OPINION

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On the effectiveness of the EPR radical equilibration technique in estimating O–H bond dissociation enthalpies of catechols and other complex polyphenols

Hong-Yu Zhang

Laboratory for Computational Biology and Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Shandong University of Technology, 255049 Zibo, P. R. China. E-mail: zhanghy@sdut.edu.cn; Fax: +86 533-2780271; Tel: +86 533-2780271

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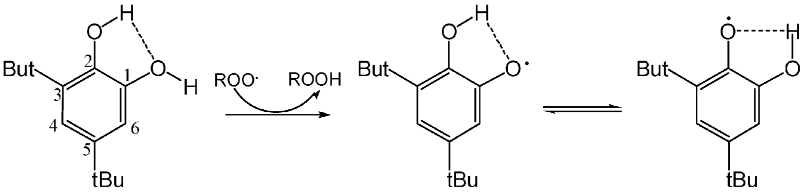
Although the EPR radical equilibration technique can give reliable O–H bond dissociation enthalpies (BDEs) for thermodynamically equilibrated species, it is still a challenge to deduce the O–H BDEs of catechols and other complex polyphenols through group-additivity analysis using this technique, if multistep reactions are involved to reach the thermodynamic equilibrium, because in this case the group additivity is disrupted.

Since the bond dissociation enthalpy (BDE) is not only a basic physico-chemical parameter, but also an important theoretical descriptor in quantitative structure-property relationship (QSPR) studies and for the rational design of medicines, especially antioxidants,[1] a variety of methods, including experimental determinations[2–4] and theoretical calculations,[5] have been employed to estimate the BDEs of various compounds.[6] Although the two types of methods give consistent values in most cases, there remain some exceptions. For instance, the EPR radical equilibration technique provides reliable O–H BDEs for many phenols, but the O–H BDE of catechol deduced from the EPR technique in combination with group-additivity analysis is very different from that estimated by quantum chemical calculations.

The O–H BDE of catechol was calculated to be 9.2–14.1 kcal mol^{-1} lower than that of phenol by means of density functional theory (DFT) on medium basis sets.[7] However, employing the EPR radical equilibration technique, the O–H BDE between 3,5-di-*tert*-butylcatechol (**1**) and its radical **1b** (Scheme 1) was determined to be 8.2 kcal mol^{-1} lower than that of phenol.[8] Through a group-additivity deduction, the O–H BDE of catechol was estimated to be only 4.6 kcal mol^{-1} lower than that of phenol.[8] As the recommended O–H BDE of catechol relative to that of phenol is approximately −7 kcal mol^{-1},[9] the previous DFT calculations likely underestimated the value, while the EPR radical equilibration technique overestimated it. To interpret this overestimation by the EPR technique, we proposed that the EPR radical equilibration technique might be inappropriate for the determination of the O–H BDE of catechol, because the effectiveness of the technique, including the group-additivity deduction, depends on two assumptions:[7d] (*i*) only a one-step reaction is involved to reach the thermodynamic equilibrium between a phenol and a phenoxyl radical; (*ii*) the entropic variation of the H-atom-exchange reaction can be neglected. However, both of these prerequisites are not unambiguous for catechols.

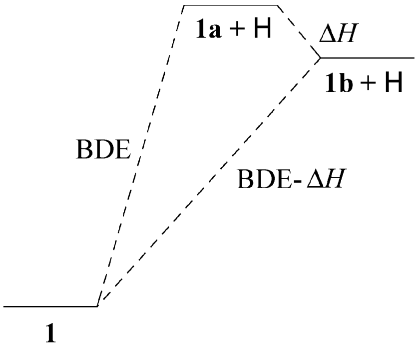
Recently, it was demonstrated that the entropic variation of the H-atom-exchange reaction between **1** and 2,6-di-*tert*-butyl-4-methylphenoxyl radical was very small,[10] which removed the second doubt on the fundamentals of the EPR equilibration technique. Nevertheless, the first doubt still exists, because as a thermodynamic equilibration method, the EPR technique gives the O–H BDE between **1** and **1b** rather than between **1** and **1a** (Scheme 1), as stated in ref. 8 and 10.[11] However, only the latter can be used to deduce the O–H BDE of catechol by group-additivity analysis; the former cannot because in this case the group additivity is disrupted by the intramolecular hydrogen bond (IHB). As revealed in a previous study,[7d] group additivity works for catechols only if the substituent groups have similar effects on the IHBs of catechols and their radicals. But for **1**, both *tert*-butyl groups are located at the *meta* positions to 1-OH, and thus have little effect on the charge of oxygen in 1-OH. As a result, the IHB in **1** is only slightly influenced by the substitution of the di-*tert*-butyl groups. In contrast, in **1b** the *tert*-butyl groups are located at the *ortho*- and *para*-positions to 2-O$^\bullet$ which will increase the charge of the oxygen 2-O and thus effectively strengthen the IHB in **1b**. Obviously, the distinct effects of di-*tert*-butyl groups on IHBs of **1** and **1b** break the group additivity. As a consequence, it is disputable to use the 2,4-di-*tert*-butyl substituent effect (−3.6 kcal mol^{-1}) to deduce the O–H BDE of catechol from the BDE between **1** and **1b**.[8,10]

However, we could estimate the O–H BDE of catechol from the BDE between **1** and **1a** through group-additivity analysis, because in this case both *tert*-butyl groups are located at *meta*-



1 **1a** **1b**

Scheme 1 H-atom-abstraction reaction of 3,5-di-*tert*-butylcatechol (**1**) and isomerization of **1**-derived radicals.



Scheme 2 Energy diagram for 3,5-di-*tert*-butylcatechol (**1**) and radicals (**1a** and **1b**) derived from the H-atom-abstraction reaction.

positions to 1-OH and 1-O$^\bullet$ and thus the substituent effects on the IHBs in **1** and **1a** are slight and also can be offset.[7d] To get the latter BDE, we have to add the enthalpic difference between **1a** and **1b** (ΔH, Scheme 2), which was estimated as 2.2–2.4 kcal mol^{-1} by high-level theoretical calculations,[10] to the EPR-technique-determined apparent BDE, 78.2 kcal mol^{-1}.[10] Thus, the O–H BDE between **1** and **1a** should be 80.4–80.6 kcal mol^{-1}. Considering that the contribution of the 3,5-*tert*-butyl groups to lowering the O–H BDE is 1.0 kcal mol^{-1},[12] the O–H BDE of catechol can be deduced as 81.4–81.6 kcal mol^{-1}, in good agreement with the recommended experimental and theoretical values.[9,10] Although the previous analysis leads to a similar O–H BDE of catechol (81.8 kcal mol^{-1}),[10] it was based on a questionable group-additivity deduction.

In brief, although the EPR equilibration technique can give reliable O–H BDEs for thermodynamically equilibrated species, it is still a challenge for the technique and other thermodynamic-equilibration-based methods to deduce the O–H BDEs of catechols and other complex polyphenols through group-additivity analysis, if multi-step reactions are involved to reach the thermodynamic equilibrium, because in this case the group-additivity analysis is invalid. In fact, the O–H BDE of pyrogallol determined by the EPR technique[8] is also 3–4 kcal mol^{-1} higher than that estimated through the time-resolved photoacoustic calorimetry technique[13] or high-level quantum chemical calculations.[9d] Nevertheless, if we know the enthalpy difference (ΔH) between the final product and the product derived from the first-step H-atom-abstracting reaction, we still can deduce the O–H BDEs of complex polyphenols through the EPR technique.

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