New Insights into the Actual H-Abstraction Activities of Important Oxygen and Nitrogen Free Radicals: Thermodynamics and Kinetics in Acetonitrile

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ABSTRACT: The H-abstraction activity of a free radical is a research hotspot and has been extensively studied. In this article, the second-order rate constants of 21 HAT reactions in acetonitrile at 298 K were chosen from several published literature. A kinetic study on the H-abstraction reaction from TEMPOH by a DPPH radical was carried out. This reaction was researched as an insertion point. By combining this reaction with the 21 HAT reactions in this paper, the thermokinetic parameters of 28 free radicals X and their corresponding antioxidants XH were obtained by the cross-HAT reaction method. The scales of the H-abstraction activities of these 28 oxygen and nitrogen free radicals were determined by using the thermokinetic parameters \( \Delta G^{o}(X) \). Applications of the thermokinetic parameter \( \Delta G^{o}(X) \) in assessing the actual H-abstraction activity of a free radical quantitatively and selecting a suitable free radical in scientific research and chemical production were discussed. Predictions of the rate constants by using thermokinetic parameters of reactants were researched, and the reliabilities of the predicted activation free energies of XH/Y reactions were also examined.

INTRODUCTION

Free radicals play important roles in many areas of biology and are therefore being actively investigated in connection with various human health problems.\(^{1-5}\) In recent years, the activities of short-lived N-oxyl radicals such as 4-substituted phthalimide-N-oxyl radicals (4-X-PINO\(^{3+}\)), 6-substituted benzotiazole-N-oxyl radicals (6-Y-BTNO\(^{3+}\)), 3-quinazolin-4-one-N-oxyl radicals (QONO\(^{3+}\)), and 3-benzotrazin-4-one-N-oxyl radicals (BONO\(^{3+}\)) play key roles in the oxidative degradation of lignin promoted by the laccase/O\(_2\) system mediated by NHPI and other hydroxylamines. Hydrogen atom transfers (HATs) from C–H and O–H bonds have been the object of extensive investigation.\(^{5,7}\) Alkoxy radicals such as the cumyloxy radical (CumO\(^{3-}\))\(^{10}\) and tert-butoxy radical (BuO\(^{3-}\))\(^{11}\) are important oxygen-centered radicals that are involved in a variety of chemical and biological processes. The nitrogen-centered radical 2,2-diphenyl-1-picrylhydrazyl (DPPH\(^{+}\)) is a relatively stable neutral radical and is frequently used as a reactive oxygen species (ROS) model to evaluate the radical-scavenging activity of an antioxidant.\(^{14}\) It has been extensively employed in kinetic studies of H-abstraction from a lot of antioxidants.\(^{15,16}\) H-abstraction reactions (eq 1) are one of the most important reactions of these radicals, and a lot of studies have been devoted to the mechanistic investigations of these processes.

\[
X + H^* + Y \rightarrow X^* + Y + H
\]  

(eq 1)

Despite the rapid development of radical chemistry, there is still no one physical parameter that can be used to quantitatively reflect the H-abstraction activity of a free radical in a certain reaction. The H-abstraction activities of different free radicals are usually determined by kinetic tests, which greatly hinder the selection of free radicals in the actual production.

In a previous work,\(^{17}\) a new physical parameter was proposed by a new kinetic model, the thermokinetic parameter \( \Delta G^{o}(X) \), which can be used not only to directly assess the actual H-abstraction activity of a free radical but also to predict the rate of HAT reaction (eq 1) by a kinetic equation (eq 2). The two parameters on the right of eq 2 are the thermokinetic parameters of the hydrogen atom donor (XH) and the free radical (Y); the definitions of both parameters are listed in eqs 3 and 4. They can evaluate the actual H-donating activity of a hydrogen atom donor \( \Delta G^{o}(XH) \) and the actual H-accepting activity of a free radical \( \Delta G^{o}(Y) \) accurately and quantitatively. In eqs 3 and 4, \( \Delta G^{o}(XH) \) is the bond dissociation free energy of the hydrogen atom donor X–H. It is the thermodynamic factor and is usually used to assess the
potential H-abstraction capacity of X. \( \Delta G^\neq_{XH/X} \) is the activation free energy of self-exchange HAT reaction for XH (XH + X \rightarrow X + XH). It is the kinetic resistance of the reaction as the thermodynamic driving force is zero, which means the intrinsic kinetic resistance barrier of XH for HAT reaction. It is often called internal resistance energy. The thermokinetic parameter \( \Delta G^{\neq o} \), which consists of both thermodynamic force and kinetic intrinsic barrier, can be used as the parameter to describe the actual H-donating ability of XH and the H-abstraction ability of X in a chemical reaction during a certain reaction time. According to eqs 3 and 4, the thermokinetic parameter \( \Delta G^{\neq o}(X) \) of X can be determined if the thermokinetic parameter \( \Delta G^{\neq o}(XH) \) and the bond dissociation free energy \( \Delta G^o(XH) \) of XH are known, and vice versa.

\[
\Delta G^\neq_{XH/Y} = \Delta G^{\neq o}(XH) + \Delta G^{\neq o}(Y) \tag{2}
\]

\[
\Delta G^{\neq o}(XH) \equiv 1/2[\Delta G^\neq_{XH/X} + \Delta G^o(XH)] \tag{3}
\]

\[
\Delta G^{\neq o}(Y) \equiv 1/2[\Delta G^\neq_{YH/Y} - \Delta G^o(YH)] \tag{4}
\]

To obtain the thermokinetic parameters of free radicals, in this article, three regular kinds of oxygen radicals including the N–O• radical, C–O• radical, and C–O−O– radical and one kind of nitrogen radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH•), were investigated by using the previously proposed kinetic equation (eq 2).\cite{18} Parent structures and marks of radicals examined in this work are listed in Scheme 1.

### RESULTS

#### Determination of the “Thermokinetic Parameter” Values of Free Radicals

Kinetic studies of the HAT reactions from substrates having C–H or O–H bonds of appropriate energies have been provided information about the activities of these radicals toward alkylarenes or phenols in the literature.\cite{18,24} At present, the difficulty was to find an appropriate free radical or HAT reaction that could be combined with the HAT reactions in the literature so as to obtain the thermokinetic parameters of the free radicals in Scheme 1 by using eq 2. After repeated selections, the HAT reaction between TEMPOH and DPPH• (Scheme 2) was chosen as the insertion point. The second-order rate constant (\( k_2 = 1.46 \times 10^4 \ \text{M}^{-1} \ \text{s}^{-1} \)) of TEMPOH/DPPH• was directly determined using the UV–vis stopped-flow method by monitoring the absorbance decay of DPPH• at 518 nm using the pseudo-first-order kinetic model. The kinetic absorbance decay curve is shown in Figure 1. The thermodynamic analytical platform for the reaction mechanism of TEMPOH/DPPH• HAT reaction in acetonitrile is analyzed and proved by stoichiometry in the Supporting Information.

The activation free energy of the HAT reaction \( \Delta G^\neq_{1(H)/DPPH•} \) is 11.77 kcal/mol, which is obtained by the Eyring equation. As the thermokinetic parameter of DPPH• \( \Delta G^{\neq o}(DPPH•) = -29.67 \ \text{kcal/mol} \) has been already available in our previous work,\cite{18} the thermokinetic parameter

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**Scheme 1.** Parent Structures and Marks of Radicals Examined in This Work

**Scheme 2.** HAT Reaction between TEMPOH and DPPH•

**Figure 1.** Decay of the 518 nm absorbance of DPPH• (0.10 mM) following the addition of TEMPOH (2.00 mM) in deaerated anhydrous acetonitrile at 298 K (black line) and the fit (red line) using the pseudo-first-order kinetic model.
of TEMPOH, $\Delta G^{(a)}[1(H)H] = \Delta G^{(a)}[1(H)H/DPPH•] - \Delta G^{(a)}(DPPH•)$, can be determined by using eq 2. The value of $\Delta G^{(a)}[1(H)H]$ is 41.44 kcal/mol. As the bond dissociation free energy of TEMPOH, $\Delta G^{(a)}[1(H)H] = 65.60$ kcal/mol, has been reported in the literature, the activation free energy of self-exchange HAT reaction between 1(H)H and its corresponding radical 1(H), $\Delta G^{(a)}[1(H)H/1(H)H]$, is 16.37 kcal/mol according to eq 3. Then, the thermokinetic parameter $\Delta G^{(a)}[1(H)]$ of 1(H) can be determined according to eq 4. The counting process is shown in Scheme 3.

Then, the cross-HAT reaction method was used to obtain other hydrogen atom donor or radical’s physical parameters by using eqs 2–4. For example, since the values of $k_2$ for HAT reactions 1(H)H/7 and 1(H)H/11 were reported in refs 19 and 20 (Table 1, entries 2 and 3), and $\Delta G^{(a)}[1(H)H] = 41.44$ kcal/mol was determined, the thermokinetic parameters of radical 7 $\Delta G^{(a)}(7)$ and radical 11 $\Delta G^{(a)}(11)$ could be obtained using eq 2. As the bond dissociation free energies of 7H $[\Delta G^{(a)}(7) = 64.50$ kcal/mol] and 11H $[\Delta G^{(a)}(11H) = 100.73$ kcal/mol] were reported in the literature, the activation free energies of self-exchange HAT reactions $\Delta G^{(a)}_{7H/7}$ and $\Delta G^{(a)}_{11H/11}$ were determined according to eq 4. Then, the thermokinetic parameters $\Delta G^{(a)}(7)$ and $\Delta G^{(a)}(11)$ could be determined according to eq 3. The counting process is shown in Scheme 3.

Using the same method, since the thermokinetic parameters $\Delta G^{(a)}(XH)$ of iAscH$^-$ [ascorbic acid, $\Delta G^{(a)}(iAscH^-) = 38.11$ kcal/mol] and TocOH [tocopherol, $\Delta G^{(a)}(TocOH) = 43.56$ kcal/mol] were obtained in our previous research, and the second-order rate constants of HAT reactions between iAscH$^-$/9(OCH$_3$) and TocOH/10 and TocOH/12 were attainable in refs 15 and 21, the thermokinetic parameters $\Delta G^{(a)}(X)$ of radicals 9(OCH$_3$), 10, and 12 could be determined according to eq 2. As the bond dissociation free energies $\Delta G^{(a)}(XH)$ of 9(OCH$_3$)H, 10H, and 12H were reported in the literature, the activation free energies of self-exchange HAT reactions $\Delta G^{(a)}_{XH/X}$ were determined according to eq 4. Then, the thermokinetic parameters $\Delta G^{(a)}(XH)$ of the corresponding antioxidants could be determined according to eq 3.

The cross-HAT reactions researched in this article are listed in Table 1. Except the second-order rate constants $k_2$ and the activation free energies $\Delta G^{(a)}(XH)$ of HATs, the Gibbs molar free energy changes $\Delta G^{(a)}_{XH/Y}$ which were derived from the subtraction of the bond dissociation free energies of two reactants XH and Y, are also listed in Table 1.

The physical parameters of 28 free radicals are listed in Table 2. In column 4, the homolytic bond dissociation free energy $\Delta G^{(a)}(XH)$ of X–H and the reference it indexes were listed. In column 5, the activation free energy $\Delta G^{(a)}_{XH/Y}$ of self-

### Table 1. Second-Order Rate Constants ($k_2$), Activation Free Energies ($\Delta G^{(a)}_{XH/Y}$), and Molar Free Energy Changes ($\Delta G^{(a)}_{YH/X}$) of HAT Reactions (X/H) in CH$_3$CN at 298 K

| entry | XH/Y   | $k_2$ \((M^{-1}s^{-1})\) | $\Delta G^{(a)}_{XH/Y}$ \(\text{kcal/mol}\) | $\Delta G^{(a)}_{YH/X}$ \(\text{kcal/mol}\) | ref |
|-------|--------|-----------------------------|-----------------------------------------------|-----------------------------------------------|-----|
| 1     | 1(H)H/14 | 1.46 × 10$^4$             | 11.77                                        | −14.20                                        | this work |
| 2     | 1(H)H/7  | 1.90                       | 17.07                                        | 1.30                                          | 19  |
| 3     | 1(H)H/11 | 5.80 × 10$^4$             | 8.22                                         | −10.63                                        | 20  |
| 4     | 13H/11   | 8.70 × 10$^4$             | 7.98                                         | −18.13                                        | 20  |
| 5     | 1(OCH$_3$)H/14 | 1.13 × 10$^4$ | 11.92                                        | −15.70                                        | 18  |
| 6     | iAscH$^-$/9(OCH$_3$) | 5.30 × 10$^4$ | 9.64                                         | −0.22                                         | 21  |
| 7     | p-OCH$_3$ | 5.40 × 10$^4$             | 8.26                                         | −9.90                                        | 22  |
| 8     | p-CH$_3$ | 2.90 × 10$^4$             | 10.00                                        | −6.90                                        | 22  |
| 9     | p-H      | 3.20 × 10$^4$             | 11.30                                        | −5.10                                        | 22  |
| 10    | p-Bz     | 2.00 × 10$^4$             | 11.58                                        | −4.60                                        | 22  |
| 11    | 9(GOH)/3(H) | 1.60 × 10$^4$ | 10.35                                        | −9.80                                        | 22  |
| 12    | p-OCH$_3$ | 1.30 × 10$^4$             | 11.84                                        | −7.20                                        | 22  |
| 13    | p-CH$_3$ | 1.30 × 10$^4$             | 11.84                                        | −7.20                                        | 22  |
| 14    | p-O(OCH$_3$)H/3(G) | 2.00 × 10$^4$ | 10.22                                        | −8.00                                        | 22  |
| 15    | p-O(OCH$_3$)H/4(G) | 1.30 × 10$^4$ | 10.47                                        | −6.40                                        | 22  |
| 16    | p-H      | 2.20 × 10$^5$             | 10.16                                        | −5.30                                        | 22  |
| 17    | p-CF$_3$ | 7.00 × 10$^5$             | 9.47                                         | −6.70                                        | 22  |
| 18    | p-CH$_3$ | 2.00 × 10$^5$             | 10.22                                        | −5.50                                        | 22  |
| 19    | 9(OCH$_3$)H/5 | 1.00 × 10$^5$ | 9.26                                         | −9.20                                        | 22  |
| 20    | 9(OCH$_3$)H/6 | 9.40 × 10$^5$ | 9.30                                         | −9.30                                        | 22  |
| 21    | TocOH/10  | 9.40 × 10$^5$             | 5.21                                         | −29.30                                       | 12  |
| 22    | TocOH/12  | 3.80 × 10$^5$             | 9.84                                         | −6.80                                        | 12  |

The uncertainty of data is smaller than 5%. The data of $\Delta G^{(a)}_{XH/Y}$ are derived from the Eyring equation $k_2 = (k_0/t)\exp(-\Delta G^{(a)}/RT)$. The data of $\Delta G^{(a)}_{XH/Y}$ are derived from the subtraction of the bond dissociation free energies of two substrates: $\Delta G^{(a)}_{XH/Y} = \Delta G^{(a)}(XH) - \Delta G^{(a)}(YH)$. 

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Table 2. $\Delta G^\circ(XH)$, $\Delta G^b_{XH/X}$, $\Delta G^d_{X}(XH)$, and $\Delta G^{\delta\delta}(X)$ of X in HAT Reaction in CH$_3$CN at 298 K

| No. | Structure | XH/X | $\Delta G^\circ(XH)$ | $\Delta G^b_{XH/X}$ | $\Delta G^d_{X}(XH)$ | $\Delta G^{\delta\delta}(X)$ | kcal/mol |
|-----|-----------|------|-------------------|-----------------|------------------|-----------------|---------|
| 1   | n-n-n   | OCH$_3$ | 65.06 $^{31}$    | 18.17           | 41.59            | -23.42          |
| 2   | n-n-n   | H     | 66.50 $^{31}$    | 16.37           | 40.44            | -25.07          |
| 3   | n-n-n   | 2H/2 | 65.60 $^{31}$    | 14.91           | 40.26            | -25.35          |
| 4   | n-n-n   | p-OCH$_3$ | 81.30 $^{32}$ | 9.38            | 45.34            | -35.96          |
| 5   | n-n-n   | p-H   | 84.70 $^{32}$    | 18.82           | 49.76            | -24.94          |
| 6   | n-n-n   | p-CO$_2$CH$_3$ | 82.90 $^{32}$ | 10.66           | 46.68            | -26.22          |
| 7   | n-n-n   | p-CH$_3$ | 80.40 $^{32}$    | 7.96            | 44.18            | -36.22          |
| 8   | n-n-n   | p-H   | 80.20 $^{32}$    | 7.66            | 43.93            | -36.26          |
| 9   | n-n-n   | p-CF$_3$ | 81.60 $^{32}$    | 7.68            | 44.64            | -36.96          |
| 10  | n-n-n   | 5H/5 | 84.10 $^{32}$    | 9.76            | 46.93            | -37.17          |
| 11  | n-n-n   | 6H/6 | 84.20 $^{32}$    | 9.92            | 47.06            | -37.14          |
| 12  | n-n-n   | 7H/7 | 64.90 $^{32}$    | 15.66           | 40.08            | -24.42          |

$\Delta G^\circ(XH)$ values are obtained from references. $\Delta G^b_{XH/X}$ values are derived from eqs 3 and 4. $\Delta G^d_{X}(XH)$ values are derived from eq 23. $\Delta G^{\delta\delta}(X)$ values are derived from eq 23. $\Delta G^d_{X}(XH)$ and $\Delta G^{\delta\delta}(X)$ are available in our previous work.  

**Discussion**

Scales of H-Abstraction Activities of Oxygen and Nitrogen Free Radicals. The logical relationship between $\Delta G^\circ(XH)$ and the structures of X is a very important subject. Here, the H-abstraction thermokinetic parameters $\Delta G^d_{X}(XH)$ of radicals are discussed, as they represent the actual activities of the free radicals to capture the hydrogen atoms in a chemical reaction during a certain reaction time. In Table 2, the thermokinetic parameters $\Delta G^d_{X}(XH)$ of 28 radicals are determined. The negative value of $\Delta G^d_{X}(XH)$ for the radical indicates that the energy is released from the initial state (X) to the transition state (X-H) in HAT reaction. According to the physical meaning of $\Delta G^d_{X}(XH)$ discussed in previous articles, the greater the negative value of $\Delta G^d_{X}(XH)$ is, the stronger the H-abstraction ability of the free radical is. From column 6 in Table 2, it is clear that the $\Delta G^d_{X}(XH)$ values of 28 radicals (X) in CH$_3$CN at 298 K range from $-23.42$ kcal/mol for 4-methoxy-2,2,6,6-tetramethylpiperidin-1-ol (4-CH$_3$TEMPO) to $-41.63$ kcal/mol for the cumyloxyl radical (CumO). Such large ranges of $\Delta G^d_{X}(XH)$ ($-23.42$ to $-41.63$ kcal/mol) indicate that the structures of radicals (X) have a great effect on the $\Delta G^d_{X}(XH)$ values. To facilitate the application of $\Delta G^d_{X}(XH)$ values and discover the dependence of $\Delta G^d_{X}(XH)$ on the structures of radicals (X), the direct-vision dependence of $\Delta G^d_{X}(XH)$ on the structures of the 28 radicals (X) is shown in Scheme 4.

From Scheme 4, it is clear that the order of H-abstraction activities for these four types of free radicals with different structures is alkoxy radicals (CumO$^*$ > BuO$^*$) > short-lived N-oxyl radicals (QONO > BONO > 6-Y-BTNO > 4-X-PINO) > alkyl peroxy radicals (CumOO$^*$ > BuOO$^*$) > phenol radicals $\approx$ DPPH$^*$ > TEMPO$^*$ derivatives. The structures of X have a great effect on the $\Delta G^d_{X}(XH)$ values. The ones with the strongest activity of H-abstraction among these free radicals are alkoxy radicals: cumyloxyl radical (CumO$^*$) and BuO$^*$. The values of $\Delta G^d_{X}(XH)$ are $-41.63$ and $-41.28$ kcal/mol, respectively.

Below these two strongest H-abstraction alkoxy radicals, the short-lived N-oxyl radicals show strong H-abstraction activities. Among these four types of short-lived N-oxyl radicals, the activities of H-abstraction are in the order of QONO > BONO > 6-Y-BTNO > 4-X-PINO. For three substituents of 6-Y-BTNO, the activities of H-abstraction are in the order of CF$_3$ > H > CH$_3$, and $\Delta G^d_{X}(XH)$ values of these three substituted BTNO are very close, which are $-36.96$ kcal/mol for CF$_3$, $-36.26$ kcal/mol for H, and $-36.22$ kcal/mol for CH$_3$. The electronic effect of the substituent has little effect on the actual H-abstraction activity. For three substituents of 4-X-PINO, the activities of H-abstraction are in the order of CO$_2$CH$_3$ > OCH$_3$ > H, and the $\Delta G^d_{X}(XH)$ values of these three substituted PINO are $-36.22$ kcal/mol for CO$_2$CH$_3$, $-35.96$ kcal/mol for OCH$_3$, and $-34.94$ kcal/mol for H. The order results from both the electronic effect and steric effect. The values of $\Delta G^d_{X}(XH)$ for QONO and BONO are $\Delta G^d_{X}(QONO) = -37.17$ kcal/mol and $\Delta G^d_{X}(BONO) = -37.14$ kcal/mol, respectively. They are also very close to each other, as these two radicals are similar in chemical structures and bond dissociation free energies.

Below these four short-lived N-oxyl radicals, there are two peroxy radicals, CumOO$^*$ and BuOO$^*$. Then, the phenol exchange HAT reaction for XH (XH + X → X + XH) was listed. The thermokinetic parameter $\Delta G^d_{X}(XH)$ of XH and the thermokinetic parameter $\Delta G^d_{X}(X)$ of radical X, which respectively could be used to describe the actual H-donating ability of XH and H-abstraction ability of radical X in a chemical reaction during a certain reaction time, were listed in columns 6 and 7.
radicals follow, 4-X-2,6-dimethyl-phenol radicals and 4-X-2,6-di-tert-butylphenol radicals, and the values of $\Delta G^\neq_o(X)$ range from 32.42 to 27.54 kcal/mol. For 4-X-2,6-dimethyl-phenol radicals, six substituents are researched and the order of $\Delta G^\neq_o(X)$ is Br > H > CH$_3$ > Cl > OCH$_3$ > CN; for 4-X-2,6-di-tert-butylphenol radicals, six substituents are researched and the order of $\Delta G^\neq_o(X)$ is CN > tBu ≈ CH$_3$ > OCH$_3$ > H. From these two series, it is not difficult to find that the electronic effect of the substituent does not exactly correspond to the H-abstraction ability of the radical. There are many factors affecting the thermokinetic parameter, including kinetic and thermodynamic factors. In this article, the packing method is used when the thermokinetic parameter $\Delta G^\neq_o(X)$ is used to describe the H-abstraction activity of a free radical. Bond polarity, molecular steric hindrance, and other factors are also included in this parameter.

The H-abstraction activity of DPPH• is in the middle of these phenol radicals, and the value of $\Delta G^\neq_o(DPPH•)$ is $-29.67$ kcal/mol. The ones with the weakest activities of H-abstraction among these free radicals are TEMPO• derivatives. TEMPO• derivatives are very stable and are usually used to examine the activities of active antioxidants, such as ascorbate derivatives.

**Applications of the Thermokinetic Parameter $\Delta G^\neq_o(X)$**. Assessing the Actual H-Abstraction Activities of Free Radicals X. According to the definition of $\Delta G^\neq_o(X)$ (eq 4), it consists of $1/2 \Delta G^e_{XH}$ and $1/2 \Delta G^o(XH)$. As is well known, $\Delta G^e(XH)$ is the bond dissociation free energy of X–H and is usually used to assess the potential H-abstraction capacity of radical X. The bigger the value of $\Delta G^o(XH)$ is, the weaker the H-abstraction capacity of the radical is. However, sometimes, the H-abstraction activity of a free radical in a certain reaction is not in accordance with the order of $\Delta G^o(XH)$. Kinetics need to be taken into account in the actual reaction. For example, the HAT reaction nos. 12 and 17 in
Table 3. Comparison of Second-Order Rate Constants of HAT Reactions in Acetonitrile at 298 K

| HAT Reactions | Parameters of Radicals |
|---------------|------------------------|
| ![HAT Reaction Scheme](image) | $\Delta \Delta G^\circ \neq 3(\text{H}) = 84.70 \text{ kcal/mol}$ |
| $k_2 = 1.60 \times 10^2 \text{ M}^{-1} \text{s}^{-1}$ | $\Delta \Delta G^\circ \neq 3(\text{H}) = -34.94 \text{ kcal/mol}$ |
| ![HAT Reaction Scheme](image) | $\Delta \Delta G^\circ \neq 4(\text{CF}_3) = 7.68 \text{ kcal/mol}$ |
| $k_2 = 7.00 \times 10^2 \text{ M}^{-1} \text{s}^{-1}$ | $\Delta \Delta G^\circ \neq 4(\text{CF}_3) = -39.66 \text{ kcal/mol}$ |

Scheme 5. HAT Reaction between BNAH and DPPH*

Table 1 are listed separately in Table 3. Two different free radicals 3(H) and 4(CF$_3$) react with the same antioxidant 4,6-methoxy-2,6-tert-butylphenol 9(OCH$_3$)$_3$H. The value of $\Delta G^\circ [3(\text{H})\text{H}]$ is 3.1 kcal/mol smaller than $\Delta G^\circ [4(\text{CF}_3)]$, indicating that the potential H-abstraction capacity of the radical 3(H) is less than that of the radical 4(CF$_3$). However, the order of second-order rate constants of these two HAT reactions is reversed. It suggests that the H-abstraction activities of free radicals cannot be evaluated solely on the basis of thermodynamic bond dissociation free energies. In Table 2, we also list another physical parameter of radical X, $\Delta G^\circ_{\text{XH/X}}$, which represents the intrinsic kinetic resistance energy of a radical in a HAT reaction. The value of $\Delta G^\circ [3(\text{H})\text{H}]$ is 7.14 kcal/mol bigger than $\Delta G^\circ [4(\text{CF}_3)]$, indicating that the intrinsic resistance barrier of the radical 3(H) in HAT reaction is bigger than that of the radical 4(CF$_3$). Considering the thermodynamic bond dissociation free energy and kinetic resistance, it is easy to find that the H-abstraction activity of a free radical can be much more accurately determined by using the thermokinetic parameter $\Delta G^\circ(X)$. Selection of Suitable Free Radicals. The thermokinetic parameter $\Delta G^\circ(X)$ can be used not only to compare the H-abstraction activities of different free radicals qualitatively and quantitatively but also to provide data support for the accurate selection of appropriate free radicals in scientific research and chemical production. For example, dihydronicotinamideadenine dinucleotide (NADH) is an extremely important natural redox cofactor, which exists extensively in vivo as an effective hydrogen and electron source to take part in a wide range of biochemical processes.$^{18}$ BNAH is usually used as the model of NADH to study its properties. If we want to oxidize BNAH, we can choose suitable free radicals as oxidants according to the thermokinetic parameters of free radicals as long as the thermodynamic feasibility is satisfied. In general, the selection of free radicals should satisfy the following principles: first, the rate constant of HAT reaction is easy to measure ($k_2$’s magnitude is between 10 and 10$^4$ M$^{-1}$ s$^{-1}$); second, the free radical is stable and has a relatively long lifetime. As $\Delta G^\circ(\text{BNAH}) = 65.80 \text{ kcal/mol}$ and $\Delta G^\circ(\text{BNAH}) = 44.35 \text{ kcal/mol}$, the value of $\Delta G^\circ(Y)$ for radicals should be within the scope of $-28.27$ to $-33.72 \text{ kcal/mol}$. The calculation process is provided in the Supporting Information. Considering the rate constant of HAT reaction, two series of phenol free radicals, DPPH*, and two alkyl peroxide radicals can be selected as oxidants for the oxidation of BNAH. Considering the stability and half-life of the free radicals, DPPH* is the most suitable oxidant for the oxidation of BNAH (Scheme 5).

Predictions of the Rate Constants and Verification of the Predictions. To investigate the reliabilities of thermokinetic parameters for these radicals and the corresponding antioxidants, 35 HAT reactions in the literature$^{21–23}$ are selected. According to the values of thermokinetic parameters of the hydrogen atom donors/acceptors in Table 2, the activation free energies $\Delta G^\circ(\text{theor})$ of the HAT reactions can be calculated using eq 2. The activation free energies measured by experiment $\Delta G^\circ(\text{exp})$ and the difference between these two values $[\Delta \Delta G^\circ = \Delta G^\circ(\text{theor}) - \Delta G^\circ(\text{exp})]$ are listed in Table 4. The relationships between $\Delta G^\circ(\text{theor})$ and $\Delta G^\circ(\text{exp})$ and between $\Delta \Delta G^\circ$ and $\Delta \Delta G^\circ(\text{exp})$ are shown in Figure 2. In Figure 2a, the black scatterplot is plotted with $\Delta G^\circ(\text{exp})$ against $\Delta G^\circ(\text{theor})$, and the line is $\Delta G^\circ(\text{theor}) = \Delta G^\circ(\text{exp})$. In Figure 2b, the black scatterplot is plotted with $\Delta G^\circ(\text{exp})$ against $\Delta \Delta G^\circ$, and the red lines on both sides are $\Delta \Delta G^\circ = \pm 1 \text{ kcal/mol}$ and $\Delta \Delta G^\circ = 1 \text{ kcal/mol}$.

From Figure 2b, it can be seen that the differences between the experimental values and the predicted values of the activation free energies $\Delta G^\circ$ are quite small. Therefore, the
prediction of the rate constants for HAT reactions by using the thermokinetic parameters in eq 2 is highly reliable and accurate. The values of $\Delta \Delta G$ are within $\pm 1.5$ kcal/mol and mostly within $\pm 1$ kcal/mol. In Figure 2, the experimental values of reaction activation free energies with large deviations are mainly concentrated in the regions of $\Delta G^{\neq \text{exp.}} < 8$ kcal/mol and $\Delta G^{\neq \text{exp.}} > 18$ kcal/mol. The reaction rates in these regions are too fast or too slow, and the second-order rate constants of the HAT reactions are above the magnitude of $10^7$ M$^{-1}$ s$^{-1}$ or below $10^{-1}$ M$^{-1}$ s$^{-1}$. Therefore, the deviation of the reaction rate may occur in the process of experimental measurement, resulting in a large difference between the experimental value and the predicted value of activation free energy. For example, in Table 5, the experimentally measured activation free energy of the HAT reaction $9(p$-OCH$_3$)H/6 is 7.70 kcal/mol, and the predicted activation free energy is 9.30 kcal/mol. The deviation is 1.60 kcal/mol. The magnitude of the second-order rate constant is $10^7$ M$^{-1}$ s$^{-1}$, and the reaction rate of $9(p$-OCH$_3$)H/6 is very fast. So, the measurement error of the reaction rate constant may be large, leading to a large deviation of the reaction rate.

| entry | XH/Y | $\Delta G^{\neq \text{exp.}}$ ($^a$) (kcal/mol) | $\Delta G^{\neq \text{theor.}}$ ($^b$) (kcal/mol) | $\Delta \Delta G^{\neq}$ (kcal/mol) | ref |
|-------|------|---------------------------------|---------------------------------|----------------------------|-----|
| 1     | 1(H)H/9(OCH$_3$) | 12.77                          | 12.98                          | 0.21                       | 21  |
| 2     | 8(G)H/3(CO$_2$CH$_3$) | 7.97                           | 8.14                           | 0.17                       | 22  |
| 3     | p-OCH$_3$ | 9.76                           | 9.87                           | 0.11                       | 22  |
| 4     | p-CH$_3$ | 11.14                          | 11.18                          | 0.04                       | 22  |
| 5     | p-H     | 11.32                          | 11.46                          | 0.14                       | 22  |
| 6     | 8(G)H/3(OCH$_3$) | 8.41                           | 8.40                           | $-0.01$                    | 22  |
| 7     | p-OCH$_3$ | 10.25                          | 10.13                          | $-0.12$                    | 22  |
| 8     | p-CH$_3$ | 11.28                          | 11.43                          | 0.15                       | 22  |
| 9     | p-H     | 11.64                          | 11.71                          | 0.07                       | 22  |
| 10    | 8(G)H/4(H) | 9.11                           | 8.10                           | $-1.01$                    | 22  |
| 11    | p-OCH$_3$ | 9.69                           | 8.82                           | 0.13                       | 22  |
| 12    | 8(G)H/4(CF$_3$) | 8.15                           | 7.40                           | $-0.75$                    | 22  |
| 13    | p-OCH$_3$ | 8.85                           | 9.13                           | 0.28                       | 22  |
| 14    | p-CH$_3$ | 10.39                          | 10.44                          | 0.05                       | 22  |
| 15    | 8(G)H/4(CH$_3$) | 9.16                           | 8.14                           | $-1.02$                    | 22  |
| 16    | p-OCH$_3$ | 9.82                           | 9.87                           | 0.05                       | 22  |
| 17    | p-Br    | 12.49                          | 11.46                          | $-1.03$                    | 22  |
| 18    | 8(G)H/5 | 7.66                           | 7.19                           | $-0.47$                    | 22  |
| 19    | p-OCH$_3$ | 8.37                           | 8.92                           | 0.55                       | 22  |
| 20    | p-CH$_3$ | 10.43                          | 10.23                          | $-0.20$                    | 22  |
| 21    | p-H     | 10.73                          | 10.50                          | $-0.23$                    | 22  |
| 22    | 8(G)H/6 | 8.32                           | 8.95                           | 0.63                       | 22  |
| 23    | p-CH$_3$ | 10.81                          | 10.26                          | $-0.55$                    | 22  |
| 24    | p-Br    | 11.10                          | 10.54                          | $-0.56$                    | 22  |
| 25    | 8(G)H/14 | 17.78                          | 16.42                          | $-1.36$                    | 23  |
| 26    | 9(G)H/14 | 17.19                          | 16.77                          | $-0.42$                    | 23  |
| 27    | p-OCH$_3$ | 18.86                          | 18.26                          | $-0.60$                    | 23  |
| 28    | 9(CH$_3$)H/3(G) | 11.88                          | 11.97                          | 0.09                       | 22  |
| 29    | p-CH$_3$ | 11.61                          | 11.71                          | 0.10                       | 22  |
| 30    | 9(CH$_3$)H/4(G) | 11.79                          | 11.67                          | $-0.12$                    | 22  |
| 31    | p-H     | 11.40                          | 10.97                          | $-0.43$                    | 22  |
| 32    | p-CF$_3$ | 10.57                          | 10.76                          | 0.19                       | 22  |
| 33    | 9(CH$_3$)H/5 | 7.70                           | 9.30                           | 1.60                       | 22  |
| 34    | 9(CH$_3$)H/6 | 10.95                          | 10.79                          | $-0.16$                    | 22  |

$^a$Derived from experimental measurements. $^b$Derived from $\Delta G^{\text{exp.}}(XH)$ and $\Delta G^{\text{exp.}}(Y)$ values in Table 2 according to eq 2. $\Delta \Delta G^\neq = \Delta G^\neq (\text{theor.}) - \Delta G^\neq (\text{exp.})$. 

Table 4. Comparison of Theoretical $\Delta G^\neq (\text{theor.})$ Values of HAT Reactions with the Corresponding Experimental Ones $\Delta G^\neq (\text{exp.})$ in Acetonitrile at 298 K
ΔΔ\(\Delta G\) ≠ of reaction 8(p-CH\(_3\))H/14 is 17.78 kcal/mol, ΔG ≠ (theor.) is 16.42 kcal/mol, and ΔΔ\(\Delta G\) ≠ is −1.36 kcal/mol. The magnitude of \(k_2\) is \(10^{-1}\) M\(^{-1}\) s\(^{-1}\), and the reaction rate of 8(p-CH\(_3\))H/14 is very slow. So, the measurement error of the reaction rate constant may be large, leading to a large ΔΔ\(\Delta G\) ≠.

Another reason for the large ΔΔ\(\Delta G\) ≠ is that the kinetic model of eq 2 is based on the classical transition state theory of chemical reaction. The molar free energy change of XH due to the X–H bond dissociation and that of Y due to the Y–H bond formation from Y and H can be described using the Morse-type free energy curves. An approximation is taken in the derivation of eq 2. That is, the activation free energy of the reaction XH/Y is approximately equal to the sum of the thermokinetic parameters Δ\(\Delta G\) ≠(XH) and Δ\(\Delta G\) ≠(Y). The closer the bond dissociation free energies of the two reactants are, the more similar the Morse curves describing the X–H bond dissociation and Y–H bond formation are, and the closer the left and right sides of eq 2 are. Therefore, the large difference between the experimental value and the predicted value of partial HAT reaction’s activation free energies is due to the large difference of bond dissociation free energies between the two reactants and their Morse curves.

## CONCLUSIONS

In this work, the H-abstraction activities of 28 well-known organic radicals (X) were focused on and researched. The second-order rate constants of 22 HAT reactions from XH to Y in acetonitrile at 298 K were restudied. The thermokinetic parameter values of 28 free radicals and the corresponding antioxidants in acetonitrile at 298 K were determined according to eqs 2–4. The reliabilities of the predicted activation free energies of XH/Y reactions were also examined. The following conclusions could be drawn:

1. The thermokinetic parameters Δ\(G^w\) ≠(X) are used to measure the H-abstraction activities of the four types of free radicals with different structures, and the values range from −23.42 kcal/mol for 4-CH\(_3\)O-TEMPO• to −41.63 kcal/mol for CumO•. The order of H-abstraction activities for these four types of free radicals is alkoxy radicals (CumO• > tBuO•) > short-lived N-oxyl radicals (QONO > BONO > 6-Y-BTNO > 4-X-PINO) > alkyl peroxide radicals (CumOO• > 'BuOO•) > phenol radicals ≈ DPPH• > TEMPO• derivatives. The structures of the radicals (X) have a great effect on the values of Δ\(G^w\) ≠(X).

2. The prediction of the rate constants for HAT reactions using thermokinetic parameters in eq 2 is highly reliable and accurate. The differences Δ\(\Delta G\) ≠ between the experimental and predicted activation free energies are within ±1.5 kcal/mol and mostly within ±1 kcal/mol.

3. There are two reasons for the large difference Δ\(\Delta G\) ≠ between the predicted and experimental activation free energies: one is that the magnitude of the second-order..
rate constant for the HAT reaction is above $10^7$ M$^{-1}$ s$^{-1}$ or below $10^{-3}$ M$^{-1}$ s$^{-1}$; the other is the large difference of bond dissociation free energies between the two reactants, which results in the large difference of Morse curves between the two reactants.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02700.

Stoichiometry and thermodynamic analytical platform of reaction between DPPH$^*$ and TEMPOH as well as the calculation process (PDF)

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**Notes**

The authors declare no competing financial interest.

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