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Direct Evidence for Base-Mediated Decomposition of Alkyl Hydroperoxides (ROOH) in the Gas Phase

Stephen J. Blanksby, G. Barney Ellison, Veronica M. Bierbaum, and Shuji Kato*
Department of Chemistry and Biochemistry, University of Colorado, Boulder Colorado, 80309

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Alkyl hydroperoxides (ROOH) are attributed a key role in the biochemical oxidation of lipids during oxidative stress.[1] In this chemistry ROOH compounds, where the R groups are unsaturated fatty acids, are viewed as transient intermediates which are readily degraded, due to the lability of the RO−OH bond, to yield potentially genotoxic aldehydes and ketones.[2] Generally, the decomposition of alkyl hydroperoxides is thought to be mediated by radical abstraction or electron transfer processes usually involving enzymes, transition metals, or recently, Vitamin C.[3] In this paper we present the first unambiguous experimental and computational evidence for *base-mediated* heterolytic decomposition of simple alkyl hydroperoxides by the mechanism outlined in Scheme 1.

Mass-selected anion bases were allowed to react with simple alkyl hydroperoxides in a flow of helium buffer gas (0.5 Torr, 300 K) using a tandem flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer.[4] Kinetics for the reaction of mass-selected F^- with CH_3OOH[5] are typical of these systems and the kinetics plot of this reaction is shown in Figure 1. The reaction is rapid ($k = 1.23 \times 10^{-9}$ cm^3 s^{-1}, 49% efficiency)[6] and the major primary product is HO^- (Scheme 2b), which produces CH_3OO^- by a secondary reaction (Scheme 2c). To examine the secondary ion chemistry of HO^-, we allowed it to react with CH_3OOH in a separate experiment. Using these data we can quantitatively account for the decay of HO^- and formation of CH_3OO^- at longer reaction times in Figure 1. Direct proton transfer to form CH_3OO^- (Scheme 2a) thus appears to be a minor process ($\Delta_{acid}H_{298}[CH_3OO{-}H] = 374.6 \pm 1.0$ kcal mol^{-1}).[7] A numerical analysis based on Scheme 2 shows that the reaction of F^- with CH_3OOH proceeds mainly via the formation of HO^- (~85%) whereas direct proton transfer is only about 10%.[8,9] The inefficient proton transfer between F^- and CH_3OOH is consistent with thermochemistry which predicts the process to be endothermic[7] by about 3 kcal mol^{-1}.

We attribute the efficient formation of HO^- ions in this reaction (Scheme 2b) to an elimination mechanism (Scheme 1) analogous to that proposed for solution reactions by Kornblum and De La Mare.[11] Interestingly, the formation of aldehydes and ketones observed by these authors under basic conditions was later attributed by others to decomposition of the peroxides by trace amounts of transition metals.[12] Such metal-mediated redox chemistry has since been observed in the gas phase.[13] Nevertheless, the Kornblum−De La Mare mechanism is still favored for solution reactions where R (Scheme 1) is electron withdrawing.[12,14] The proposed mechanism is similar to the gas-phase $E_{CO}2$ reaction[15] for the elimination of NO^- from alkyl nitrites (e.g. CH_3ONO). In both reactions, deprotonation from the α-carbon leads to carbon−oxygen double bond formation with concerted elimination of the anionic leaving group.

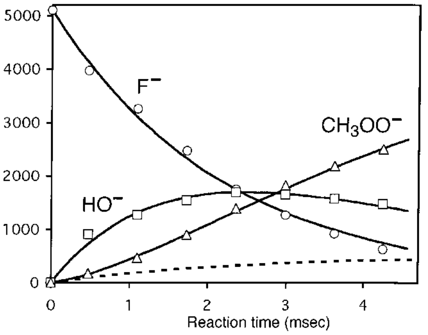
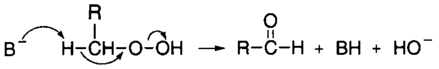
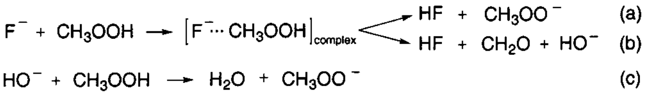


Figure 1. Kinetics plot for the reaction of F^- with CH_3OOH at 300 K. Ion counts have been corrected for mass discrimination and the reaction time is computed using a standard approach.[10] The solid lines are the best fits using Scheme 2; the broken line represents the yield of CH_3OO^- due to direct proton transfer (Scheme 2a) extracted from the analysis.

Scheme 1



Scheme 2



To probe the mechanism of this reaction in the gas phase, we allowed F^- to react with CD_3OOH. HO^- is found to be the major primary product (HO^-:DO^- ~6:1), consistent with the proposed mechanism involving base attack on an α-deuteron. The minor amount of DO^- is possibly due to H/D scrambling that involves DF and HO^- in the complex prior to dissociation. The observed ratio also rules out possible decomposition of CD_3OO^- within a hot ion−dipole complex, $[HF{\cdots}CD_3OO^-]^* \rightarrow HF + CD_2O + DO^-$.[16] Further, no anion was observed at *m*/*z* 49, thus excluding the possible elimination−addition reaction, $F^- + CD_3OOH \rightarrow DF + HOCD_2O^-$. The reactions of other alkyl hydroperoxides were also investigated. The reaction $F^- + CH_3CH_2OOH$ produced HO^- as a major product. In contrast the reaction $F^- + (CH_3)_3COOH$ produced negligible amounts of hydroxide while adduct formation was the major pathway. These observations demonstrate the importance of the α-hydrogen to the base-mediated decomposition (cf. Scheme 1).

Supporting evidence for the efficiency of the $E_{CO}2$ mechanism comes from observing the reverse reaction, $CH_3OO^- + HF$. This reaction proceeds at nearly every collision with a rate coefficient[6] of $k = 2.43 \times 10^{-9}$ cm^3 s^{-1} and yields HO^- as the major primary reaction product (Scheme 3b, 81%) despite the possibility for exothermic proton transfer (Scheme 3a). The primary fraction for F^- formation is only 19% after correction for secondary product ion formation via $HO^- + HF \rightarrow H_2O + F^-$. The predominance of HO^- formation suggests a reaction pathway whereby proton transfer occurs within the initial ion−dipole complex followed by a rearrangement of the complex to facilitate the $E_{CO}2$ reaction and

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* To whom correspondence should be addressed. E-mail: shuji.kato@colorado.edu.

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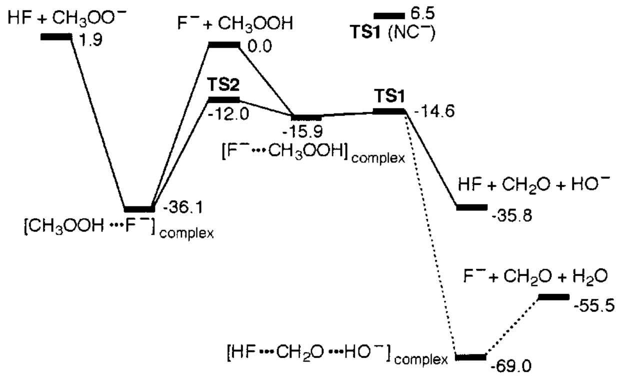
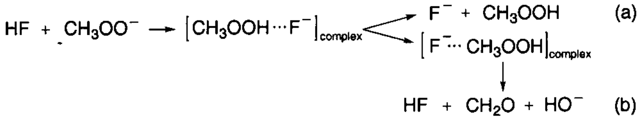


Figure 2. Relative energetics (kcal mol^{-1}) on the [F$^-$, CH$_3$OOH] potential energy surface (electronic energy + ZPE). The **TS1(NC$^-$)** energy has been scaled to the energy of the reactants NC$^-$ + CH$_3$OOH.

Scheme 3



regenerate HF (Scheme 3b). The HF provides an alternative chemical pathway for CH$_3$OO$^-$ decomposition that effectively lowers the activation barrier. As far as we are aware, this reaction represents the first reported example of a *neutral-catalyzed* decomposition of an anion in the gas phase.

Computational studies were conducted for F$^-$ + CH$_3$OOH at the CCSD(T)/aug-cc-pVDZ//B3LYP/6-31+G(d) level of theory[17] using GAUSSIAN98.[18] Figure 2 shows a transition state, **TS1**, 14.6 kcal mol^{-1} below the entrance channel. **TS1** has an antiperiplanar structure with C−H and O−O bonds elongated by about 0.2 Å relative to free CH$_3$OOH. Atomic motion in the imaginary frequency (647i cm^{-1}) shows concerted (i) H−F bond formation, (ii) C−O bond contraction, and (iii) O−O bond rupture. These observations suggest **TS1** is part of a synchronous E2 reaction mechanism. Intrinsic reaction coordinate[19] calculations on **TS1** show this saddle point connects (i) the ion−dipole complex [F$^-$···CH$_3$OOH]$_{complex}$ and (ii) the major observable product channel HF + CH$_2$O + HO$^-$, which is 35.8 kcal mol^{-1} below the entrance channel. Formation of a product complex, [HF···CH$_2$O···HO$^-$]$_{complex}$, followed by proton transfer within the complex prior to dissociation would result in the ensemble F$^-$ + CH$_2$O + H$_2$O, which is a further 19.7 kcal mol^{-1} more negative in energy. Although it would be difficult to detect this experimentally, perhaps regeneration of F$^-$ produces an artificially low reaction efficiency (49%, see earlier) for this exothermic reaction. Such regeneration of the anionic base would suggest *base-catalyzed* decomposition of the alkyl hydroperoxide in the gas phase.

Calculations also identify **TS2**, which connects [CH$_3$OOH···F$^-$]$_{complex}$ and [F$^-$···CH$_3$OOH]$_{complex}$. Following the reaction coordinate from HF + CH$_3$OO$^-$, the calculations predict (i) initial proton transfer may be followed by (ii) rearrangement of the nascent ion−dipole complex via **TS2** and finally (iii) E$_{CO}$2 reaction to produce HO$^-$. This scheme is entirely consistent with the experimental assignment of a neutral-catalyzed decomposition of CH$_3$OO$^-$.

The E$_{CO}$2 reaction pathway was also calculated for NC$^-$ + CH$_3$OOH. NC$^-$ is a significantly weaker gas-phase base than F$^-$ (i.e. $\Delta_{acid}H_{298}$[HCN] $\ll$ $\Delta_{acid}H_{298}$[HF]) so, although the E$_{CO}$2 reaction is still exothermic by 22 kcal mol^{-1}, the critical transition state, **TS1(NC$^-$)**, is calculated to be 6.5 kcal mol^{-1} above the entrance channel (Figure 2). Experimentally, we observed no reaction between NC$^-$ and CH$_3$OOH. Both theory and experiment demonstrate that NC$^-$ cannot decompose CH$_3$OOH via the E$_{CO}$2 pathway at thermal energies. However, if the acidities of the α-hydrogens were increased, as for example in allyl hydroperoxide (CH$_2$=CHCH$_2$OOH), then **TS1** may be lowered relative to the entrance channel and even weak gas-phase bases such as NC$^-$ may facilitate decomposition of the alkyl hydroperoxide. We intend to investigate such systems, as they are good models for endogenous lipid hydroperoxides.

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Supporting Information Available: Geometries, electronic energies, zero-point energies, and imaginary frequencies used for Figure 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Primary products also include minor amounts of CH$_3$O$^-$ (3%) and the [F$^-$•CH$_3$OOH] adduct (2%) which are not shown in Figure 1. No HOO$^-$ was detected, demonstrating that direct nucleophilic substitution at carbon does not occur, which is consistent with the calculated 11.2 kcal mol^{-1} endothermicity of this process.

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