Kinetic solvent effects on peroxyl radical reactions†

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Received (in Cambridge, UK) 9th January 2008, Accepted 25th January 2008
First published as an Advance Article on the web 8th February 2008
DOI: 10.1039/b800369f

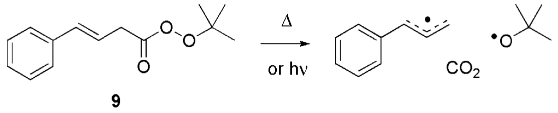
Kinetic solvent effects on peroxyl radical reactions are easily determined using a new peroxyester-based radical clock method.

The reactions of peroxyl radicals have long been of tremendous interest. They play important roles in both biological and industrial contexts, as intermediates in radical-mediated peroxidation reactions that are involved in the oxidative degradation of biological molecules, primary petroleum products, fine chemicals and polymers. The mechanisms of the reactions important in these processes have been extensively studied, and more recent attention has focused on understanding structure–activity relationships of radical-trapping antioxidants (*e.g.* phenols and aromatic amines) which are useful for inhibiting peroxyl radical-mediated oxidation.

Various approaches, such as the rotating sector method, flash photolysis, pulse radiolysis and inhibited autoxidations, have yielded important kinetic and mechanistic information for peroxyl radical–molecule reactions. However, these applications are generally restricted to a handful of research groups with the necessary specialized equipment and expertise to carry out the measurements. Moreover, the systematic study of kinetic solvent effects (KSEs) on these reactions has been difficult to carry out by these methods.[1]

An interesting alternative, recently suggested by Porter and co-workers,[2] employs a kinetic competition approach between the unimolecular β-fragmentation of a non-conjugated peroxyl radical (**3**) and its trapping in a bimolecular reaction (with X–H, Scheme 1). While the utility of this approach has been demonstrated for determining rate constants for H-atom transfer (HAT) from simple phenols to peroxyl radicals in benzene,[2] it has a major limitation: it requires that $X^\bullet$, the radical derived from X–H, carry the oxidation chain reaction. This presents a problem for studying phenols that yield either persistent (*e.g.* butylated hydroxy toluene, BHT)[3] or highly-stabilized (*e.g.* 6-amino-3-pyridinols)[4] radicals or other X–H that give rise to radicals that have difficulty carrying the chain (*e.g.* aromatic amines). Furthermore, because this chain-propagating reaction is so slow (k_p, Scheme 1), a large concentration of substrate is required (*e.g.* 2.6 M **1a**) to ensure sufficient oxidation products are formed to allow accurate, reproducible rate constants to be determined; again precluding the study of KSEs on these reactions.

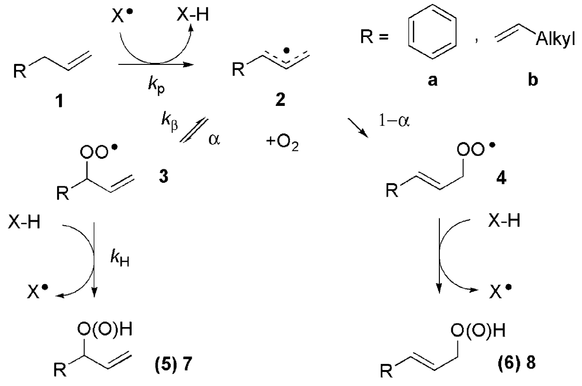
In an attempt to address these limitations, we have investigated the decomposition of the homoconjugated peroxyester **9** as a source of the delocalized carbon-centred radical **2a**, which is oxygenated to the nonconjugated (**3**) and conjugated (**4**) peroxyl radicals in Scheme 1 (eqn (1)). This approach makes possible the determination of KSEs on the β-fragmentation of peroxyl radicals which, in turn, allows the determination of KSEs on the reactions of radical-trapping antioxidants with peroxyl radicals.



(1)

Thermal decompositions of peroxyesters including **9** have been extensively studied under anaerobic conditions and are believed to occur with concerted rupture of the O–O and C–C bonds, leading to an alkyl radical (phenylallyl **2a** in the case of **9**), an alkoxyl radical (*t*-butoxyl in the case of **9**) and carbon dioxide.[5] When we subjected **9** to thermal decomposition (37 °C, 4 h)[6] under aerobic conditions in the presence of a good H-atom donor (*e.g.* α-tocopherol, α-TOH), the same non-conjugated and conjugated hydroperoxides (**5a** and **6a**) were formed as in the kinetically-controlled autoxidations of **1a** that form the basis of the peroxyl radical clock approach described by Porter and co-workers.[2]

As in the autoxidation of **1a**,[2] the ratio of **5a** to **6a** formed upon decomposition of **9** (analyzed by GC following PPh_3 reduction to **7a** and **8a**, respectively) was found to be dependent on the concentration of α-TOH (Fig. 1). The rate constant for β-fragmentation of **3a** could be determined (from the equation in the inset of Fig. 1) to be $k_\beta = 1.7(\pm 0.1) \times 10^5\ s^{-1}$ at 37 °C using $k_H = 3.5 \times 10^6\ M^{-1}\ s^{-1}$ at 37 °C for α-TOH,[2] in good agreement with that determined in the autoxidation of **1a**



Scheme 1

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† Electronic supplementary information (ESI) available: Experimental procedures and raw data for Tables 1–3. See DOI: 10.1039/b800369f

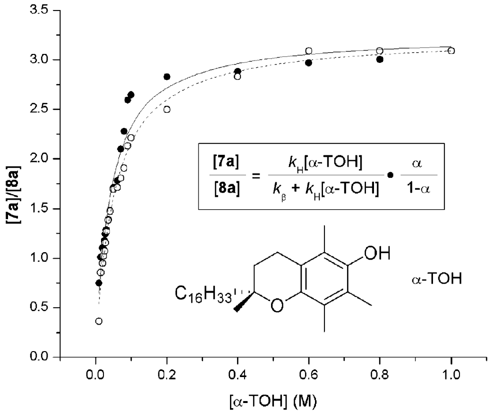
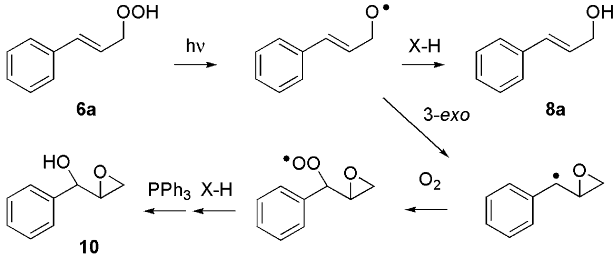


Fig. 1 Ratio of **7a** to **8a** formed from the decomposition of **9** as a function of [α-TOH] following 4 h at 37 °C in benzene (●,—) and following 30 min irradiation (300 nm) at 25 °C in benzene (○,—).

($k_\beta = 2.6(\pm0.3) \times 10^5\ s^{-1}$),[2] but with only 10 mM peroxyester as a precursor to **2a**. The values of α also agree well: 0.76 ± 0.01 *vs*, 0.74 ± 0.12 (at 37 °C).[2]

In order to minimize the incubation time necessary for generation of sufficient radicals for clocking experiments, photochemical decomposition of **9** was also carried out. Irradiation at 300 nm for 30 min was found to be sufficient to generate comparable amounts of products for accurate and reproducible analysis (completion is only a few percent under these conditions). However, the photolytic decomposition of **9** resulted in a slightly different product profile compared to its thermal decomposition. Along with the formation of the expected alcohols (**7a** and **8a**) following work-up, two new products were identified in the chromatograms, corresponding to the diastereomers of 1,2-epoxy-3-hydroxy-3-phenylpropane (**10**). Indeed, under the photolytic conditions, the O–O bond in **6a** is homolytically cleaved to yield the corresponding alkoxyl radical, which can undergo a 3-*exo* cyclization to a resonance-stabilized benzyl radical intermediate in competition with HAT from α-TOH (or any H-donor, X–H).[7] This alkyl radical can then undergo subsequent reactions with O_2, α-TOH and then PPh_3 (on work-up) to yield **10** (Scheme 2). Epoxides expected from an analogous cyclization of the alkoxyl radical derived from **5a** were not observed,[8] presumably since either a primary alkyl radical or dearomatized intermediate would arise. Thus, in experiments carried out by photochemical decomposition of **9**, the ratios of products are corrected for epoxide formation, *i.e.*, the ratio on the *y*-axis in Fig. 1 is actually [**7a**]/([**8a**] + [**10**]). This affords $k_\beta = 1.4(\pm0.1) \times 10^5\ s^{-1}$ and $\alpha = 0.76 \pm 0.01$ at 25 °C, in very good agreement with the data obtained at 37 °C (Fig. 1).



Scheme 2

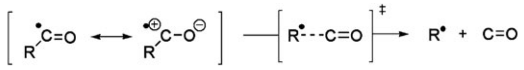
Table 1 KSEs on the β-fragmentation of peroxyl radical **3a**

Solvent	$k_H/M^{-1}\ s^{-1a}$	k_β/s^{-1b}	α^c
Hexane	2.0×10^7	$3.5(\pm0.4) \times 10^5$	0.77 ± 0.01
Benzene	3.4×10^6	$1.4(\pm0.1) \times 10^5$	0.76 ± 0.01
Anisole	1.5×10^6	$6.9(\pm0.1) \times 10^4$	0.77 ± 0.01
t-Amyl alcohol	5.6×10^{5d}	$3.7(\pm0.2) \times 10^4$	0.76 ± 0.01
Acetic acid	8.8×10^5	$3.5(\pm0.2) \times 10^4$	0.75 ± 0.01
Ethyl acetate	2.3×10^5	$2.1(\pm0.1) \times 10^4$	0.73 ± 0.01
Propionitrile	3.8×10^{5e}	$1.8(\pm0.2) \times 10^4$	0.70 ± 0.01

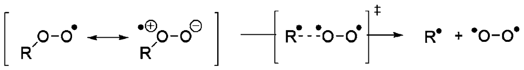
[a] Rate constants for reaction of α-TOH with cumylperoxyl radicals at 25 °C,[9] used to derive k_β and α as in Scheme 1. [b] Determined at 25 °C. [c] The partitioning of O_2 upon addition to the phenylallyl radical **2a** as in Scheme 1. [d] Determined in *t*-butanol. [e] Determined in acetonitrile.

The rate constant for the reaction of α-TOH with cumylperoxyl radicals (k_H) has been determined by laser flash photolysis in several solvents,[9] allowing us to determine the KSE on the β-fragmentation of **3a**.[10] The results are shown in Table 1.

A significant KSE is observed on the β-fragmentation of **3a**, where as the polarity of the solvent increases, k_β decreases. For the selection of solvents we have examined in this study, the decrease in k_β is roughly 20-fold on going from the least polar (hexane) to the most polar (propionitrile) solvent (Table 1). The trend is reminiscent of the KSE observed on the α-fragmentation of acyl radicals (eqn (2)), for which a smaller effect is observed with a decrease in rate constant of roughly 4-fold on going from hexane to acetonitrile.[11] These results suggest that the peroxyl radical is better solvated than the transition state (TS) for C–OO• bond dissociation as the polarity of the medium increases, as is believed to be the case in the α-fragmentation of acyl radicals.[11] The larger KSE on peroxyl radical fragmentation is consistent with a greater decrease in dipolar interactions[12] with solvent on approaching the TS (eqn (3)) as compared to acyl radical fragmentation (eqn (2)).



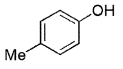
(2)



(3)

Since we have now determined k_β for **3a** in several solvents, the peroxyl radical clock approach can be applied to determine KSEs on peroxyl radical–molecule reactions. For our initial studies we have chosen a small, but representative set of antioxidants of varying structure and reactivity: 4-methylphenol (**11**), 2,4,6-trimethylphenol (**12**), 2,6-di-*tert*-butyl-4-methylphenol (**13**) and diphenylamine (**14**). First, to validate the approach, we restricted our studies to benzene since comparable literature data were available obtained using conventional approaches (Table 2). For **11–13**, the rate constants obtained using the peroxyester approach were within a factor of 2 of the literature data, confirming its accuracy. For **14**, our rate constant is roughly 3.5-fold greater than the literature value. However, it should be pointed out that the

Table 2 Rate constants for reactions of **11–14** with peroxyl radicals at 25 °C in benzene using the peroxyester-based radical clock approach. Literature values at 30 °C are presented for comparison



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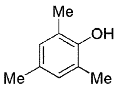

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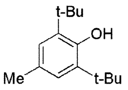

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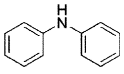
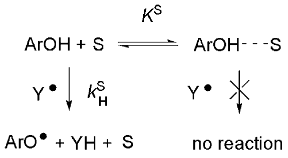


14

	Clock k_H/M^{-1} s^{-1}	Lit. k_H/M^{-1} s^{-1}	Ref.
11	$4.4(\pm0.1) \times 10^4$	2.6×10^4	13
12	$1.7(\pm0.3) \times 10^5$	8.5×10^4	14
13	$3.0(\pm0.2) \times 10^4$	1.9×10^4	14
14	$5.3(\pm0.6) \times 10^4$	1.5×10^4	15



$$k_H^S = \frac{k_H^0}{1 + K^S}$$

Scheme 3

literature value was estimated from an inhibited autoxidation of styrene for which no well-defined inhibition period was observed.[15]

Until now, only KSEs for reactions of alkoxyl radicals (*i.e.* *t*-butoxyl) and hydrazyl radicals (*i.e.* 2,2-diphenyl-1-picrylhydrazyl, DPPH•) with phenols have been systematically determined.[1] The KSEs observed in these reactions are dominated by the H-bonding interaction between the phenols (ArOH) and H-bond accepting solvents (S), which effectively 'tie up' the phenolic O–H, preventing abstraction of the H-atom by the radical (Y•, Scheme 3).

Ingold and co-workers have expressed the rate constant for HAT from phenol to a radical in a given solvent (k_H^S) in terms of the H-bond accepting ability of the solvent (given by its β_2^H parameter[16]) and the H-bond donating ability of the phenol (given by its α_2^H parameter[17]) as in eqn (4).[18] This equation is believed to be valid for the prediction of KSEs on HAT reactions since they are assumed to be independent of the nature of the abstracting radical, *i.e.* any interaction of the abstracting radical with the solvent does not substantially affect its reactivity.[18] However, since eqn (4) was derived from data for reactions of phenols with *t*-butoxyls and DPPH•, we wondered whether the reactions of phenols with peroxyls—arguably the most important radical reaction undergone by phenols—would also obey the relationship.

$$\log k_H^S = \log k_H^0 - 8.3\alpha_2^H\beta_2^H \tag{4}$$

Plots of log k_H *vs*, solvent β_2^H parameter for **11–14** were linear with good correlation coefficients (Table 3), confirming that KSEs on the reactions of peroxyl radicals with phenols (and **14**) are dominated by H-bonding of the phenolic O–H to the solvent. While it is gratifying that the slopes of these correlations for **11–13** are indeed proportional to α_2^H, they are larger than expected from eqn (4) ($-8.3\alpha_2^H$, see Table 3). Thus, there would appear to be a slightly larger solvent dependence of peroxyl radical reactions with phenols as compared to *t*-butoxyl radicals or DPPH•. While the reactivities of *t*-butoxyl radicals and DPPH• have been described as solvent-independent,[19,20] the reactivities of peroxyl radicals may be expected to display some solvent dependence, as they are subject to significant dipole–dipole[12] and H-bonding[21] interactions.

Table 3 KSEs on the reactions of **11–14** with peroxyl radicals given as the slopes of correlations of log k_H^S *vs*, β_H^2 (see ESI†) compared with that expected from eqn (4)

	Slope (*R*)	α_2^H	$-8.3\alpha_2^H$
11	−5.9 (0.98)	0.573	−4.8
12	−4.9 (0.99)	0.374	−3.1
13	−2.9 (0.98)	0.216	−1.8
14	−2.5 (0.99)	0.324	−2.7

This work was supported by the Natural Sciences and Engineering Research Council of Canada and Queen's University. DAP also acknowledges the Canada Research Chairs program.

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