

# Rationalisation of the activities of phenolic (vitamin E-type) antioxidants

Christopher J. Rhodes\*, Thuy T. Tran, Philip Denton and Harry Morris

*School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom St., Liverpool, L3 3AF, UK*

**Abstract.** Using Transition-State Theory, experimental rate constants, determined over a range of temperatures, for reactions of vitamin E type antioxidants are analysed in terms of their enthalpies and entropies of activation. It is further shown that computational methods may be employed to calculate enthalpies and entropies, and hence Gibbs Free Energies, for the overall reactions. Within the Linear Free Energy Relationship (LFER) assumption, that the Gibbs Free Energy of activation is proportional to the overall Gibbs Free Energy change for the reaction, it is possible to rationalise, and even to predict, the relative contributions of enthalpy and entropy for reactions of interest, involving potential antioxidants.

## 1. Introduction

Chain-breaking antioxidants are an essential constituent of cell membranes, which are thereby protected against oxidative stress and peroxidation. The “chain” of free radical propagation is broken by the interception of ROO• radicals (Eq. (1)), and the  $\alpha$ -tocopherol component of vitamin-E has been shown to account for most, if not all, of the antioxidant activity of the lipid fraction of human blood plasma and red blood cells [1]. It is proposed that the tocopherols react more rapidly with ROO• radicals, than other similar phenols do, in consequence of the fused six-membered heterocyclic ring, which allows delocalisation of the odd-electron onto the oxygen atom and stabilises the resulting phenoxy radical (ArO•).



A comprehensive series of rate constants has been reported by Burton et al. [2] for the reaction of peroxy radicals with the tocopherols and related phenols, using the *inhibited autoxidation of styrene method*; and some of the values thus obtained were in general agreement with those determined from additional kinetic measurements made using laser-flash photolysis combined with ESR detection. However, while a relative order of antioxidant efficiencies may be derived from such measurements of a given reaction series, the experimental procedures involved are far from trivial. An alternative strategy might be provided through computational methods, but theoretical calculations of actual transition-states for reactions involving such complicated molecules are extremely difficult. This has led to the formulation of quantitative structure activity relationships, QSAR, based on Linear (Gibbs) Free Energy Relationships (LFER) [3], in which it is assumed that there is a correlation between the Gibbs Free Energy of activation, and the Gibbs Free Energy change for the overall reaction, and for many systems [4] such a correlation does indeed exist between the rate constant for a given reaction involving phenolic antioxidants and the

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\*Corresponding author. E-mail: C.J.Rhodes@livjm.ac.uk.

Gibbs Free Energy difference between the reactant molecule (ArOH) and the product radical (ArO•). In many QSAR investigations, it has been assumed that the contribution of entropy to this relationship is negligible [5], and consequently correlation between the enthalpy change and rate constant has been sought. As already noted, the molecules being considered have complex structures, and so computations of their thermodynamic properties are normally semi-empirical, and are carried-out within either the AM1 and PM3 parameterisations of programs like MOPAC [6]: such programs are capable of performing vibrational analyses, from which entropy values may subsequently be calculated, in addition to the enthalpies of the species involved in a given reaction.

In the cases where the temperature dependence of rate constants has been determined experimentally for a series of reactants, the Arrhenius parameters of activation energy ( $E_a$ ) and frequency factor ( $A$ ) may be determined, from which, by the application of Transition-State Theory, the relative enthalpies and entropies of activation may be estimated. In most cases reported, the series of rate constants has been determined at a single temperature, and so this is not possible. However, as we show later, such data are adequately rationalised using the LFER approach, with calculated enthalpies and entropies, as indicated above.

## 2. The theoretical basis for understanding antioxidant activity

According to Transition-State Theory [7], the rate of a reaction ( $k_1$ ) can be related to its entropy  $\Delta S^\ddagger$  and enthalpy  $\Delta H^\ddagger$  of activation (Eq. (2)):

$$\ln k_1 = \ln(kT/h) - \Delta H^\ddagger/RT + \Delta S^\ddagger/R \quad (2)$$

in which  $k$  and  $h$  are the Boltzmann and Planck constants, respectively. Comparison with the empirical Arrhenius expression gives Eqs (3) and (4), and so, from an experimental measurement of the Arrhenius parameters of activation energy ( $E_a$ ) and frequency factor ( $A$ ), the entropy  $\Delta S^\ddagger$  and enthalpy  $\Delta H^\ddagger$  of activation can be calculated:

$$E_a = \Delta H^\ddagger + RT, \quad (3)$$

$$\ln(A) = \ln(kT/h) + \Delta S^\ddagger/R. \quad (4)$$

The Gibbs Free Energy of activation,  $\Delta G^\ddagger$ , for the reaction may then be obtained from these quantities, using Eq. (5):

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger. \quad (5)$$

Of the numerous studies made of the antioxidant properties of vitamin-E type antioxidants, the comprehensive set of data provided by Mukai et al. [8] appears particularly amenable to this kind of theoretical study. The data refers to the temperature dependence of the reaction between the vitamin-E and a series of synthetic tocopherols and the sterically hindered, and stabilised, 2,6-di-tert-butyl-4-(4-methoxyphenyl)phenoxy radical, which has a reactivity that conveniently shifts the rates for the reaction (Eq. (6)) into the accessible range for stopped-flow investigations.



Table 1

Rate constants and calculated thermodynamic parameters of the activated complex for some tocopherols having high antioxidant activity. Original temperature dependence data from [8]

Tocopherol	$10^{-3} k_s^{SS}$ /dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>	$10^{-7} A_{obs}^{SS}$ /dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>	$E_{obs}^{SS}$ /kJ mol <sup>-1</sup>	$\Delta H_{activation}^{\#}$ /kJ mol <sup>-1</sup>	$\Delta S_{activation}^{\#}$ /J mol <sup>-1</sup> K <sup>-1</sup>	$T\Delta S_{activation}^{\#}$ /kJ mol <sup>-1</sup>	$\Delta G_{298, activation}^{\#}$ /kJ mol <sup>-1</sup>
K <sub>1</sub> -Chromanol-1	35.4	1.04	14.3	11.82	-145.6	-43.38	55.21
K <sub>1</sub> -Chromenol-2	24.8	2.35	17.0	14.52	-138.8	-41.36	55.89
Ubichromanol-3	0.42	3.09	27.7	25.22	-136.5	-40.69	65.91
Ubichromenol-4	0.56	0.77	23.9	21.42	-148.1	-44.13	65.55
Tocopherol-5	9.10	1.05	17.5	15.04	-145.5	-43.36	58.38
Tocopherol-6	5.40	0.55	17.2	14.72	-150.9	-44.96	59.68
Tocopherol-7	3.49	0.37	17.3	14.82	-154.8	-45.94	60.77
Tocopherol-8	0.88	1.01	28.8	26.32	-126.7	-37.75	64.07
Tocopherol-9	6.99	0.40	15.8	13.52	-153.5	-45.74	59.26
$\alpha$ -Tocopherol	6.12	1.01	18.7	16.22	-145.8	-43.46	59.68

<sup>SS</sup>Original kinetic data from [8].

The rate constants for this reaction, measured at 30°C, are shown in Table 1, together with the Arrhenius parameters of activation energy ( $E_a$ ) and frequency factor ( $A$ ), from which the entropy  $\Delta S^{\#}$  and enthalpy  $\Delta H^{\#}$  of activation (also shown) were derived using Eqs (3) and (4). The correlation of  $\Delta S^{\#}$  and  $\Delta H^{\#}$  with the observed rate constant is shown in Fig. 1. For the enthalpy ( $\Delta H^{\#}$ ) and Gibbs Free Energy ( $\Delta G^{\#}$ ) of activation, the data shows that the rate constant falls within the series in consequence of an increase in the activation energy for the process. Clearly, there is a reasonable linear correlation between the rate constant for the process and  $\Delta H^{\#}$  ( $r = -0.888$ ), and at first sight, the entropy values ( $\Delta S^{\#}$ ) seem random; however, when the two are combined (Eq. (5)) to give the Gibbs Free energy of activation ( $\Delta G^{\#}$ ), on which the reaction rate actually depends, a very considerable improvement in the linear correlation with rate constant is obtained, with  $r = 0.999$ . What is perhaps of greater interest is the relative magnitude of the enthalpy and entropy contributions to the Gibbs Free Energy of the transition-state, which indicates that for this set of antioxidants reacting with this particular radical, the entropy contribution ( $T\Delta S^{\#}$ ) is at least (and generally much more than) double that of the enthalpy. We may compare this result with that of Jackson and Hosseini [9] who found that  $\Delta H$  was either zero (or very small) and that  $\Delta S$  was  $20 \pm 11$  J/mol/K (giving  $6.0 \pm 3.3$  kJ/mol for  $T\Delta S$ ) for the reaction between the 2,6-di-tert-butyl-4-methoxyphenoxy radical and vitamin-E type molecules, using equilibrium methods, indicating an almost complete control of the process by the overall entropy change.

### 3. The computational approach

Most kinetic measurements of the reaction between peroxy radicals and phenolic antioxidants (Eq. (1)) have been limited to the determination of rate constants at a single temperature [10]. This is mainly because the majority of such investigations have sought a direct gauge of the relative efficiencies of a series of antioxidants, and that a full measure of the temperature dependence of reaction rates is very laborious and experimentally exacting. Therefore, it is not possible to appeal to Transition-State Theory for the extraction of the relevant thermodynamic activation parameters,  $\Delta H^{\#}$ ,  $\Delta S^{\#}$ , and hence  $\Delta G^{\#}$ , as was done above.

In contrast, if reliable values can be obtained computationally for the species ArOH and ArO<sup>•</sup>, within the framework of LFER, and hence QSAR, it should be possible not only to rationalise experimental rate

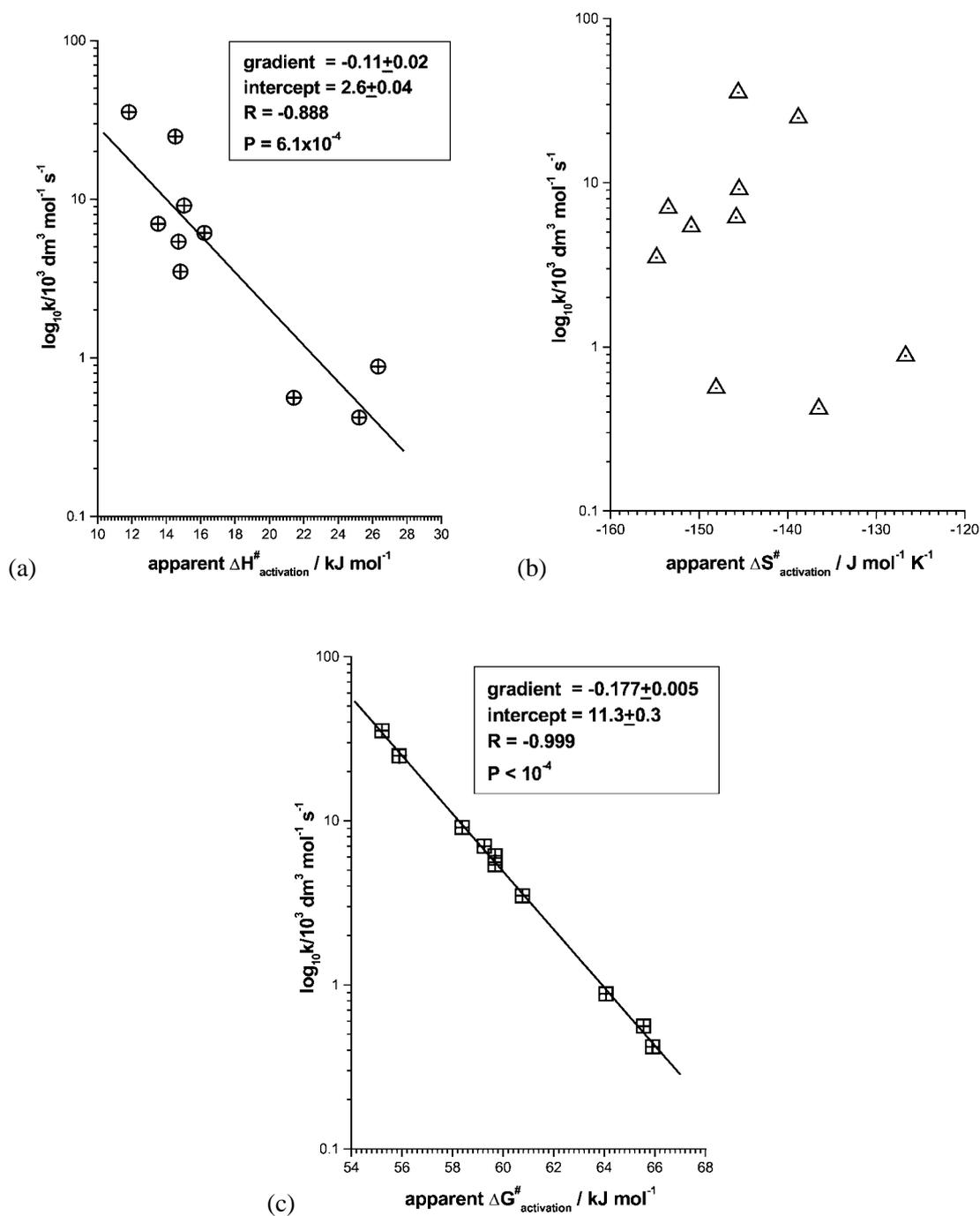


Fig. 1. Correlations between the enthalpy (a), entropy (b) and Gibbs Free Energy of activation (c) with the observed rate constant. Original temperature dependence data from [8].

constant data in terms of the relative importance of  $\Delta H$  and  $\Delta S$  to  $\Delta G$  for the overall reaction, but to enable predictions of the rates of reaction and relative efficiencies of unexplored, potential antioxidants.

This general strategy may be put to the test using the series of data reported by Burton et al. [2], which are rate constants measured at 30°C for the reaction of peroxy radicals with the tocopherols and related phenols, using the *inhibited autoxidation of styrene method*. Since there is an indirect quality to these measurements, efforts were made to confirm the values of the rate constants, so determined, using laser-flash photolysis, coupled with ESR detection, which are in very reasonable agreement, particularly when allowing for the difference in temperature employed (24°C). In consequence of the complexity of the molecules involved, all computations were carried-out within the semi-empirical framework of MOPAC7, using the PM3 parameterisation [6]. A normal coordinate vibrational analysis was made, from which the entropies of the initial ArOH (antioxidant) and its corresponding ArO• radical (Eq. (1)) were calculated, along with their enthalpies. Figure 2 shows the results of these calculations for a series of tocopherols and related phenols, plotted against the experimental rate constants, taken from Burton et al. [2]. The energy of the parent ArOH molecule was calculated within the restricted Hartree Foch, RHF, approximation and of the radical within the unrestricted Hartree Foch approximation, UHF. The agreement obtained between  $\ln k_1$  and values of  $\Delta G_{300\text{ K}}(\text{ArOH} \rightarrow \text{ArO}\cdot)$  ( $r = 0.930$ ) is by far improved from that with  $\Delta H_{300\text{ K}}(\text{ArOH} \rightarrow \text{ArO}\cdot)$  alone ( $r = 0.752$ ). In both cases, the linear correlation between the rate constant and the thermodynamic parameter is negative, as expected (*vide infra*, and Appendix).

Burton et al. [2] have proposed an equation which relates bond dissociation energy in phenols with the rates of their reaction with ROO• radicals (Eq. (7)):

$$D[\text{ArO-H}] \text{ (kcal/mol)} = 100.4(\pm 1.1) - 3.07(\pm 0.20) \log_{10}(k_1/\text{M}^{-1}\text{s}^{-1}). \quad (7)$$

They assume that the entropy contribution to the process remains constant throughout the series, while commenting that this may not be strictly valid (see later, that constant entropies of activation are indicated for reactions involving non-tocopherol-type phenols, and which are, in fact, around twice the size of the activation enthalpies). The  $\Delta H_{300\text{ K}}(\text{ArOH} \rightarrow \text{ArO}\cdot)$  values (Fig. 2) correspond to bond dissociation energies for which the correlation with  $\log_{10} k_1$  is indicative, but not good ( $r = 0.752$ ). Since these  $\Delta H$  values are computed quantities, it might be argued that they are in error, although it is well known that, at least relative,  $\Delta H$  values are obtained reliably from semi-empirical methods, which are parameterised against empirical data. However, as shown above, once the computed  $\Delta S$  values are also incorporated, as in the plot of  $\log_{10} k_1$  against  $\Delta G$ , the correlation is distinctly improved ( $r = 0.93$ ). We conclude that the computed  $\Delta H$  values are, indeed, valid but the  $\Delta S$  values are not constant throughout the series, and their inclusion provides a reasonable estimate of  $\Delta G$ , which is proportional to  $\Delta G^\ddagger$ , the quantity that actually determines the reaction rate (according to the LFER assumption which seem to hold true for many organic reactions in solution [3]). The  $\Delta S$  values appear to be small, however, making a contribution,  $T\Delta S$ , of only 0–15% of  $\Delta H$ .

The driving-force behind antioxidant type reactions (e.g., Eq. (1)) is the enthalpy and Gibbs Free Energy change for the process,  $\text{ROO}\cdot \rightarrow \text{ROOH}$ . For a given ROO• radical, this will be constant over a set of antioxidants, and activity will be thermodynamically feasible if the Gibbs Free Energy change for the associated reaction,  $\text{ArOH} \rightarrow \text{ArO}\cdot$ , is such that  $\Delta G(\text{ROO}\cdot + \text{ArOH} \rightarrow \text{ROOH} + \text{ArO}\cdot)$  is negative. Burton et al. [2] have demonstrated that an enhanced reactivity exists for phenols in which an oxygen substituent occupies the “para” position of the phenolic ring: this, they propose, is due to further delocalisation of the unpaired electron through the conjugated ring system into the oxygen 2p-orbital. Furthermore, the reactivity appears to follow the dihedral angle between the p-orbitals of the substituent and of

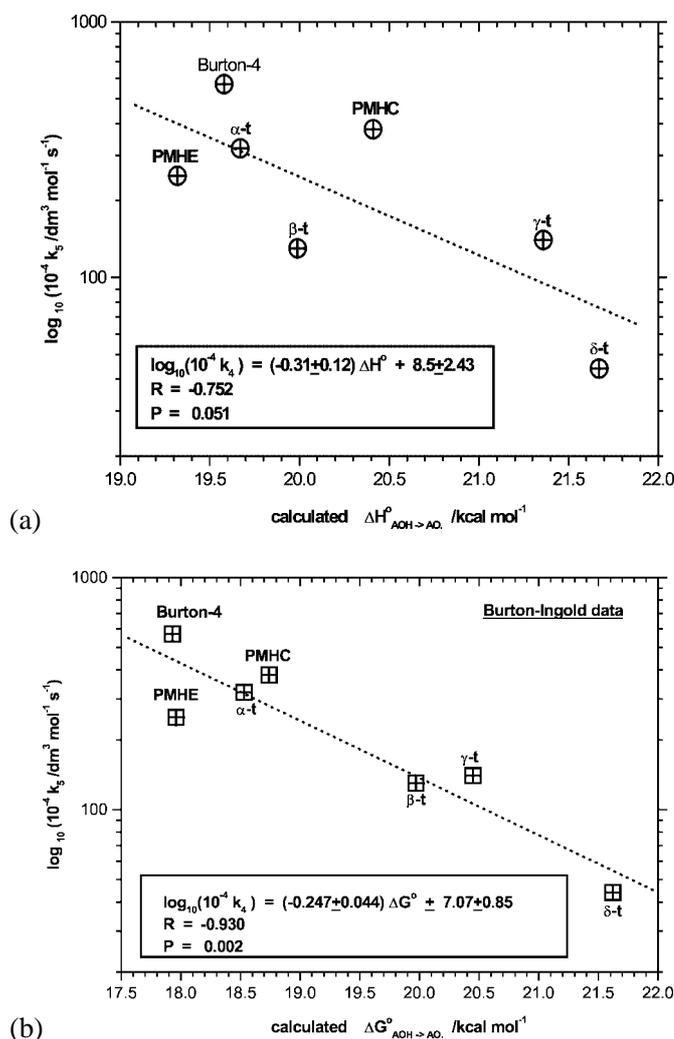


Fig. 2. Correlation between the values of  $\Delta H^{\circ}_{300}$  and  $\Delta G^{\circ}_{300}$ , computed using the PM3 parameterization of MOPAC7, with  $\ln k_1$  for a series of tocopherols. Rate constants taken from [2].

the aromatic ring, and is at a maximum when they are fully aligned, which they argue is the point at which the delocalisation is maximal, and the radical is fully stabilised. The original argument was based on a comparison of the rate constants ( $k_1$ ) for the reaction of peroxy radicals with 2,3,5,6-tetramethylphenol, pentamethylphenol and 2,3,5,6-tetramethyl-4-methoxyphenol [11]. We have calculated values of the enthalpy change ( $\Delta H_{300\text{ K}}$ ) for the process  $\text{ArOH} \rightarrow \text{ArO}^{\bullet}$ , which are listed in Table 2, along with the experimental rate constants for the reaction (Eq. (1)) involving these phenols; the resulting plot of  $\log_{10} k_1$  vs  $\Delta H_{300\text{ K}}$  is shown in Fig. 3. It is clear that the enthalpies of the reaction  $\text{ArOH} \rightarrow \text{ArO}^{\bullet}$  fall in order of the substituents  $\text{H} > \text{Me} > \text{MeO}$  (*viz* the  $\text{ArO}^{\bullet}$  radical is increasingly stabilised along the series), which is consistent with the interpretation of Burton et al. The linear regression between  $\log_{10} k_1$  and  $\Delta H_{300\text{ K}}$  is shown in Eq. (8):

$$\log_{10}(10^{-4} k_1) = 13.8 \cdot 0.5 - (0.59 \cdot 0.02) \Delta H_{300\text{ K}} \quad (8)$$

Table 2

Effect of the 4-substituent on the antioxidant efficiency of 2,3,5,6-tetramethyl phenol derivatives. Rate constants taken from [10,11]

4-substituent	$\Delta H_f$ , parent molecule /kcal mol <sup>-1</sup>	$\Delta H_f$ , parent molecule /kcal mol <sup>-1</sup>	$\Delta H_f$ , parent molecule /kcal mol <sup>-1</sup>	Rate constant 10 <sup>-4</sup> k/dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>
-H	-55.658	-33.475	+22.183	5.6
-CH <sub>3</sub>	-62.797	-41.241	+21.556	14
-OCH <sub>3</sub>	-89.020	-68.258	+20.762	39

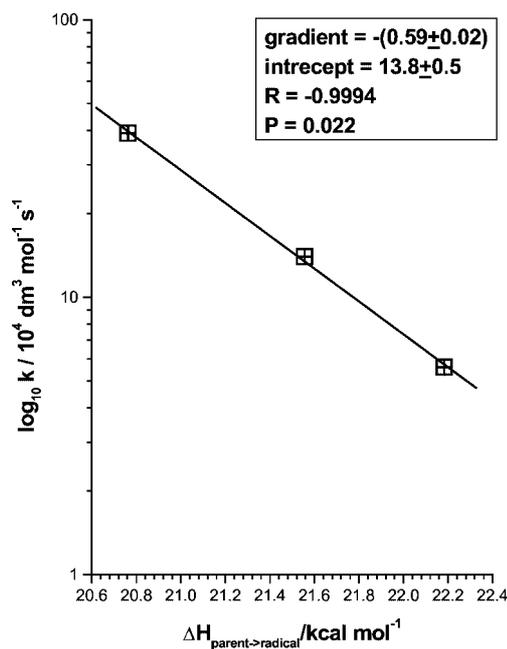


Fig. 3. The effect of the 4-substituent on the antioxidant efficiency of some substituted 2,3,5,6-tetramethylphenols. Rate constants taken from [10,11].

and suggests that 99.8% of the variation in  $\log_{10} k_1$  values can be attributed to variations in the calculated values of  $\Delta H_{300\text{ K}}$  reaction. If it is assumed that the molecules obey a Linear Gibbs Free Energy Relationship, then the Gibbs Free Energy of activation is related to the Gibbs Free Energy of reaction by a simple scaling factor,  $\alpha$ ; since the relationship shown by Eq. (8) is linear in  $\Delta H$ , it implies either that the entropy of activation and of reaction is the same for all three phenols, or that the entropies are proportional to  $\Delta H$  (i.e.  $\Delta S = a\Delta H + b$ ) (see Appendix). If the entropy values are constant within the series, the gradient in the relationship is  $-\alpha/RT$  and the intercept is  $\log_{10}(kT/h) - \alpha\Delta H_{300\text{ K}}/RT + \Delta S^\ddagger/R$ . The calculated scaling factor,  $\alpha$ , is therefore,  $0.596 \times (13.8 \pm 0.5) = 8.23 \pm 0.3$ . The partial enthalpies of activation (contribution of the phenol antioxidant, ArOH, to the enthalpy of activation) are, therefore, 2.69, 2.62 and 2.52 kcal/mol for 1,2,5,6-tetramethylphenol, pentamethylphenol and 1,2,5,6-tetramethyl-4-methoxyphenol, respectively.

For the antioxidants, 2,3,5,6-tetramethylphenol and pentamethylphenol, the rate constants have been determined both at 30°C and 60°C [11], from which the Arrhenius parameters of activation energy,  $E_a$ , and frequency factor,  $A$ , may be determined; application of Transition-State Theory, as discussed earlier,

Table 3

Rate constants and calculated thermodynamic parameters of the activated complex for 2,3,5,6-tetramethylphenol and pentamethyl phenol in their reaction with the poly(styrene-peroxyl) radical. Rate constants taken from [10,11]

Tocopherol	$10^{-4} k_{30^\circ\text{C}}$ /dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>	$10^{-4} k_{60^\circ\text{C}}$ /dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>	$E_a$ /kJ mol <sup>-1</sup>	$10^{-7} A$ /dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>	$\Delta H_{\text{activation}}^\#$ /kJ mol <sup>-1</sup>	$\Delta S_{\text{activation}}^\#$ /kJ mol <sup>-1</sup> K <sup>-1</sup>	$T\Delta S_{298, \text{activation}}^\#$ /kJ mol <sup>-1</sup>
2,3,5,6-Me <sub>4</sub> -phenol	3.0	5.6	20.3	5.2	17.7	-114.7	-34.4
Me <sub>5</sub> -phenol	8.6	14.0	15.9	2.9	13.1	-119.5	-35.9

gave the results shown in Table 3. In accord with the previous discussion, it should be noted that the entropies of activation thus derived for these two compounds are sensibly constant.

#### 4. Conclusions

The application of Transition-State Theory to experimental rate constants allows the dissection of both the enthalpy and entropy of activation, if they are measured over a range of temperatures, from the Arrhenius parameters of activation energy ( $E_a$ ) and frequency factor ( $A$ ). Furthermore, computational methods can be used to calculate enthalpies and entropies and hence Gibbs Free Energies for reactions involving antioxidants. Within the Linear (Gibbs) Free Energy Relationship (LFER) assumption, that the Gibbs Free Energy of Activation ( $\Delta G^\#$ ) is proportional to the Gibbs Free Energy for the overall reaction, it is possible to rationalise the relative contributions of enthalpy and entropy to a given overall reaction. Furthermore it should be possible to predict the relative efficiencies of compounds previously unexplored as potential antioxidants. Finally, we note that the reactivity of the vitamin E tocopherols was found by both Mukai et al. and Burton et al., to follow the order,  $\alpha$ -tocopherol >  $\beta$ -tocopherol >  $\gamma$ -tocopherol >  $\delta$ -tocopherol, despite the difference in the magnitude of the rate constants between the two series of quite different hydrogen-atom abstracting radicals.

#### Appendix. A representation of the linear Gibbs Free Energy relationship

In a linear Gibbs Free Energy relationship it is assumed that there is a linear correlation between the Activation Gibbs Free Energy,  $\Delta G^\#$  and the Gibbs Free Energy change for the reaction,  $\Delta G_{\text{reaction}}$  (see Fig. 4)

$$\Delta G_i^\# = \Delta G_0^\# + \alpha \Delta G_{\text{reaction}}$$

$\Delta G_0^\#$  is a constant, positive, value for the series of compounds and, since  $\Delta G_{\text{reaction}}$  is negative, the coefficient,  $\alpha$ , will be positive. The rate constant,  $k_2$ , can be expressed as (assuming that  $\kappa$  is unity, viz: all activation complex breaks down to give product)

$$k_i = \frac{kT}{h} e^{-\Delta G_i^\# / RT}$$

which gives

$$k_i = \frac{kT}{h} e^{-\Delta G_0^\# / RT} \cdot e^{-\alpha \Delta G_i^\# / RT}$$

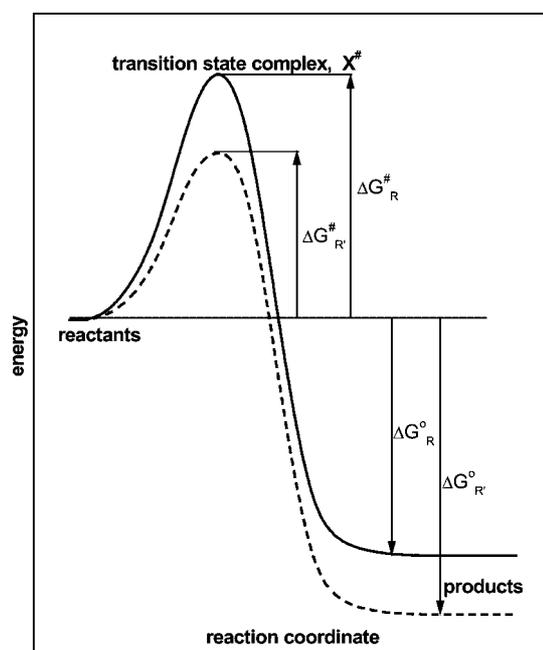


Fig. 4.

or

$$\ln k_i = \ln \frac{kT}{h} - \frac{\Delta G_0^\#}{RT} - \frac{\alpha \Delta G_{\text{reaction}}}{RT}.$$

Thus a plot of  $\ln k_i$  versus  $\Delta G_{\text{reaction}}$  should be linear with

$$\text{intercept} = \ln \frac{kT}{h} - \frac{\Delta G_0^\#}{RT} = 29.46 - \frac{\Delta G_0^\#}{R},$$

$$\text{gradient} = -\frac{\alpha}{RT}.$$

In terms of the enthalpy and entropy terms then

$$\Delta H_1^\# = \Delta H_0^\# + \alpha \Delta H_{\text{reaction}}$$

and

$$\Delta S_1^\# = \Delta S_0^\# + \alpha \Delta S_{\text{reaction}}.$$

Thus

$$\ln k_i = \ln \frac{kT}{h} + \frac{\Delta S_1^\#}{R} - \frac{\Delta H_1^\#}{RT}$$

giving

$$\ln k_i = \ln \frac{kT}{h} + \frac{\Delta S_0^\ddagger + \alpha \Delta S_{\text{reaction}}}{R} - \frac{\Delta H_0^\ddagger + \alpha \Delta H_{\text{reaction}}}{RT}.$$

A plot of  $\ln k_i$  versus  $\Delta H_{\text{reaction}}$  will be linear if either  $\Delta S_{\text{reaction}}$  is constant for the series of compounds or there is a linear correlation between  $\Delta H_{\text{reaction}}$  and  $\Delta S_{\text{reaction}}$ . For the case where the entropy is constant we have

$$\begin{aligned} \text{intercept} &= \ln \frac{kT}{h} - \frac{\Delta G_0^\ddagger}{RT} + \frac{\alpha \Delta S_{\text{reaction}}}{R}, \\ \text{gradient} &= -\frac{\alpha}{RT} \end{aligned}$$

whilst for a linear correlation of the form  $\Delta S_{\text{reaction}} = a\Delta H_{\text{reaction}} + b$

$$\begin{aligned} \text{intercept} &= \ln \frac{kT}{h} - \frac{\Delta G_0^\ddagger}{RT} + \frac{\alpha b}{R}, \\ \text{gradient} &= -\frac{\alpha}{RT}(1 - aT). \end{aligned}$$

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