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Role of Hyperconjugation in Determining Carbon–Oxygen Bond Dissociation Enthalpies in Alkylperoxyl Radicals

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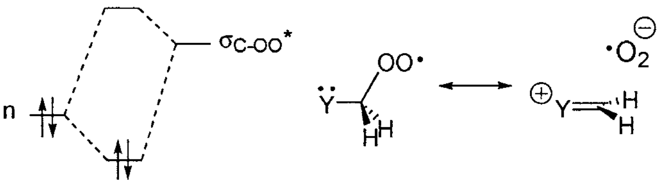
ABSTRACT



Theoretical calculations of carbon–oxygen bond dissociation enthalpies in substituted methylperoxyl radicals ($YCH_2OO^\bullet$) reveal that bond strengths are not governed solely by the stability of YCH2$^\bullet$ radicals but are largely affected by hyperconjugation when Y is electron-donating or conjugating. In many cases, this hyperconjugative effect is greater than stabilization of the methyl radical by Y. All electron-withdrawing Y exert small destabilizing effects via inductive withdrawal of electrons from the polarized C–OO$^\bullet$ bond.

The reaction of oxygen with carbon-centered radicals is of fundamental importance in chemistry and biology.[1] Thus, the equilibrium described in eq 1 is an important product-determining step in radical chain oxidation. Unfortunately, little is known about the thermochemistry of the C−OO$^\bullet$ bond that is made and broken in this equilibrium.[2]

$$R^\bullet + O_2 \rightleftharpoons ROO^\bullet \qquad (1)$$

Most recently, Mulder and co-workers (hereafter Mulder) as well as Knyazev and Slagle (hereafter KS)[3] have worked to address this deficiency. Both investigations provide somewhat unexpected results. KS showed that increasing alkyl substitution at the peroxyl-bearing carbon leads to a stronger C−OO$^\bullet$ bond, favoring the right-hand side of the equilibrium in eq 1, contrary to trends in radical stability of carbon-centered radicals. Although Mulder's data show a modest correlation with the stability of the carbon-centered radical, there are many notable exceptions. To account for these, Mulder suggests the possibility of an anomeric effect in structures where a heteroatom is bonded to the peroxyl-bearing carbon, such as in peroxyl radicals derived from triethylamine and tetrahydrofuran.

We explore here the effects of substituents in determining C−OO$^\bullet$ BDEs in alkylperoxyl radicals substituted with both electron-donating (ED) and electron-withdrawing (EW) groups. We find that C−OO$^\bullet$ BDEs are largely unrelated to the stability of the alkyl radical formed by β-fragmentation. Instead, in methylperoxyls substituted with ED groups, C−OO$^\bullet$ BDEs are affected by substantial hyperconjugative interactions between the substituents on the peroxyl-bearing carbon and the C−O bond.[4] In methylperoxyls substituted with EW groups, where no interaction with the empty $\sigma_{C-O}{}^*$ is possible, the remaining effect involves simply the inductive withdrawal of electrons from, and hence destabilization of, the polarized C−O bond.

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(1) Ingold, K. U. *Acc. Chem. Res.* **1969**, *2*, 1. (b) Porter, N. A. *Acc. Chem. Res.* **1986**, *19*, 262. (c) Bowry, V. W.; Ingold, K. U. *Acc. Chem. Res.* **1999**, *32*, 27. (d) Tallman, K. A.; Pratt, D. A.; Porter, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 11827.

(2) Kranenburg, M.; Ciriano, M. V.; Cherkasov, A.; Mulder, P. *J. Phys. Chem. A* **2000**, *104*, 915 and references therein.

(3) Knyazev, V. D.; Slagle, I. R. *J. Phys. Chem. A* **1998**, *102*, 1770.

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Table 1. G3(MP2) Calculated $C-OO^{\bullet}$ and C−H BDEs in $YCH_2-OO^{\bullet}$ and YCH_2-H, Respectively; Available Experimental Values Presented alongside in Parentheses[a]

Y	$C-OO^{\bullet}$ BDE (expt)	C−H BDE (expt[d])
$N(CH_3)_2$	28.7	94.0 (83.9 ± 1.9)[e]
NH_2	35.0	94.3 (93.3 ± 2.0)
OCH_3	34.5	96.5 (96.1)
OH	35.7	97.3 (96.0 ± 0.4)
CH_3	35.7 (35.5 ± 2.0)[b]	102.2 (101.1 ± 0.4)
$CH{=}CH_2$	19.7 (18.4 ± 0.6)[c]	88.6 (86.5 ± 2.1)
H	32.4 (32.7 ± 0.9)[b]	105.3 (104.9 ± 0.1)
Cl	29.9 (29.3 ± 2.5)[b]	100.5 (100.1 ± 0.5)
CF_3	31.1	107.2 (106.7 ± 1.1)
CN	20.2	97.6 (93.9 ± 2.0)
CHO	24.6	96.6 (94.3 ± 2.2)
COOH	25.4	99.6
NO_2	28.6	102.2

[a] All values in kcal/mol. [b] Reference 3. [c] Reference 5. [d] Reference 6. [e] In light of the fact that the experimental C−H BDE in methylamine is almost 10 kcal/mol higher and in excellent agreement with the calculated value, the experimental value of 83.9 kcal/mol is most certainly in error.

G3(MP2) calculations[7] were performed on a series of peroxyl radicals, $YCH_2-OO^{\bullet}$, where Y was varied and the $C-OO^{\bullet}$ BDEs calculated. C−H BDEs were also calculated for YCH_2-H at the same level of theory for comparison. The results are presented in Table 1 along with available experimental data.

We note the excellent agreement between calculated and experimental $C-OO^{\bullet}$ BDEs for Y = H, CH_3, Cl, and $CH{=}CH_2$. Thus, it is reasonable to assume that our calculations reflect reality to an acceptable degree. This is extended to the C−H BDEs in YCH_2-H, which have been studied extensively (most recently by Radom and co-workers[8]) and are included here only for the sake of comparison with the $C-OO^{\bullet}$ BDEs. This comparison is illustrated in Figure 1, where we have plotted the $C-OO^{\bullet}$ BDEs in $YCH_2-OO^{\bullet}$ against C−H BDEs in YCH_2-H. Obviously, no linear correlation exists ($R^2 = 0.149$).

Since, in either case, the radical formed upon bond-breaking is the same, there must be some significant interaction between Y and the $C-OO^{\bullet}$ bond in $YCH_2OO^{\bullet}$. To attempt to quantify this, we have employed the following isodesmic scheme:[9]

$$YCH_2-H + CH_3^{\bullet} \rightarrow YCH_2^{\bullet} + CH_3-H \qquad (2)$$

$$YCH_2-H + CH_3-OO^{\bullet} \rightarrow CH_3-H + YCH_2-OO^{\bullet} \qquad (3)$$

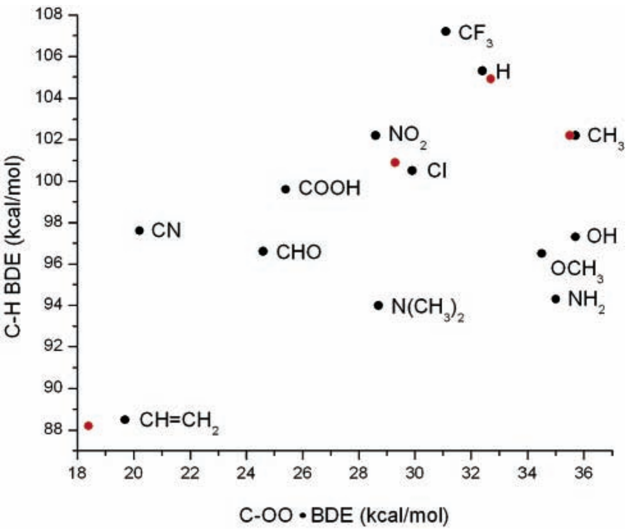

Figure 1. Plot of $YCH_2-OO^{\bullet}$ BDEs versus YCH_2-H BDEs: (red) experimental data; (black) calculated data.

Here, the enthalpy change for reaction 2 quantifies the effect that the substituent Y has on the stability of the methyl radical, and thus the quantity ΔH_2 is defined as the radical stabilization enthalpy (RSE). The enthalpy change for reaction 3 quantifies the effect of the substituent Y on the $C-OO^{\bullet}$ bond in the parent peroxyl, ΔH_3; hence we have termed it the peroxyl stabilization enthalpy (PSE) for use here. The results of G3(MP2) calculations of ΔH_2 (RSE) and ΔH_3 (PSE) are included in Table 2.

Table 2. G3(MP2) Calculated ΔH_2 and ΔH_3; Available Experimental Values Presented alongside in Parentheses[a]

Y	RSE/ΔH_2 (expt)	PSE/ΔH_3 (expt)
$N(CH_3)_2$	−11.3 (−21.0)[b,c]	−7.6
NH_2	−11.0 (−11.6)[b]	−13.6
OCH_3	−8.8 (−8.8)[b]	−10.9
OH	−8.0 (−8.9)[b]	−11.3
CH_3	−3.1 (−3.8)[b]	−6.4 (−6.6)[b]
$CH{=}CH_2$	−16.7 (−18.4)[b]	−4.0 (−4.1)[b]
H	0.0 (0.0)[b]	0.0 (0.0)[b]
Cl	−4.8 (−4.8)[b]	−2.3 (−1.4)[b]
CF_3	+1.9 (+1.8)[b]	+3.2
CN	−7.7(−11.0)[b]	+4.5
CHO	−8.7(−10.6)[b]	+0.9
COOH	−5.7	+1.3
NO_2	−3.1	+0.7

[a] All values in kcal/mol. [b] Derived from data in Table 1. [c] See footnote e, Table 1.

Although the RSEs follow the predictable trends that have already been pointed out in the literature,[10] consistent with

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(4) Hoffmann, R.; Radom, L.; Pople, J. A.; Schleyer, P. v. R.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221. When σ^* is a π-acceptor, this is generally termed *negative* hyperconjugation.

(5) Knyazev, V. D.; Slagle, I. R. *J. Phys. Chem. A* **1998**, *102*, 8390.

(6) *CRC Handbook of Chemistry and Physics*, 83rd ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2002 and references therein.

(7) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1999**, *110*, 4703. Performed with the Gaussian-98 suite of programs. *Gaussian 98, rev. A.7*; Gaussian, Inc.: Pittsburgh PA, 1998.

(8) Henry, D. J.; Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Phys. Chem. A* **2001**, *105*, 6750.

(9) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393.

(10) See ref 8 and citations therein.

the extent to which Y is able to delocalize the unpaired electron spin, the trend in the values of PSE is less evident. It appears that π-ED groups, such as those containing a lone pair, have substantial stabilizing effects on the C−OO• bond. However, the most strongly π-ED group ($N(CH_3)_2$) has an effect comparable to that of a methyl substituent, which can serve only as a relatively weak π-donor via the antisymmetric linear combination of σ_{C-H}. Conversely, the EW CN and CF_3 groups destabilize the C−OO• bond, but the EW NO_2, CHO, and COOH groups have essentially no effect.

Examination of the minimum energy conformations of these substituted methylperoxyl radicals sheds some light on the effect of substituent groups. In aminomethylperoxyl (Figure 2, left), optimal overlap is achieved between the N 2p-type lone pair and the σ_{C-O}* of the methylperoxyl moiety thereby producing a substantial (13.6 kcal/mol) stabilizing effect.[11,12] In the case of the trimethylaminoperoxyl radical, the minimum energy structure reveals that steric effects force the N 2p-type lone pair out of optimal orientation for overlap with the σ_{C-O}*.[13] In the nitromethylperoxyl radical, the minimum energy conformation (Figure 2, right) has the nitro group eclipsing the C−OO• bond, permitting hyperconjugation of the π* of the NO_2 group and the combination of σ_{C-H}'s of the methylperoxyl moiety. The same conformational preference exists in the CHO- and COOH-substituted methylperoxyl radicals. The reason for the larger destabilization of CF_3 when compared to NO_2, CHO, and COOH is explained by the fact that the CF_3 can act only as a weak π-acceptor to the combination of σ_{C-H}'s on the methylperoxyl moiety. The reason for the larger destabilization of CN compared to NO_2, CHO, and COOH is unclear to us and is under further investigation.

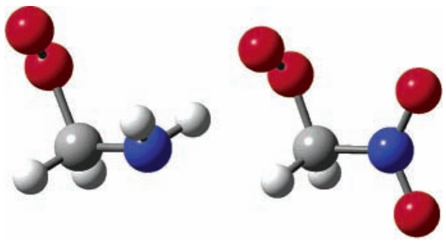

Figure 2. UMP2(full)/6-31G(d) minimum energy conformations of (left) aminomethylperoxyl and (right) nitromethylperoxyl from G3(MP2) calculations.

Since hyperconjugation can help explain where the equilibrium lies in eq 1, we can use it to help understand why certain carbon-centered radicals appear unreactive to O_2. Compounds that yield carbon-centered radicals that are unreactive to O_2 can be effective antioxidants and Scaiano and co-workers[14] have undertaken a study of the structure−activity relationships that govern the stability of carbon-centered radicals to reaction with O_2. Some of their results are shown in the first two columns of Table 3.

We have calculated the C−OO• BDEs in some models of these systems, and the results are also presented in Table 3. Our models substitute a vinyl group for the phenyl group in **1** and **2** to permit calculations at the G3(MP2) level of theory.[15] Theory and experiment are in remarkable agreement for these systems. For every case in which the radical has been shown to be unreactive to O_2, we calculate a negative ΔG in the model for β-fragmentation of the peroxyl radical to the carbon radical and O_2.

For the series **1a**−**c** the stabilities of the carbon-centered radicals change by only 3.1 kcal/mol (from the C−H BDEs), while the C−OO• BDEs change by 12.1 kcal/mol for the series. The strong C−OO• bond in **1c** is due to hyperconjugation of the methyl group, and the weak bond in **1a** is due to the strong electron-withdrawing character of the CN group.

Hyperconjugation also explains why **3** reacts with O_2 but **2** does not. Addition of O_2 occurs only at the benzylic position in **2**,[16] but O_2 may add at either end of the allylic radical in **3**. If addition to **3** occurs α to the carbonyl, the C−OO• BDE in the nonconjugated peroxyl radical formed is 6.6 kcal/mol (similar to **2**) and the free energy change for oxygen addition to the radical is positive (+4.4). If, on the other hand, O_2 adds α to the oxygen and methyl group in **3**, the C−OO• BDE of the conjugated peroxyl radical formed is 15.1 kcal/mol and the free energy change for O_2 addition is negative (−3.2).

In summary, despite the fact that both EW and ED groups stabilize carbon-centered radicals, they mediate the equilibrium in eq 1 very differently. Where EW groups simply destabilize the C−OO• bond via inductive withdrawal of electrons, ED (including conjugating) groups have an extra interaction that strengthens the bond. This hyper-

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[11] From Mulder's measured C−OO• BDE in $(Et)_2NCH(OO^\bullet)CH_3$ and the C−H BDE in TEA, it is possible to derive a PSE for the $N(Et)_2$ and CH_3 groups combined. This value is 9 kcal/mol, This is less than the additive contributions of $N(CH_3)_2$ and CH_3 (7.6 + 6.4 = 14 kcal/mol). This is likely due to the steric interaction that will make the N 2p-type lone pairs' overlap with the C−OO• bond even worse than for the trimethylaminoperoxyl radical. Similarly, the value of the C−OO• BDE for the 2-peroxyl of THF is −13 kcal/mol. In this case, restricted rotation does not permit optimal overlap between the O 2p-type lone pair and the C−O bond, and thus the effects of OCH_3 and CH_3 are also unlikely to be additive (10.9 + 6.4 = 17.3 kcal/mol).

[12] If hyperconjugation is operative, the C−O bond should be somewhat longer in the cases where Y is strongly ED. Indeed, r(C−O) in aminomethylperoxyl is 0.04 Å longer than that in methylperoxyl, 1.491 vs 1.450 Å. Moreover, the dioxygen moiety becomes more negative (−0.429) compared with methylperoxyl (−0.197), consistent with charge-transfer resonance structures; see the graphical abstract.

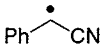
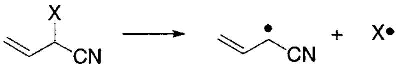
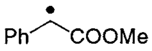
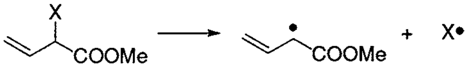
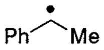
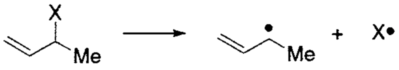
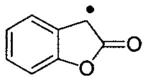
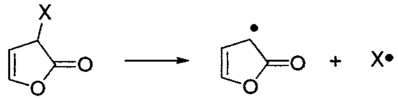
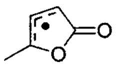
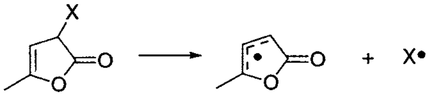
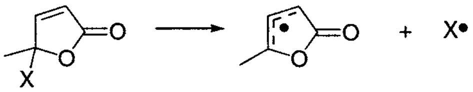
[13] As such, the RSE of −11.3 kcal/mol is greater than the PSE of −7.6 kcal/mol, making the C−OO• bond in trimethylaminoperoxyl weaker than in methylperoxyl by the difference of 3.7 (28.7 vs 32.4) kcal/mol.

[14] Font-Sanchis, E.; Allaga, C.; Focsaneanu, K.-S.; Scaiano, J. C. *Chem. Commun.* **2002**, 1576. (b) Bejan, E. V.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **2001**, *3*, 4059. (c) Scaiano, J. C.; Martin, A.; Yap, G. P. A.; Ingold, K. U. *Org. Lett.* **2000**, *2*, 899.

[15] It is well-documented that the benzylic and allylic radical stabilization enthalpies are very similar. See, for example: Hrovat, D. A.; Borden, W. T. *J. Phys. Chem.* **1994**, *98*, 10460−10464.

[16] Although in **2** the radical spin is delocalized into the aromatic ring, addition of oxygen to the ortho and/or para positions does not occur in benzylic radicals because of the energetic penalty incurred for breaking aromaticity. Pratt, D. A.; Mills, J. H.; Porter, N. A. In preparation.

Table 3. G3(MP2) Calculated C−OO• and C−H BDEs in Models of Peroxyl Radicals and Their Precursors Studied for Reactivities to Oxygen; G3(MP2) Calculated Free Energies of Reaction for C−OO• Bond Homolysis Also Shown. All Values in kcal/mol

	Radical	Reacts with O_2[a]	Model	X = OO• BDE	X = OO• ΔG	X = H BDE
1a		No		9.9	-1.0	82.8
1b		Yes		12.6	1.8	82.8
1c		Yes		22.0	10.6	85.9
2		No		5.7	-5.1	78.9
3		Yes		6.6	-4.4	78.7
				15.1	3.2	78.5

[a] Determined as whether the decay of the UV−vis absorbance of the radical generated by laser flash photolysis differs in the presence or absence of O_2, and thus is best understood as the forward rate (O_2 addition) being slower than the reverse rate (*β*-fragmentation, see ref 14a for **1a**−**c** and 14b for **2** and **3**).

conjugative effect, which relies on a filled n or π orbital on the substituent, can have very large effects on the equilibrium between the alkyl radicals and their corresponding peroxyls.[17]

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(17) Hyperconjugation by definition requires that this interaction will exist between any electron-donating substituent and polarized C−X bond where X is more electronegative than C. However, it is usually not important to the homolytic reactivity of these compounds because their C−X bonds are relatively strong. This is not true of alkylperoxyl radicals that have very weak C−O bonds.