Quinone methide dimers lacking labile hydrogen atoms are surprisingly excellent radical-trapping antioxidants†

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Hydrogen atom transfer (HAT) is the mechanism by which the vast majority of radical-trapping antioxidants (RTAs), such as hindered phenols, inhibit autoxidation. As such, at least one weak O–H bond is the key structural feature which underlies the reactivity of phenolic RTAs. We recently observed that quinone methide dimers (QMDs) synthesized from hindered phenols are significantly more reactive RTAs than the phenols themselves despite lacking O–H bonds. Herein we describe our efforts to elucidate the mechanism by which they inhibit autoxidation. Four possible reaction paths were considered: (1) HAT from the C–H bonds on the carbon atoms which link the quinone methide moieties; (2) tautomerization or hydration of the quinone methide(s) in situ followed by HAT from the resultant phenolic O–H; (3) direct addition of peroxyl radicals to the quinone methide(s), and (4) homolysis of the weak central C–C bond in the QMD followed by combination of the resultant persistent phenoxyl radicals with peroxyl radicals. The insensitivity of the reactivity of the QMDs to substituent effects, solvent effects and a lack of kinetic isotope effects rule out the HAT reactions (mechanisms 1 and 2). Simple (monomeric) quinone methides, to which peroxyl radicals add, were found to be ca. 100-fold less reactive than the QMDs, ruling out mechanism 3. These facts, combined with the poor RTA activity we observe for a QMD with a stronger central C–C bond, support mechanism 4. The lack of solvent effects on the RTA activity of QMDs suggests that they may find application as additives to materials which contain H-bonding accepting moieties that can dramatically suppress the reactivity of conventional RTAs, such as phenols. This reactivity does not extend to biological membranes owing to the increased microviscosity of the phospholipid bilayer, which suppresses QMD dissociation in favour of recombination. Interestingly, the simple QMs were found to be very good RTAs in phospholipid bilayers – besting even the most potent form of vitamin E.

Introduction

The efficient inhibition of autoxidation continues to be a widely-pursued objective, given the indispensability of hydrocarbon-based products (either petroleum-derived or plant-derived) in day-to-day life and their propensity to undergo autoxidation. Nevertheless, the inhibitors which are commonly added to these products have remained essentially the same for decades.1,2 The most ubiquitous radical-trapping antioxidants (RTAs) are hindered phenols, such as butylated hydroxytoluene (BHT). BHT and related phenols react with the peroxyl radicals (ROO⋅) that propagate the autoxidation chain reaction. The mechanism is well understood to involve hydrogen atom transfer (HAT) from the phenolic O–H to a chain-carrying peroxyl radical followed by rapid combination of the resultant phenoxyl radical with a second peroxyl radical (Fig. 1A). A vast literature has established that substituents can have a substantial impact on the rate of the initial H-atom transfer, which is characterized by the inhibition rate constant (kinh).3,4 Electron-donating groups accelerate the rate as they stabilize the electron-deficient phenoxyl radical and the transition state leading to its formation, whereas electron-withdrawing groups have the opposite effect.

† Electronic supplementary information (ESI) available: Additional kinetic and thermodynamic data and analyses, synthesis and characterization data, computed optimized geometries, energies, and Cartesian coordinates. See DOI: 10.1039/d0sc02020f
quinone methide dimers (hereafter QMDs) lack phenolic H-atoms. In our preliminary report, we suggested four possible reaction paths that would account for this observation (Fig. 1C): (1) HAT from the C–H bonds on the carbon atoms which link the quinone methide moieties; (2) tautomerization or hydration of the quinone methide(s) followed by HAT from the resultant phenolic O–H; (3) direct addition of peroxyl radicals to the quinone methide to form persistent phenoxyl radicals, and (4) homolysis of the weak central C–C bond in the QMDs followed by combination of the resultant persistent phenoxyl radicals with peroxyl radicals. Herein, we offer the details of our efforts to elucidate the mechanism.

Results

Synthetic procedures
A set of hindered resveratrol analogues (1a–j) were synthesized wherein the resorcinol ring was replaced with aryl rings bearing substituents of differing electrons (Chart 1). These phenols were dimerized via anodic oxidation in the presence of 2,6-lutidine to produce quinone methide dimers (2a–j). After base-mediated isomerization of one quinone methide, Lewis acid activation and Friedel–Crafts cyclization afforded a series of substituted quadrangularin (quad) A analogues (3a–e).

Inhibited autoxidations
The reactivities of the QMDs as RTAs were determined by the classical inhibited autoxidation approach using a co-autoxidation of 1-hexadecene and PBD-BODIPY (Fig. 2A). Inclusion of the latter enables monitoring of reaction progress via conventional spectrophotometry by loss of its absorbance at λmax = 588 nm upon addition of peroxyl radicals to its 1-phenylbutadiene moiety. Rate constants for the reaction of peroxyl radicals with the 10 QMDs (2), their 10 precursor stilbenoid phenols (1), and 5 quadrangularin A analogues derived therefrom (3) (kinh) and corresponding reaction stoichiometries (n) were determined from the initial rate and inhibited period (tinh) of the inhibited autoxidations, respectively, according to the expressions in Fig. 2B. Representative results are shown in Fig. 2C–E for series of equivalently-substituted 1, 2 and 3, respectively.

All 10 of the QMDs studied were determined to be excellent RTAs, with kinh ≈ 4 × 10^6 M^-1 s^-1 at 37 °C. The striking difference in reactivity between the QMDs and the equivalently-substituted precursor stilbenoid phenols and product quadrangularin A analogues is evident simply upon consideration of the raw inhibited autoxidation reaction progress data (compare the prominent inhibited periods in Fig. 2D to the retarded autoxidations in Fig. 2C and E, respectively), which amount to a difference in kinh of >10-fold. This is even more impressive given that the stilbenoid phenols from which the QMDs are derived are already ~10-fold more reactive than the archetype hindered phenolic RTAs, such as BHT (kinh = 2 × 10^4 M^-1 s^-1). Indeed, the reactivity of the QMDs under these conditions is on par with that of α-tocopherol, the most potent form of vitamin E and among the most reactive RTAs.
The observed inhibition periods correspond to the trapping of \(~2\) radicals by the QMDs, which is similar to the precursor phenols, but roughly half that observed for the quadrangularin A analogues. The stoichiometries of the phenols are consistent with precedent (cf. Fig. 1A), and since the quadrangularin A analogues contain two phenolic moieties, it follows that they trap twice as many peroxyl radicals. We also carried out inhibited autoxidations at 70 °C and found that the superiority of QMDs compared to their precursor and product phenols is maintained (see ESI for the raw data). However, pushing the temperature to 100 °C reveals a noticeable drop in reactivity. The stoichiometry exhibited by the QMDs was also found to attenuate at progressively higher temperatures; see the kinetic data summarized in Table 1.

Mechanistic studies

Without a labile H-atom, the mechanism by which QMDs act as RTAs was not immediately obvious. The lack of substituent effects on the reactivity of the QMDs (\(\rho \sim 0\) at 37 °C, Fig. 2F) is in direct contrast to the sensitivity observed for the precursor phenols (\(\rho = -0.18\) at 37 °C), which is consistent with known structure-reactivity relationships for phenolic RTAs, in general (vide supra). The reactivities of the quadrangularin A analogues, which are also phenols, are lower than the precursor stilbenoid phenols and essentially independent of their substitution. This difference can be rationalized based upon the reduced conjugation between the substituted phenyl rings and the reactive hindered phenolic moieties in the quadrangularin A analogues relative to the stilbenoid phenols, which are fully conjugated (see ESI for the calculated minimum energy structures). Upon increasing the temperature, the trends among the two sets of phenols remain consistent (see ESI for the plots), but those for the QMDs change – demonstrating a slight positive correlation at 70 °C which increases slightly along with the diminution of reactivity at 100 °C (Fig. 3A).

The first mechanistic possibility we considered involves H-atom transfer from the benzylic positions adjacent to the methide carbons of the QMD. Although HAT from a benzylic carbon to a peroxyl radical is generally a sluggish reaction (\(k \sim 1 \text{ M}^{-1} \text{s}^{-1}\)), in this case HAT restores the aromaticity of one of the aryl rings, which suggests it may be significantly enhanced. To probe this mechanism, an analogue of 2d was synthesized wherein both benzylic H-atoms were replaced with D-atoms (structure shown in Fig. 3B; for synthetic details see Experimental section), and inhibited autoxidations were carried out as above. The results of this experiment (shown in Fig. 3B) revealed no kinetic isotope effect. Corresponding DFT computations on a model reaction (HAT from an analogous monomeric quinone methide to a methylperoxyl radical, shown in Fig. 3C) yield \(k_{\text{HAT}} = 0.3 \text{ M}^{-1} \text{s}^{-1}\) from \(\Delta G^2 = 20.9 \text{ kcal mol}^{-1}\) and \(k_{\text{D}}/k_{\text{H}} = 6.12\) Clearly, this mechanism fails to account for the reactivity of the QMDs.

The second mechanistic possibility we considered involves \textit{in situ} tautomerization of the QMD to a stilbenoid phenol that can react with peroxyl radicals (Fig. 1C). The simple fact that the \(k_{\text{inh}}\) values for the QMDs exceed that of the precursor stilbenoid
Table 1 Inhibition rate constants ($k_{inh}$) and stoichiometries ($n$) for substituted QMDs (2), stilbene phenols (1) and quadrangular A analogues (3) measured from inhibited co-autoxidations of 1-hexadecene (2.9 M) and PBD-BODIPY (10 μM) initiated by AIBN (6 mM) at 37 °C, BbOO'Bb (87 mM) at 70 °C, and dicumyl peroxide (1 mM) at 100 °C

| QMDs          | 37 °C   |          |          |          | 70 °C   |          |          |          | 100 °C  |          |          |
|---------------|---------|----------|----------|----------|---------|----------|----------|----------|---------|----------|----------|
|               | $k_{inh}$ (10^5 M⁻¹ s⁻¹) | n | $k_{inh}$ (10^5 M⁻¹ s⁻¹) | n | $k_{inh}$ (10^5 M⁻¹ s⁻¹) | n |
| 3,4-Dioxyl     | 2a      | 48 ± 9   | 1.8 ± 0.1 | 59 ± 10  | 1.6 ± 0.1 | 9.9 ± 0.6 | 0.44 ± 0.01 |
| 4-Obn         | 2b      | 48 ± 8   | 1.7 ± 0.1 | 44 ± 2   | 1.6 ± 0.1 | ND       | ND       |
| 4-SMe         | 2c      | 46 ± 6   | 1.8 ± 0.1 | 59 ± 4   | 1.4 ± 0.1 | 10 ± 1   | 0.49 ± 0.01 |
| H             | 2d      | 45 ± 3   | 1.8 ± 0.1 | 86 ± 6   | 1.7 ± 0.1 | 17 ± 2   | 0.52 ± 0.01 |
| 3,5-(Obn)₂    | 2e      | 40 ± 8   | 2.0 ± 0.1 | 120 ± 10 | 1.9 ± 0.1 | 22 ± 2   | 0.61 ± 0.05 |
| 3-CF₃         | 2f      | 41 ± 4   | 1.8 ± 0.1 | 110 ± 10 | 1.6 ± 0.1 | ND       | ND       |
| 4-CF₃         | 2g      | 43 ± 9   | 1.8 ± 0.1 | 98 ± 10  | 1.6 ± 0.1 | ND       | ND       |
| 2-CF₃         | 2h      | 45 ± 3   | 1.9 ± 0.1 | 62 ± 8   | 1.4 ± 0.1 | 14 ± 2   | 0.50 ± 0.02 |
| 4-No₂         | 2i      | 45 ± 6   | 1.3 ± 0.1 | 40 ± 10  | 1.2 ± 0.1 | ND       | ND       |
| 2-No₂         | 2j      | 42 ± 9   | 1.5 ± 0.1 | 47 ± 10  | 1.0 ± 0.1 | ND       | ND       |
| Stilbene phenols |        |          |          |          |          |          |          |          |          |          |          |
| 3,4-Dioxyl     | 1a      | 2.1 ± 0.2 | 2.2 ± 0.1 | 6.2 ± 0.3 | 1.6 ± 0.1 | 2.9 ± 0.1 | 1.1 ± 0.1 |
| 4-Obn         | 1b      | 3.1 ± 0.2 | 2.1 ± 0.1 | 11 ± 1   | 1.9 ± 0.1 | ND       | ND       |
| 4-SMe         | 1c      | 1.7 ± 0.1 | 2.2 ± 0.1 | 5.9 ± 0.7 | 1.5 ± 0.1 | 2.8 ± 0.3 | 1.1 ± 0.1 |
| H             | 1d      | 1.6 ± 0.1 | 2.0 ± 0.3 | 4.6 ± 0.4 | 1.5 ± 0.1 | 2.6 ± 0.2 | 1.0 ± 0.1 |
| 3,5-(Obn)₂    | 1e      | 1.4 ± 0.1 | 2.3 ± 0.1 | 19 ± 5   | 1.7 ± 0.1 | 2.5 ± 0.1 | 1.3 ± 0.1 |
| 3-CF₃         | 1f      | 1.1 ± 0.2 | 2.3 ± 0.3 | 3.7 ± 0.1 | 1.5 ± 0.1 | ND       | ND       |
| 4-CF₃         | 1g      | 1.3 ± 0.1 | 2.3 ± 0.3 | 3.5 ± 0.4 | 1.6 ± 0.2 | 2.3 ± 0.2 | 1.2 ± 0.1 |
| 2-CF₃         | 1h      | 1.0 ± 0.1 | 2.3 ± 0.3 | 3.6 ± 0.4 | 1.3 ± 0.1 | ND       | ND       |
| 4-No₂         | 1i      | 1.0 ± 0.1 | 2.3 ± 0.3 | 2.8 ± 0.3 | 1.6 ± 0.1 | ND       | ND       |
| 2-No₂         | 1j      | 1.0 ± 0.1 | 2.3 ± 0.3 | 2.7 ± 0.2 | 1.4 ± 0.1 | ND       | ND       |
| Quad A analogues |       |          |          |          |          |          |          |          |          |          |          |
| 3,4-Dioxyl     | 3a      | 1.3 ± 0.1 | 4.1 ± 0.1 | 2.8 ± 0.3 | 4.2 ± 0.4 | 1.9 ± 0.2 | 3.6 ± 0.1 |
| 4-Obn         | 3b      | 2.6 ± 0.4 | 5.5 ± 0.5 | 16 ± 1   | 6.3 ± 0.4 | ND       | ND       |
| 4-SMe         | 3c      | 0.8 ± 0.1 | 3.8 ± 0.1 | 1.2 ± 0.1 | 3.5 ± 0.3 | 1.6 ± 0.1 | 2.0 ± 0.1 |
| H             | 3d      | 1.0 ± 0.1 | 4.1 ± 0.3 | 2.2 ± 0.2 | 4.0 ± 0.3 | 1.7 ± 0.1 | 2.9 ± 0.1 |
| 3,5-(Obn)₂    | 3e      | 1.1 ± 0.1 | 3.8 ± 0.3 | 2.7 ± 0.4 | 3.5 ± 0.4 | 1.9 ± 0.1 | 2.8 ± 0.1 |

phenoxy radicals in the presence of H₂O or D₂O. Furthermore, QMD-inhibited co-autoxidations of dioxane and PBD-BODIPY in chlorobenzene (PhCl) and a 2:1 PhCl/DMSO mixture. Previous studies conducted under identical conditions have shown a predictable attenuation of $k_{inh}$ for HAT from X-H groups to peroxyl radicals due to a combination of the H-bond accepting capacities of the substrate (1,4-dioxane; $\beta_{H2}^{X} = 0.41$) and co-solvent (DMSO; $\beta_{H2}^{X} = 0.78$). The results are shown in Fig. 3E, which reveal no suppression in the reactivity of the QMD in the presence of H₂O or D₂O. Furthermore, QMD-inhibited co-autoxidations of dioxane and PBD-BODIPY in PhCl to which 1% v/v MeOH or 1% v/v MeOD were added were indistinguishable (Fig. 3F), suggesting no exchangeable protons are involved in the RTA activity. The third mechanistic possibility, addition of a peroxyl radical to one of the methide carbons of the QMD (Fig. 1C), has some precedent. Volodkin found quinone methides to be modest antioxidants ($k_{inh} \sim 10^5 M^{-1} s^{-1}$), but since the rate constants they determined were much lower than those we found for the QMDs, and they investigated a limited number of structurally similar compounds, it is possible that quinone methide reactivity is enhanced when part of a QMD. When we calculated the TS for addition of a peroxyl radical to a model QMD (non-tert-butylated 2d, see Fig. 4A), we found a barrier of $\Delta G^\ddagger = 16.0$ kcal mol⁻¹, which corresponds to $k_{add} = 9 \times 10^3$ M⁻¹ s⁻¹ upon application of transition state theory – close to the reported values for simple QMs, but about 4500-fold lower than the $k_{inh}$ values derived from the inhibited autoxidations. From this discrepancy between theory and experiment, the addition mechanism is fully consistent with the lack of substituent effects on the reactivity at ambient temperature and the absence of kinetic solvent effects and either O–H/O–D or C–H/C–D kinetic isotope effects.
at 60 °C in styrene and cumene, respectively)\(^7\) prompted us to synthesize it to corroborate Volodkin's results using our own approach and under the same conditions that the reactivity of the QMDs had been determined. Inhibited co-autoxidations of PBD-BODIPY in 1-hexadecene and of STY-BODIPY in cumene (both in chlorobenzene) yielded \(k_{\text{inh}} = 8.2 \times 10^3\) and \(7.2 \times 10^3\) M\(^{-1}\) s\(^{-1}\), respectively, at 37 °C (see Fig. 4B for a direct comparison of the reactivity of 4a and 2d, tabulated in Table 2).\(^8\) We believe that these values are slightly higher than those obtained by Volodkin due to differences in the experimental conditions employed.\(^9\) Nevertheless, these results confirm that simple QMs are much less reactive than the QMDs.\(^9\)

Given that the observed reactivity of 4a was highly coincident with the corresponding hindered phenols, we considered that the simple QMs undergo hydration \textit{in situ} to produce hindered phenols that are the active RTAs, and that the QMDs are simply more resistant to hydration – making them appear more reactive. Thus, we prepared the hydrated form of 4a and evaluated its reactivity in a 1-hexadecene/PBD-BODIPY co-autoxidation to find nearly indistinguishable reactivity to that of 4a. To confirm that 4a and hydrated 4a react \textit{via} different mechanisms, we carried out additional experiments wherein DMSO was added as a co-solvent. While the reactivity of 4a was unchanged, a significant suppression in the reactivity of the hydrated 4a was observed, consistent with the sequestration of the phenolic H-atom as part of an H-bonded complex with DMSO (Fig. 4C).

We were also able to monitor the QM chromophore (\(\lambda_{\text{max}} \sim 300\) nm) by UV-vis spectrophotometry and found that it disappeared steadily during the inhibited period of the autoxidation (Fig. 6D).

The confirmation of the lackluster – but authentic – RTA activity of the quinone methide 4a suggests that there is something special about the QMD structure which confers greater reactivity compared to monomeric quinone methides. To provide further insight on this point, we carried out autoxidations inhibited by the tautomerized QMD precursor to quadrangularin A analogue 5a and an isomer thereof (5b) – both of which contain one hindered phenol and one quinone methide moiety. Both compounds exhibited kinetics consistent with the phenolic moiety (refer to Table 2 and Fig. 4D), in agreement with the larger \(k_{\text{inh}}\) of the phenols compared to the quinone methides.

The fourth mechanistic possibility (Fig. 1C) involves trapping of peroxy radicals by combination with the small amount of persistent phenoxyl radical that is in equilibrium with the QMD (Fig. 5A).\(^23,24\) We had previously shown that QMD 2e does not possess the weakest C-C bond (with a BDE of 17.0 vs. 6.1 kcal mol\(^{-1}\)),\(^25\) it is sufficiently weak that a relevant concentration of phenoxyl radical exists at ambient temperatures. Based upon the equilibrium constant we previously reported for 2e (\(K_{\text{eq}} = 5.5 \times 10^{-10}\) M at 37 °C),\(^24\) the phenoxyl radical concentration at the beginning of an autoxidation inhibited by 1 µM of the QMD is ~23 nM. If establishment of this equilibrium is fast relative to propagation of the autoxidation, then...
Table 2  Inhibition rate constants ($k_{inh}$) and stoichiometries ($n$) of QMs and phenols during inhibited co-autoxidations of cumene (3.6 M) and STY-BODIPY (10 μM) or hexadecene (2.9 M) and PBD-BODIPY initiated by AIBN (6 mM) in chlorobenzene at 37 °C alongside calculated addition rate constants ($k_{calc}$, gas phase, 37 °C) and literature $k_{inh}$ values ($k_{inh}$, cumene or styrene, 60 °C)  

| Y   | Z   | $k_{calc}$ (10^4 M⁻¹ s⁻¹) | $k_{inh}^{lit}$ (10^4 M⁻¹ s⁻¹) | $n$ | $k_{hexadecene}^{inh}$ (10^4 M⁻¹ s⁻¹) | $n$ | $k_{cumene}^{inh}$ (10^4 M⁻¹ s⁻¹) | $n$ |
|-----|-----|---------------------------|--------------------------------|-----|-------------------------------------|-----|----------------------------------|-----|
| 4a  | Me  | Me                        | 1.6                            | 0.9 | ND                                  | ND  | ND                               | ND  |
| 4a  | H   | Me                        | 10                             | 0.058 | 1.1                          | 8.2 ± 0.2 | 2.0 ± 0.1 | 0.72 ± 0.03 | 2.2 ± 0.1 |
| 4a-H₂O | NA | ND                        | 0.01                           | 0.018 | 0.5                          | Retards | 0.34 ± 0.03 | 1.9 ± 0.1 |
| 5a  | Ph  | Ph                        | 0.0002                         | Does not inhibit | ND | ND | ND | ND |
| 5b  | ND  | ND                        | 8.1 ± 0.2                      | 2.2 ± 0.1 | 0.75 ± 0.06 | 2.4 ± 0.1 |
| 5b  | 0.01 | ND                        | 6.4 ± 0.1                      | 2.4 ± 0.1 | 1.10 ± 0.03 | 2.4 ± 0.1 |

* Data from ref. 17. * Stoichiometry set to $n = 2.0$ to determine $k_{inh}$. [4a-H₂O] = 5 μM. ' The data primarily reflect HAT.
Furthermore, we were unable to identify crossover products when equivalent amounts of 2d and 6 were heated together (see ESI for spectral data†). Indeed, only poorly resolved (low intensity) spectra were obtained when concentrated samples of 6 (10 mM) were placed in the cavity of an EPR spectrometer, in contrast to the strong signals observed from samples of 2d (1 mM, see Fig. 5E), which can be readily identified as being fully consistent with the radicals derived therefrom (see ESI†). Nonetheless, integration of the spectra observed from samples of 6 yields \( K_{\text{eq}} = 4.2 \times 10^{-11} \) M at 20 °C. This can be directly compared with a value of \( K_{\text{eq}} = 1.7 \times 10^{-10} \) M at 20 °C that we obtained with 2d, and assuming \( \Delta S \) is similar for C–C bond homolysis in 2d and 6, suggests that the difference in their C–C BDEs is at least 3.5 kcal mol\(^{-1}\). Most importantly, this compound is a very poor RTA (\( k_{\text{inh}} \sim 2 \times 10^5 \) M\(^{-1}\) s\(^{-1}\)) compared to the other QMDs (see Fig. 5F) and is even several-fold worse than the simple QM 4a.

**Discussion**

We recently prepared QMD 2e as the key intermediate in the total synthesis of pallidol and quadrangularin A – natural products resulting from the oxidative dimerization of resveratrol.\(^6\) We were very surprised to find that 2e and related QMDs are potent RTAs (\( k_{\text{inh}} \sim 4 \times 10^5 \) M\(^{-1}\) s\(^{-1}\) at 37 °C); ca. 10-fold more reactive than the phenols from which they are derived. In fact, the QMDs were similarly reactive to \( \alpha \)-tocopherol – the most biologically active form of vitamin E and the standard to which all other RTAs are compared – despite lacking labile H-atoms, the key structural feature of canonical RTAs.

The preparation of 2e and its subsequent stereoselective conversion to pallidol and quadrangularin A was enabled by its reversible fragmentation to two persistent phenoxyl radicals.\(^5,24\) The foregoing mechanistic investigations suggest that this equilibrium is also responsible for the impressive RTA activity of 2e and related QMDs. Although the persistent phenoxyl radicals are present in small quantities at equilibrium (ca. 1% of the QMD under the conditions which were investigated here), their combination with peroxyl radicals is quite rapid (\( k_{\text{inh}} \sim 2 \times 10^8 \) M\(^{-1}\) s\(^{-1}\) at 37 °C). Thus, one molecule of QMD can be expected to trap two peroxyl radicals – consistent with the inhibition times observed in the QMD-inhibited autoxidations, from which \( n \sim 2 \) were derived.

It is noteworthy that the resultant peroxodic adducts still contain QM moieties which can, in principle, react with additional peroxyl radicals. Indeed, simple QMs such as 4a react with peroxyl radicals with rate constants similar to those of the hindered phenols from which they are derived (e.g. 4a-H\(_2\)O, \( k_{\text{inh}} \sim 8 \times 10^7 \) M\(^{-1}\) s\(^{-1}\) at 37 °C). Since the initial addition of a peroxyl radical forms a phenoxyl that can subsequently combine with a peroxyl radical as do the phenoxyl radicals in equilibrium with the QMDs, the simple QMs were also found to trap 2 peroxyl radicals (see Fig. 6B). Thus, in principle, QMDs should trap a total of 6 peroxyl radicals, as is shown in the overall mechanistic scheme in Fig. 6A.

The inhibited autoxidation data for the isomerized QMD structures 5a and 5b (Fig. 4D) provide some insight to why the

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**Fig. 5** (A) Dissociation equilibrium for substituted QMDs (2) and key resonance structures of the resultant radical monomers; (B) UV-visible absorbance spectra of the phenoxyl radical derived from 2d as a function of temperature; (C) representative Van’t Hoff plots used to determine \( \Delta H_{\text{C–C}} \) and \( \Delta S_{\text{C–C}} \) at 37 °C, 70 (□), and 100 (●) °C for meta- and para-substituted QMDs; (E) EPR spectra of the radicals present in solutions of 2d (1 mM, blue) and 6 (10 mM, red) in benzene at 20 °C; (F) comparison of diaryl (6R=Ph, blue) vs. dialkyl (6R=MMe, red) QMDs (5 \( \mu \)M) as inhibitors of the AIBN-initiated autoxidation of cumene in PhCl at 37 °C.
QMDs only appear to trap 2 peroxy radicals in our experiments. Each of these compounds, which feature one phenolic moiety and one QM moiety react as if only the phenol were present with $n \sim 2$ and $k_{\text{inh}} = 8.1 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$ and $6.4 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$, respectively, which are subject to the same substantial KSEs. The lack of retardation of oxidation due to the QM moiety implies that it is significantly less reactive to peroxy radicals than a simple monomeric QM. Indeed, when we monitored the QMD-inhibited autoxidations by looking at the whole spectrum rather than simply at 330 nm only a slower phase is observed on going from 37 °C to 70 °C and then a noticeable drop on going from 70 °C to 100 °C. We believe this simply reflects the reversible nature of the phenoxyl-peroxyl radical combination. It is well known that the activities of hindered phenolic RTAs diminish at elevated temperatures and that $n$ values erode from 2 to 1 due to the reversible nature of the phenoxyl-peroxyl radical combination. It is well known that the activities of hindered phenolic RTAs diminish at elevated temperatures and that $n$ values erode from 2 to 1 due to the reversible nature of the phenoxyl-peroxyl radical combination. It is well known that the activities of hindered phenolic RTAs diminish at elevated temperatures and that $n$ values erode from 2 to 1 due to the reversible nature of the phenoxyl-peroxyl radical combination. It is well known that the activities of hindered phenolic RTAs diminish at elevated temperatures and that $n$ values erode from 2 to 1 due to the reversible nature of the phenoxyl-peroxyl radical combination. It is well known that the activities of hindered phenolic RTAs diminish at elevated temperatures and that $n$ values erode from 2 to 1 due to the reversible nature of the phenoxyl-peroxyl radical combination. It is well known that the activities of hindered phenolic RTAs diminish at elevated temperatures and that $n$ values erode from 2 to 1 due to the reversible nature of the phenoxyl-peroxyl radical combination.

The step-wise homolytic substitution mechanism of the QMDs is reminiscent of that by which the dimeric form of the Ciba (now BASF) antioxidant Irganox HP-136 reacts. The HP-136 dimer was determined to have largely solvent-independent RTA kinetics, with $k_{\text{inh}} = 4.3 \times 10^7 \text{ M}^{-1} \text{s}^{-1}$ and $n = 0.8$ from styrene autoxidations in chlorobenzene at 30 °C. The QMDs

Fig. 6  (A) Proposed mechanism for peroxy radical-trapping by aryl-containing QMDs; (B) mechanism by which QMs trap peroxy radicals and the dependence of stoichiometry on [QM]; (C) spectral changes associated with inhibitors 2d (blue and red) and (D) 4a (green) in the co-autoxidations of 1-hexadecene (2.9 M) and PBD-BODIPY (black traces); (E) co-autoxidations of cumene (3.6 M) and STY-BODIPY (10 μM) initiated by AIBN (6 mM) in chlorobenzene at 37 °C inhibited by 2d (1–50 μM) with an inset showing the second phase of inhibition translated to the uninhibited trace (broken line).
are therefore roughly 10-fold more reactive than the HP-136 dimer, presumably due to their weaker central C–C bond: 14–17 kcal mol$^{-1}$ vs. 23 kcal mol$^{-1}$ for (HP-136)$_2$. Thus, the QMDs add to a short list of molecules which lack labile H-atoms but are nevertheless reactive RTAs. Two of the few other examples of which we are aware are tetrasulfides$^{32}$ and trisulfide-1-oxides.$^{33}$ These compounds undergo concerted (bimolecular) homolytic substitution by peroxyl radicals to produce stable and persistent perthiyl radicals that do not propagate the autoxidation, but combine to give tetrasulfides. Although these substitution reactions are also insensitive to solvent effects, they are much slower at ambient temperatures ($k_{\text{inh}} \sim 10^3$ and $10^4$ M$^{-1}$ s$^{-1}$ for the tetrasulfides and trisulfide-1-oxides, respectively, compared to $k_{\text{inh}} \sim 10^6$ M$^{-1}$ s$^{-1}$ for the QMDs at 37 °C), limiting their applications to elevated temperatures.

The lack of solvent effects and high reactivity of the QMDs at ambient temperatures prompted us to carry out one additional set of experiments (see Fig. 7). It has recently come to light that the poor performance of phenolic antioxidants as inhibitors of lipid peroxidation in biological membranes is the result of strong H-bonding interactions between phenols and the phosphate diester moiety of the membrane phospholipids (Fig. 8A).$^{34}$ Indeed, the reactivity of $\alpha$-tocopherol ($\alpha$-TOH), Nature’s premier lipophilic RTA, toward peroxyl radicals is suppressed almost 1000-fold on going from chlorobenzene to a phospholipid bilayer ($k_{\text{inh}} \sim 10^6$ vs. $10^3$ M$^{-1}$ s$^{-1}$). As such, we wondered if QMDs would be effective RTAs in this context, and evaluated their ability to suppress (phospholipid)peroxidation using our recently described FENIX assay.$^{34}$ Disappointingly, we found that they were quite poor inhibitors. Alas, the large microviscosity of the phospholipid bilayer$^{35}$ presumably suppresses cage escape and combination of the QMD-derived phenoxyl radicals with lipid peroxyl radicals (Fig. 8B). This result further supports a stepwise substitution by peroxyl radicals on the QMDs in contrast to the concerted substitution favoured for the tetrasulfides and trisulfide-1-oxides, which do not depend on the viscosity of the medium. Alongside the foregoing experiment, we evaluated the RTA activity of a simple QM (4a) as a control. In fact, the QM turned out to be a much better RTA under these conditions, even besting $\alpha$-TOH (see Fig. 8C).
Solution – undergo addition, is fully consistent with what is observed in QMDs, but that the lacklustre reactivity of simple QMs, which microviscosity of the lipid phase suppresses the reactivity of. Experiments in phospholipid bilayers reveal that the high H-bonding interactions. This fact suggests that QMDs may be reactivity is not in moiety to react with additional peroxyl radicals. This mode of reaction had thawed, it was poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with additional portions of CH2Cl2, and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% to 50% DCM/ hexanes) to afford compound S2 (100 mg, 83% yield). H NMR (500 MHz, chloroform-d) δ 7.43–7.27 (m, 12H), 7.16 (d, J = 9.1 Hz, 1H), 7.14 (s, 2H), 7.01 (s, 2H), 6.98 (s, 1H), 6.87 (d, J = 8.9 Hz, 2H), 6.77 (m, 2H), 5.04 (s, 2H), 5.01 (s, 2H), 5.01 (s, 1H), 4.97 (s, 1H), 4.12 (s, 1H), 4.04 (s, 1H), 1.34 (s, 18H), 1.29 (s, 18H). 13C NMR (176 MHz, chloroform-d) δ 158.27, 158.05, 152.37, 151.33, 138.22, 137.43, 137.32, 137.20, 136.74, 135.58, 135.55, 134.49, 134.05, 128.70, 128.65, 128.06, 127.97, 127.56, 127.52, 127.17, 124.18, 123.96, 123.05, 116.37, 114.67, 112.94, 70.13, 70.03, 53.62, 50.27, 34.52, 34.47, 30.46, 30.45. IR (Neat): 3634, 3589, 2957, 2870, 1647, 1594, 1507, 1434, 1237, 1158, 1136, 1029, 734, 697 cm−1. HRMS (ESI) m/z calculated for C69H66O63 ([M]+) 826.4956, found 826.4952.

Conclusions

This work establishes the mechanistic basis which underpins the surprisingly potent RTA activity of quinone methide dimers (QMDs) of the general formula. These dimers, which are formed by the oxidative coupling of hindered stilbenoid phenols, have previously served as synthetic precursors to resveratrol oligomer natural products. Despite lacking any H-bonding on the reactivity of canonical RTAs. This work corroborates previous data which shows that the diaryl QMD scaffold is privileged in that it opens up a new mode of reactivity via its reversible fragmentation. The resultant persistent phenoxyl radicals can combine with peroxyl radicals leaving the second quinone methide moiety to react with additional peroxyl radicals. This mode of reactivity is not influenced by solvent, in contrast to traditional phenolic RTAs, whose H-atom transfer reactions are slowed by H-bonding interactions. This fact suggests that QMDs may be useful RTAs for applications in non-viscous H-bonding media. Experiments in phospholipid bilayers reveal that the high microviscosity of the lipid phase suppresses the reactivity of QMDs, but that the lacklustre reactivity of simple QMs, which undergo addition, is fully consistent with what is observed in solution – making it the only class of RTA reported to date whose solution phase reactivity directly translates to lipid bilayers.

Experimental section

General

All chemicals and solvents obtained from commercial suppliers were used as received unless indicated otherwise. 1-Hexadecene and cumene were purified and stored as previously described. The synthesis, purification, and characterization of substituted stilbenes (1), QMDs (2), and quad A analogues (3) as well as hybrid phenol–QMs (5 and 6) used in this study are described in previous reports. The synthesis, purification, and characterization of 4a, 4c, 4a-H2O, 4b, 4b-OH and S4 were carried out according to literature reports.

4-((1S,2S)-6-(Benzyloxy)-2-(4-(benzyloxy)phenyl)phenyl)-3-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2,3-dihydro-1H-inden-1-yl)-2,6-di-tert-butylphenol (S2). Compound S1 (120 mg, 0.145 mmol) was dried down into a flame-dried round bottom flask charged with a stir bar. The atmosphere was evacuated and replaced with N2, and the starting material was dissolved in CH2Cl2 (14 mL, 0.01 M reaction concentration). The solution was cooled to the reaction temperature, and BF3·OEt2 (0.036 mL, 0.29 mmol, 2 equiv.) was added dropwise. The reaction was stirred for 3 hours, at which point it was raised from the ice bath and quenched via the addition of saturated NaHCO3. Once the reaction had thawed, it was poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with additional portions of CH2Cl2, and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% to 50% DCM/ hexanes) to afford compound S2 (100 mg, 83% yield). H NMR (500 MHz, chloroform-d) δ 7.43–7.27 (m, 12H), 7.16 (d, J = 9.1 Hz, 1H), 7.14 (s, 2H), 7.01 (s, 2H), 6.98 (s, 1H), 6.87 (d, J = 8.9 Hz, 2H), 6.77 (m, 2H), 5.04 (s, 2H), 5.01 (s, 2H), 5.01 (s, 1H), 4.97 (s, 1H), 4.12 (s, 1H), 4.04 (s, 1H), 1.34 (s, 18H), 1.29 (s, 18H). 13C NMR (176 MHz, chloroform-d) δ 158.27, 158.05, 152.37, 151.33, 138.22, 137.43, 137.32, 137.20, 136.74, 135.58, 135.55, 134.49, 134.05, 128.70, 128.65, 128.06, 127.97, 127.56, 127.52, 127.17, 124.18, 123.96, 123.05, 116.37, 114.67, 112.94, 70.13, 70.03, 53.62, 50.27, 34.52, 34.47, 30.46, 30.45. IR (Neat): 3634, 3589, 2957, 2870, 1647, 1594, 1507, 1434, 1237, 1158, 1136, 1029, 734, 697 cm−1. HRMS (ESI) m/z calculated for C69H66O63 ([M]+) 826.4956, found 826.4952.

{(2S,3S)-1-((E)-3,5-Di-tert-butyl-4-hydroxybenzylidene)-2,3-dihydro-1H-inden-5-ol (3b). Compound S2 (73 mg, 0.088 mmol) was dried down in a flame-dried round bottom flask charged with a stir bar. Pentamethyldizene (134 mg, 0.88 mmol) was added in a single portion, and the solids were dissolved in dichloromethane (9 mL, 0.01 M reaction concentration) under an inert atmosphere. The reaction mixture was cooled to −78 °C, at which point BCl3 (0.53 mL, 0.53 mmol, 1.0 M in CH2Cl2) was added via syringe, turning the reaction mixture deep purple. The reaction was stirred at this temperature for 1.5 h, at which point it was lifted from the dry ice bath and quenched with saturated NaHCO3. The reaction was stirred vigorously while the ice thawed and until the reaction mixture stopped changing.
colour. Once the quench was complete (at this point the reaction was a pale-yellow colour), the reaction was poured into a separatory funnel containing DI H2O. The layers were separated, and the aqueous layer was extracted with additional CH2Cl2. The combined organic layers were washed with brine, dried over MgSO4 and concentrated under reduced pressure. The crude material was purified by flash chromatography using a 0 to 15% acetone in DCM gradient to afford compound 3b (49 mg, 86% yield). 1H NMR (700 MHz, chloroform-d) δ 7.31 (d, J = 8.3 Hz, 2H), 7.12 (s, 2H), 7.12 (d, J = 8.1 Hz, 1H), 7.00 (s, 2H), 6.95 (s, 1H), 6.71 (d, J = 8.7 Hz, 2H), 6.63 (dd, J = 8.1, 2.8 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 5.01 (s, 1H), 4.97 (s, 1H), 4.60 (s, 1H), 4.52 (s, 1H), 4.08 (s, 1H), 4.00 (s, 1H), 1.33 (s, 18H), 1.29 (s, 18H). 13C NMR (176 MHz, chloroform-d) δ 154.79, 154.67, 152.22, 152.21, 145.37, 145.10, 137.79, 137.68, 136.19, 135.45, 134.56, 132.58, 127.44, 126.93, 126.40, 124.26, 124.01, 122.45, 116.78, 115.01, 113.50, 53.72, 50.45, 34.50, 34.45, 30.48, 30.45. IR (Neat): 3628, 2926, 2836, 668 cm⁻¹. HRMS (ESI) m/z calculated for C44H55O4Na+ ([M + Na]+): 649.4774, 649.4775.

**2,6-Di tert-butyl-4-(1-3,5-dien-1-ylidene)-2,3-dimethylbutylidene)cyclohexa-2,5-dien-1-one (6).** Phenol S4 (25 mg, 0.100 mmol) was added to a 10 mL reaction flask charged with a stir bar and KPF6 (74 mg, 0.4 mmol, 4.0 equiv.). The solids were dissolved in MeCN (8 mL) and 2,6-lutidine (12 µL, 0.1 mmol, 1.0 equiv.) was added to the reaction solution. See ESI† for details regarding the electrochemical setup. The reaction was stirred at 750 rpm for 1 h at a constant voltage of 0.8 V. Upon completion of the reaction (as judged by TLC), the electrodes were removed and rinsed into a collection flask with DCM (~40 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed under reduced pressure, the crude material was resuspended in DCM, and the electrolyte was filtered away with a plug of Celite. The filtrate was then concentrated and purified by column chromatography (1% to 10% EtOAc/DCM) to afford compound 6 as a yellow foam (23.8 mg, 95% yield, ~7: 1 dr). 1H NMR (500 MHz, chloroform-d) δ 7.22 (d, J = 2.4 Hz, 1H, major diastereomer), 7.19 (d, J = 2.4 Hz, 1H, minor diastereomer), 6.84 (d, J = 2.4 Hz, 1H, minor diastereomer), 6.80 (d, J = 2.4 Hz, 1H, diastereomer), 6.10 (d, J = 10.1 Hz, 1H, major + minor diastereomers overlapped), 3.02 (dd, J = 9.7, 8.0, 5.2 Hz, 1H, major diastereomer), 2.98–2.91 (m, 1H, minor diastereomer), 1.31 (s, 9H), 1.27 (s, 9H). 1H NMR (500 MHz, 101 MHz, CDCl3): δ 7.15 (d, J = 2.4 Hz, 2H), 7.12 (d, J = 2.4 Hz, 2H), δ-H’s of quinone methides: 6.81 (minor diastereomer, d, J = 2.4 Hz, 2H), 6.69 (major diastereomer, d, J = 2.4 Hz, 2H), δ-H’s of quinone methides: 6.49 (minor diastereomer, s, 2H), 6.38 (major diastereomer, s, 2H), 314.2517. 13C NMR (101 MHz, CDCl3): δ 154.0, 136.3, 129.6, 128.8, 136.3, 34.5, 30.4. HRMS (EI, [M+]?): m/z calced for C22H21O1D7 315.2582, found 314.2517.

**4,4′-(2,3-Bis[(phenyl-d5)butane-1,4-diylidene-2,3-d2)bis(2,6-di tert-butylcyclohexa-2,5-dien-1-one) (2d-d5).** A solution of stilbene 1d-d5 (25 mg, 0.080 mmol) in dry THF (0.9 mL) was added to 0°C in an ice bath and purged with nitrogen for 5 minutes. KHMQS (0.090 mmol, 1 M in THF, 0.09 mL) was added slowly and the resulting bright yellow solution was stirred for 10 minutes at 0°C. Ferrocenium hexafluorophosphate (28 mg, 0.090 mmol) was added in two 14 mg portions within a 15 minute interval. The resulting orange solution was stirred at 0°C for 1 hour after which it was filtered through a pad of Celite, concentrated in vacuo and then purified by flash column chromatography using a gradient of 95:2.5:2.5 to 90:5:5 hexanes/ EtOAc/DCM to obtain the final product as a white solid (0.130 g, 69%). 1H-NMR (400 MHz, CDCl3): δ 7.35 (s, 2H), 7.07 (s, 1H), 5.28 (s, 1H), 1.48 (s, 18H). 13C NMR (101 MHz, CDCl3): δ 154.0, 136.3, 129.6, 128.8, 136.3, 34.5, 30.4. HRMS (ESI, [M+]?): m/z calced for C22H23OD6 314.2517, found 314.2517.

**General procedures for inhibited Co-autoxidations**

The inhibited co-autoxidations were carried out following our reported methods.4-11 Autoxidations of 1-hexadecene (2.9 M) and PBD-BODIPY (10 µM) in chlorobenzene were initiated by...
AIBN (6 mM) at 37 °C, 1,4-dioxane (2.9 mM) and initiator (10 μM) in dichlorobenzene and degassed (3 cycles of freeze–thaw) and placed under an atmosphere of N₂ prior to acquisition. The radical concentration was determined using the quantitative EPR package of the Bruker Xnova software. Spectral simulations were performed using EasySpin.41

**Calculations**

Calculations were conducted using the B3LYP method (CBSB7 basis set) and CBS-QB3 (complete basis set) method as implemented in the Gaussian 16 suite of programs.46 Rate constants were calculated using transition state theory at 37 °C. Dispersion corrections were applied using Grimme’s D3 approach.47 Hyperfine coupling constants were predicted by spin density distributions at the B3LYP/TZVP level of theory.48

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation and through generous access to the computational resources of the Centre for Advanced Computing (http://cac.queensu.ca). J. P. C. acknowledges the support of the Ontario Graduate Scholarships Program. We also acknowledge the financial support for this research from the NIH (R01-GM121656), the Camille Dreyfus Teacher–Scholar Award Program, and the University of Michigan. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship under Grant No. DGE 1256260.
Notes and references

1. K. U. Ingold, Chem. Rev., 1961, 61, 563.
2. K. U. Ingold and D. A. Pratt, Chem. Rev., 2014, 114, 9022.
3. G. W. Burton and K. U. Ingold, Acc. Chem. Res., 1986, 19, 194.
4. D. A. Pratt, G. A. DiLabio, P. Mulder and K. U. Ingold, Acc. Chem. Res., 2004, 37, 334.
5. B. S. Matsuura, M. H. Keylor, B. Li, Y. Lin, S. Allison, D. A. Pratt and C. R. J. Stephenson, Angew. Chem., Int. Ed., 2015, 54, 3754.
6. K. J. Romero, M. S. Galliher, M. A. R. Raycroft, J.-P. R Chauvin, I. Bosque, D. A. Pratt and C. R. J. Stephenson, Angew. Chem., Int. Ed., 2018, 57, 17125.
7. J. A. Howard and K. U. Ingold, Can. J. Chem., 1962, 40, 1851.
8. E. A. Haidasz, A. T. M. Van Kessel and D. A. Pratt, J. Org. Chem., 2016, 81, 737.
9. G. W. Burton, T. Doba, E. Gabe, L. Hughes, F. L. Lee, L. Prasad and K. U. Ingold, J. Am. Chem. Soc., 1985, 107, 7053.
10. DFT optimization of 3d reveals that the hindered phenol and resorcinol rings are not co-planar, with a dihedral angle of 32°. See the ESI† for a comparison to 1d.
11. J. A. Howard and K. U. Ingold, Can. J. Chem., 1967, 45, 973.
12. The presence of perdeuterated phenyl rings on 2d-d12 is not expected to have an effect on kinh at 37 °C.
13. Employing CBS-QB3, ΔG‡ = 19.1 kcal mol⁻¹, which corresponds to k = 6 M⁻¹ s⁻¹ and kδ/kδ = 6.
14. G. Litwinienko and K. U. Ingold, Acc. Chem. Res., 2007, 40, 222.
15. L. A. Farmer, E. A. Haidasz, M. Griesser and D. A. Pratt, J. Org. Chem., 2017, 82, 10523.
16. We have also used 'H NMR to explore the effect of H₂O and MeOH on 2e in benzene-d₆. Incubated at 37 °C, we observed neither tautomerization of, nor addition to, 2e on the timescale of the inhibited co-oxidations.
17. N. V. Zolotova, F. A. Galieva, M. B. Tokareva, E. T. Denisov and A. A. Volodkin, Kinet. Katal., 1979, 20, 48.
18. One QMD was studied as part of ref. 17 (structure 6 where R = C(O)OCH₃); however, its reactivity (4 × 10⁴ M⁻¹ s⁻¹ in cumene at 60 °C) was reported to be on par with hindered phenols. Interestingly, the observed reactivity is intermediate to that which we have determined for diaryl QMDs (10⁶ M⁻¹ s⁻¹) and a dialkyl QMD (10⁴ M⁻¹ s⁻¹, vide infra) and may reflect an intermediate central C=C BDE. Consistent with our results, the authors report n = 1.8 for this dicarboxymethyl QMD.
19. We also found a higher energy TS structure involving the QMD that is analogous to the low energy TS involving the QM shown in Fig. 4a, but it is higher in energy by 1.7 kcal mol⁻¹. We also employed CBS-QB3 in the case of a truncated QMD (4ë, R = H) and found ΔG‡ = 10.8 kcal mol⁻¹, which corresponds to kadd = 4 × 10⁶ M⁻¹ s⁻¹ ~ in startlingly good agreement with rate constants derived from the inhibited co-oxidation experiments.
20. The ~11-fold reduction in kinh in going from 1-hexadecene to cumene is consistent with computed results indicating kadd of t-butylperoxyl radicals to an analogue of 4a is ~37-fold slower than addition of i-propyl peroxyl radicals.
21. The kinetic data acquired by Volodkin et al. was collected at much higher concentrations of QM (>100 μM, which is at least 100-fold larger than the concentrations used here).
22. To understand the basis of the discrepancy in the computed and experimental values we computed transitions states for higher-substituted peroxyl radicals to find a progressive increase in the barrier and corresponding decrease in the predicted rate constant from 1 × 10⁴ M⁻¹ s⁻¹ to 1 × 10³ M⁻¹ s⁻¹ on going from methylperoxyl to t-butylperoxyl radicals. Moreover, incorporation of the effects of bulk solvation increased the barrier and decreased the predicted rate constant further, exhibiting a range of 1 × 10⁴ M⁻¹ s⁻¹ to 1 × 10³ M⁻¹ s⁻¹, in good agreement with the experimental results. See the ESI† for further details.
23. H. D. Becker, J. Org. Chem., 1969, 34, 1211.
24. M. H. Keylor, B. S. Matsuura, M. Griesser, J.-P. R. Chauvin, R. A. Harding, M. S. Kirillova, X. Zhu, O. J. Fischer, D. A. Pratt and C. R. J. Stephenson, Science, 2016, 354, 1260.
25. J. M. Wittman, R. Hayoun, W. Kaminsky, M. K. Coggins and J. M. Mayer, J. Am. Chem. Soc., 2013, 135, 12956.
26. J. Jonsson, J. Lind, T. Reitberger, T. E. Eriksen and G. Merenyi, J. Phys. Chem., 1993, 97, 8229.
27. M. Frenette, C. Aliaga, E. Font-Sanchis and J. C. Sciaiano, Org. Lett., 2004, 6, 2579.
28. Tripletic measurements of kinh and n are reported in Table S3 of the ESI†. The stoichiometry of this QMD is ~2 which may be attributable to a 5-exo-trig cyclization of the pheinoxyl formed subsequent to the first peroxyl addition followed by combination with a second peroxyl. A similar cyclization has been reported previously: A. P. Krysin, A. M. Genaev, L. M. Pokrovskii and M. M. Shakirov, Russ. J. Chem. Org., 2014, 50, 367.
29. (a) W. G. Lloyd and R. G. Zimmerman, Ind. Eng. Chem. Prod. Res. Dev., 1965, 4, 180; (b) E. C. Horswill, J. A. Howard and K. U. Ingold, Can. J. Chem., 1966, 44, 985; (c) J. Igarashi, R. K. Jensen, J. Lusztyk, S. Korcek and K. U. Ingold, J. Am. Chem. Soc., 1992, 114, 7727.
30. V. Filippenko, M. Frenette and J. C. Sciaiano, Org. Lett., 2009, 11, 3634.
31. M. Frenette, P. D. MacLean, R. C. Barclay and J. C. Sciaiano, J. Am. Chem. Soc., 2006, 128, 16432.
32. J.-P. R. Chauvin, M. Griesser and D. A. Pratt, Chem. Sci., 2019, 10, 4999.
33. J.-P. R. Chauvin, E. A. Haidasz, M. Griesser and D. A. Pratt, Chem. Sci., 2016, 7, 6347.
34. (a) R. Shah, L. A. Farmer, O. Zilka, A. T. M. Van Kessel and D. A. Pratt, Cell Chem. Biol., 2019, 26, 1594; (b) M. Conrad and D. A. Pratt, Nat. Chem. Biol., 2019, 15, 1137.

(for K. J. R.). Finally, we would like to acknowledge Luke A. Farmer for his technical assistance in acquiring EPR spectra.
35. U. Cogan, M. Shinitzky, G. Weber and T. Nishida, *Biochemistry*, 1973, **12**, 521.

36. Data for α-TOH in liposomes/PBS buffer comes from J.-F. Poon, O. Zilka, D. A. Pratt and that for α-TOH in styrene/PhCl comes from O. Zilka, R. Shah, B. Li, J. P. Friedman Angeli, M. Griesser, M. Conrad and D. A. Pratt, *ACS Cent. Sci.*, 2017, **3**, 232.

37. (a) C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, 1956, **78**, 3797; (b) C. E. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, 1958, **81**, 1176; (c) L. K. Dyall and S. Weinstein, *J. Am. Chem. Soc.*, 1972, **94**, 2196; (d) J. A. Richards and D. H. Evans, *J. Electroanal. Chem.*, 1977, **81**, 171.

38. (a) A. P. Krysin and A. N. Fedorenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1533; Izv. Akad. Nauk SSSR, Ser. Khim., 1989, 1671; (b) T. Matsuura and Y. Kitaura, Tetrahedron, 1969, **25**, 4501; (c) A. A. Volodkin, et al., *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1969, 1467; Izv. Akad. Nauk SSSR, Ser. Khim., 1969, 1583.

39. (a) D. Richter, N. Hampel, T. Singer, A. R. Ofial and H. Mayr, *Eur. J. Org. Chem.*, 2009, 3203; (b) V. Reddy and R. V. Anand, *Org. Lett.*, 2015, **17**, 3390.

40. A. Nishinaga, H. Iwasaki, T. Shimizu, Y. Toyoda and T. Matsuura, *J. Org. Chem.*, 1986, **51**, 2257.

41. Y. Jaiswal, Y. Kumar and A. Kumar, *J. Org. Chem.*, 2018, **83**, 1223.

42. G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad and K. U. Ingold, *J. Am. Chem. Soc.*, 1985, **107**, 7053.

43. S. Stoll and A. Schweiger, *J. Magn. Reson.*, 2006, **178**, 42.

44. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.

45. J. A. Montgomery Jr, M. J. Frisch, J. W. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 1999, **110**, 2822.

46. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ransinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, *Gaussian 16, Revision A.03*, Gaussian, Inc., Wallingford CT, 2016.

47. S. Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456.

48. A. Schäfer, C. Huber and R. Ahlrichs, *J. Chem. Phys.*, 1994, **100**, 5829.