* **2009**, *113*, 3068–3077.
- (3) (a) Bors, W.; Heller, W.; Michel, C.; Saran, M. *Methods Enzymol.* **1990**, *186*, 343–355. (b) Terao, J.; Piskula, M.; Yao, Q. *Arch. Biochem. Biophys.* **1994**, *308*, 278–284. (c) Jovanovic, S. V.; Steenken, S.; Tosic, M.; Marjanovic, M.; Simic, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 4846–4851. (d) van Acker, S. A.; van den Berg, D. J.; Tromp, M. N.; Griffioen, D. H.; van Bennekom, W. P.; van der Vijgh, W. J.; Bast, A. *Free Radical Biol. Med.* **1996**, *20*, 331–342. (e) Rice-Evans, C. A.; Miller, N. J.; Paganga, G. *Free Radical Biol. Med.* **1996**, *20*, 933–956. (f) Arora, A.; Nair, M. G.; Strasburg, G. M. *Free Radical Biol. Med.* **1998**, *24*, 1355–1363. (g) Barclay, L. R. C.; Edwards, C. E.; Vinqvist, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 6226–6231. (h) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173–1183. (i) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Barclay, L. R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190–5196. (j) Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 928–931. (k) Foti, M. C.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **2002**, *124*, 12881–12888. (l) Lucarini, M.; Pedulli, G. F.; Guerra, M. A. *Chem.–Eur. J.* **2004**, *10*, 933–939. (m) Foti, M. C.; Daquino, C.; Geraci, C. *J. Org. Chem.* **2004**, *69*, 2309–2314. (n) Foti, M. C.; Daquino, C. *Chem. Commun.* **2006**, 3252–3254.
- (4) Examples of widely cited papers on catechols and flavonoids: Bors et al. (ref 3a, cited more than 700 times), Terao et al. (ref 3b, cited more than 300 times), Jovanovic et al. (ref 3c, cited more than 550 times), Van Acker et al. (ref 3d, cited more than 450 times), Rice-Evans et al. (ref 3e, cited more than 2100 times!), and Arora et al. (ref 3f, cited almost 200 times). The citation indices have been extracted from the SCOPUS database.
- (5) (a) Avila, D. V.; Brown, C. E.; Ingold, K. U.; Luszyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466–470. (b) Wayner, D. D. M.; Luszyk, E.; Pagé, D.; Ingold, K. U.; Mulder, P.; Laarhoven, L. J. J.; Aldrich, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 8737–8744. (c) Avila, D. V.; Ingold, K. U.; Luszyk,

J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929–2930. (d) MacFaul, P. A.; Ingold, K. U.; Luszyk, J. *J. Org. Chem.* **1996**, *61*, 1316–1321. (e) Valgimigli, L.; Ingold, K. U.; Luszyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 3545–3549. (f) Valgimigli, L.; Ingold, K. U.; Luszyk, J. *J. Org. Chem.* **1996**, *61*, 7947–7950. (g) Valgimigli, L.; Banks, J. T.; Luszyk, J.; Ingold, K. U. *J. Org. Chem.* **1999**, *64*, 3381–3383. (h) Lucarini, M.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **1998**, *63*, 4497–4499. (i) Franchi, P.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Lunelli, B. *J. Am. Chem. Soc.* **1999**, *121*, 507–514. (j) de Heer, M. I.; Mulder, P.; Korth, H.-G.; Ingold, K. U.; Luszyk, J. *J. Am. Chem. Soc.* **2000**, *122*, 2355–2360. (k) Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Guerra, M. *J. Am. Chem. Soc.* **2003**, *125*, 8318–8329. (l) Amorati, R.; Franchi, P.; Pedulli, G. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 6336–6338.

(6) (a) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, *68*, 3433–3438. (b) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 5888–5896. (c) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2005**, *70*, 8982–8990. (d) Litwinienko, G.; Ingold, K. U. *Acc. Chem. Res.* **2007**, *40*, 222–230.

(7) (a) See: Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans.* **1989**, *2*, 699–711. (b) Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans.* **1990**, *2*, 521–529.

(8) Korth, H.-G.; de Heer, M. I.; Mulder, P. *J. Phys. Chem. A* **2002**, *106*, 8779–8789.

JP908635K