Reaction Mechanisms

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Acid-Mediated Formation of Radicals or Baeyer–Villiger Oxidation from Criegee Adducts

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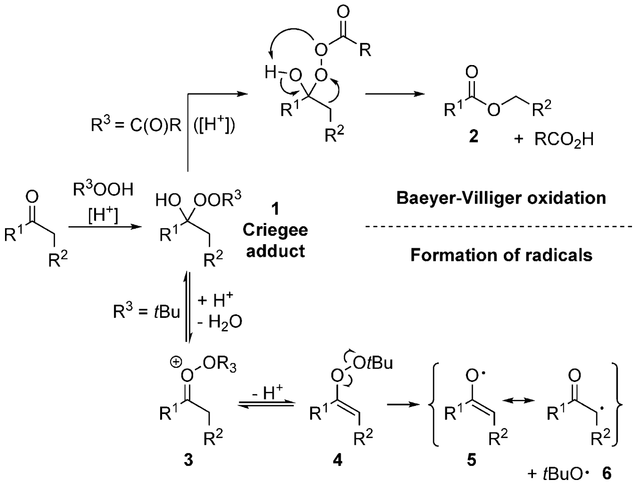
***Abstract:** The acid-mediated reaction of ketones with hydroperoxides generates radicals, a process with reaction conditions similar to those of the Baeyer–Villiger oxidation but with an outcome resembling the formation of hydroxyl radicals via ozonolysis in the atmosphere. The Baeyer–Villiger oxidation forms esters from ketones, with the preferred use of peracids. In contrast, alkyl hydroperoxides and hydrogen peroxide react with ketones by condensation to form alkenyl peroxides, which rapidly undergo homolytic O–O bond cleavage to form radicals. Both reactions are believed to proceed via Criegee adducts, but the electronic nature of the peroxide residue determines the subsequent reaction pathways. DFT calculations and experimental results support the idea that, unlike previously assumed, the Baeyer–Villiger reaction is not intrinsically difficult with alkyl hydroperoxides and hydrogen peroxide but rather that the alternative radical formation is increasingly favored.*

The Baeyer–Villiger oxidation is an important chemical reaction that converts ketones into esters and lactones.[1] Peracids and hydrogen peroxide under acidic conditions are the oxidants of choice but the latter is usually less efficient although economically and environmentally preferable. We have recently found that under strikingly similar conditions, the action of an alkylhydroperoxide or hydrogen peroxide and a strong Brønsted acid catalyst on a ketone opens a previously overlooked reaction pathway to generate radicals. Here we provide further mechanistic details and show how the electronic nature of the peroxide influences the outcome of the reaction.

The mechanism of the Baeyer–Villiger oxidation is generally accepted to involve two distinct steps, both of which can be catalyzed by acids (Scheme 1).[1b] The first step is the addition of the peroxide to the carbonyl compound to afford a tetrahedral intermediate **1**, known as a Criegee adduct (not to be confused with the Criegee carbonyl oxide intermediate involved in the ozonolysis of olefins[2]). In the second step, rearrangement of the Criegee adduct affords the desired ester **2**.



Scheme 1. Distinct pathways for the Baeyer–Villiger oxidation and radical formation via Criegee adducts.

We had postulated[3] that the mechanism of the acid-mediated radical formation involves Criegee adducts as well, but instead of the Baeyer–Villiger rearrangement taking place, the acid catalyzes elimination of water via peroxycarbenium ion[4] **3** to form an alkenyl peroxide **4** (Scheme 1). This highly reactive species rapidly fragments into radicals **5** and **6**, which can undergo addition reactions to olefins[3] and mediate C–H functionalization reactions.[5]

Interestingly, the formation and reactivity of alkenyl peroxides has been studied extensively by theoretical chemists in the context of atmospheric chemistry, in contrast to the chemistry of these compounds in solution. Gas-phase ozonolysis of alkenes leads to Criegee carbonyl oxide intermediates that can rearrange to alkenyl hydroperoxides, which rapidly decompose into resonance-stabilized carbonyl and hydroxyl radicals.[6] Ozonolysis of biogenic and other alkenes is thus believed to be the major source of atmospheric hydroxyl radicals at night.[7]

In order to improve or expand both the Baeyer–Villiger oxidation and the radical formation, one has to better understand their commonalities and differences. At first we looked for further indications that the radical formation indeed takes place as suggested. As a model reaction, we chose the previously reported oxidative functionalization of styrene with cyclohexanone and *tert*-butyl hydroperoxide (*t*BuOOH), catalyzed by *p*-toluenesulfonic acid (pTsOH) (Scheme 2a).[3] On closer inspection of the resulting reaction mixture, we detected the α-oxygenated ketones **8a** and **8b** as byproducts next to the main product **7**. The oxygenated **8a** was formed in around 10% yield, irrespective of whether an aqueous or an organic solution of *t*BuOOH was used, while

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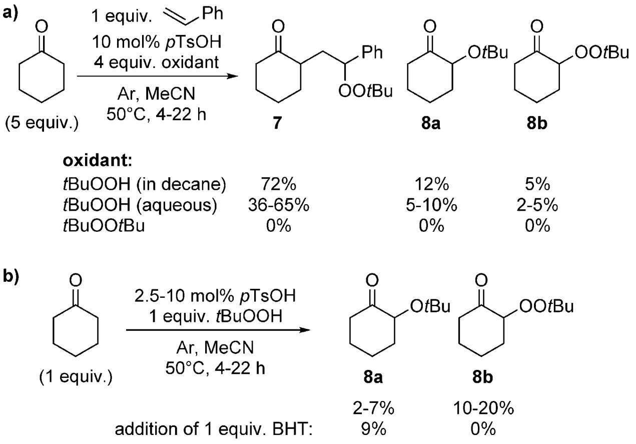
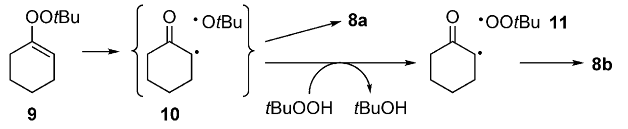


Scheme 2. a) Product distribution in the addition reaction to styrene, dependent on the oxidant used; yields of **8** are relative to cyclohexanone. b) Product distribution in the acid-catalyzed reaction of cyclohexanone with *t*BuOOH, effect of radical inhibitor. BHT = bis(2,6-*tert*-butyl)-4-methylphenol.

the peroxygenated **8b** was formed in around half the amount. Di-*tert*-butylperoxide did not mediate the reaction, supporting the premise that a condensation reaction to an alkenyl peroxide is necessary.

In the absence of styrene, the reaction leads to the formation of **8a** and **8b** in slightly larger amounts, with the latter now as the major compound (Scheme 2b). When one equivalent of the radical inhibitor BHT was added, **8a** was formed in essentially unchanged amount while formation of **8b** was completely suppressed. The formation of **8a** can be rationalized by geminate recombination of radical pair **10**, formed by decomposition of alkenylperoxide **9**. Escape from the solvent cage, fast hydrogen atom transfer (HAT) between the oxyl radical and excess *t*BuOOH,[8] and subsequent recombination of the ketone with the peroxyl radical **11** will lead to **8b** (Scheme 3). This coupling of two radicals, present in only low concentrations, might appear unlikely. However, tertiary peroxyl radicals are known to be stabilized and relatively unreactive, and dimerize relatively slowly, while their reaction with alkyl radicals is very fast.[9]



Scheme 3. Suggested formation of **8a** and **8b**.

This model can explain the results shown in Scheme 2. In the presence of styrene, **8a** is formed in larger amounts than **8b**, possibly because the peroxyl radical formed after cage escape and HAT is largely consumed by addition to styrene.[10] In its absence, **8b** is the major product of the two. The addition of BHT quenches all radicals that escape their solvent cage, but the geminate recombination of **10** within the cage is not affected.

These experimental findings clearly support the mechanism proposed in Scheme 1, but the question regarding the difference between Baeyer–Villiger oxidation and radical formation remains. We therefore evaluated the postulated mechanism using density functional theory (DFT) calculations of a simple model system derived from acetone. At first we compared the O–O bond dissociation enthalpies (BDE) of several postulated peroxide intermediates. For comparison, we looked at compounds derived from *t*BuOOH, peracetic acid (as a simple model for peracids in general), and hydrogen peroxide. As can be seen in Figure 1, *t*BuOOH (**12**), bisperoxides **13a** and **13b**, as well as Criegee adducts **14a** and **14b**, all have BDEs in the 33 to 42 kcal mol^{-1} range, in accordance with known values for peroxide bonds.[11] By contrast, the alkenyl peroxides **15a–c** were considerably less stable, with BDE values between 6 and 17 kcal mol^{-1}. This is in accordance with previous studies of related compounds, which also suggested that alkenyl, alkynyl, and aryl peroxides generally do not exist as stable species.[6a,b,d,12] Knowing that *t*BuOOH requires temperatures above 100 °C to decompose at synthetically useful rates, we can safely assume that products **13** and **14** require similarly elevated temperatures for relevant rates of homolytic O–O bond cleavage.[13]

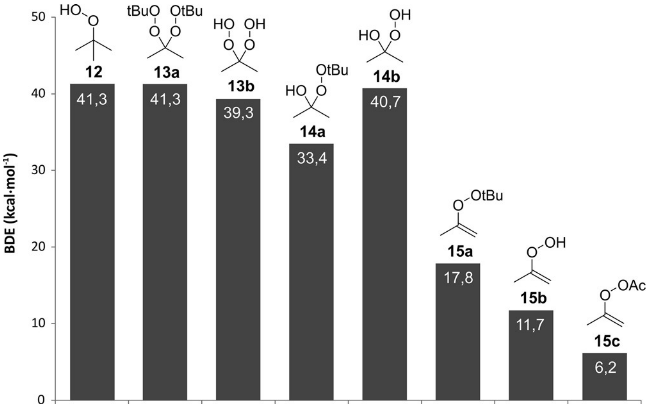


Figure 1. O–O bond dissociation enthalpies (BDE) of peroxide species potentially formed under the reaction conditions; calculated in vacuum using the ωB97XD functional with the aug-cc-pVTZ basis set.

Interestingly, the acyl-substituted **15c** was found to be the least stable species within the series of alkenyl peroxides evaluated, with an extremely low BDE value of 6.2 kcal mol^{-1} (see Figure 1). As peracids are the oxidants of choice in Baeyer–Villiger reactions, the formation of **15c** cannot be significant under reaction conditions. We therefore compared the two reaction pathways for the three different oxidants (*t*BuOOH, H_2O_2 and AcOOH, Figure 2).

We used Criegee adducts **14** (plus methane sulfonic acid) as references and starting points. As can be seen, the Baeyer–Villiger products **16** are thermodynamically more favored than the alkenyl peroxides by about 70 kcal mol^{-1}, for all cases evaluated. The decisive factor must therefore be the kinetic barrier for each product. We first calculated the transition states leading to Baeyer–Villiger products (**TS1**) and found them to be 14.2 kcal mol^{-1} above the reactants for **14a**, 15.5 kcal mol^{-1} for **14b**, and 13 kcal mol^{-1} for **14c**. As

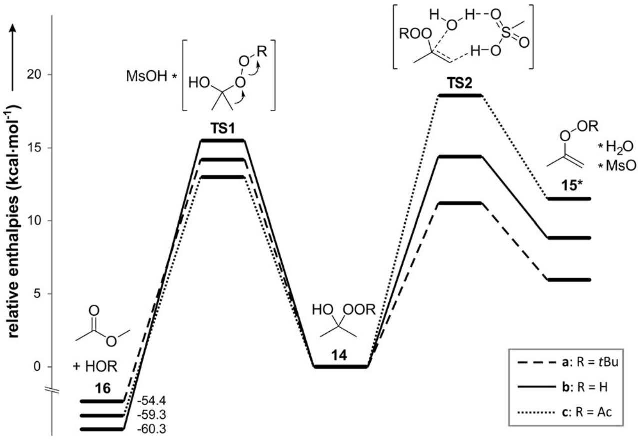
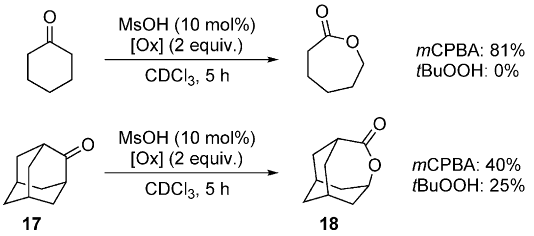


Figure 2. Comparison of Baeyer–Villiger rearrangement and formation of alkenyl peroxides from Criegee adducts **14**, calculated using the ωB97XD functional with the 6-31++G(d,p) basis set for geometries and frequencies and the aug-cc-pV(T+d)Z basis set for energies, and the IEFPCM solvent model (with acetone as a solvent). Where not shown, the total enthalpies include the enthalpy of one molecule of methanesulfonic acid.



Scheme 4. Comparison of oxidants for the Baeyer–Villiger oxidation. Yields were determined by ^{1}H NMR analysis of the reaction mixture using an internal standard.

expected, the rearrangement is easiest for the acyl-substituted Criegee adduct and more difficult for the adducts with the two other substituents.[14]

When evaluating the alternative pathway of alkenyl peroxide formation, we observed an opposite trend. We found an acid-catalyzed concerted E2-type pathway from the Criegee adducts **14** via transition state **TS2** to the alkenyl peroxides **15**, formed as a hydrogen-bonded product complex **15*** (see the Supporting Information for more details). This pathway is easiest for **14a** (11.2 kcal mol^{-1}), followed by **14b** (14.4 kcal mol^{-1}), and most unfavorable for **14c** (18.6 kcal mol^{-1}). Comparing the two different pathways for each substituent perfectly explains the selectivities observed experimentally. In the case of peracetic acid, **TS1c** is lower in energy than **TS2c** by 5.6 kcal mol^{-1}. Starting from *t*Bu-substituted **14a**, **TS2a** is lower than **TS1a** by 3 kcal mol^{-1}. For these two cases, the selectivity for one pathway or the other is therefore very clear: peracids form Baeyer–Villiger products while hydroperoxides form alkenyl peroxides. In the case of hydrogen peroxide, the energy difference between **TS1b** and **TS2b** is much smaller (1.1 kcal mol^{-1} in favor of **TS2b**) and suggests that both pathways contribute to a similar extent.

One interesting outcome of these calculations is that for all three peroxides, the barriers to Baeyer–Villiger rearrangement are quite close to each other (within 2.5 kcal mol^{-1}).[14] Most strikingly, the rearrangement is actually easier for *t*BuOOH than for H_2O_2, by 1.3 kcal mol^{-1}. This is in contradiction with what would be expected from the Baeyer–Villiger literature, in which *t*BuOOH is virtually never reported as an oxidant,[15] in contrast to hydrogen peroxide.[1] In order to gain further experimental evidence in support of this phenomenon, we subjected two different ketones to reactions with two different oxidants (Scheme 4).

As expected, *meta*-chloroperbenzoic acid (*m*CPBA) was very efficient in delivering the corresponding lactones from cyclohexanone and adamantanone (**17**). *t*BuOOH gave no trace of caprolactone in the oxidation of cyclohexanone, consistent with our previous experimental results;[3,5] instead **8a** was detected in usual amounts (10%). However, bicyclic adamantanone, which cannot form an internal double bond, cleanly underwent rearrangement to lactone **18** with both peroxides. The efficiency of *t*BuOOH was only slightly lower than with *m*CPBA, in line with the small energy differences presented in Figure 2. This strongly supports the fact that the Baeyer–Villiger reaction is not intrinsically problematic with hydrogen peroxide or *t*BuOOH, but rather that a competing pathway—formation of alkenyl peroxides—is increasingly favored with these oxidants.

In summary, we have found experimental evidence for the intermediacy of alkenyl peroxides in the acid-mediated formation of radicals from ketones and hydroperoxides. The mechanism helps to rationalize previous reports of radical polymerization or hydrogen peroxide decomposition that lacked a satisfying explanation.[16] Alkenyl peroxides could also be utilized in new synthetic applications and might have implications for industrial autoxidation processes, where the necessary starting materials are formed from hydrocarbons.[17] Finally, this chemistry could play a role in organic aerosol particles containing carbonyl compounds, hydroperoxides, and acid.[18]

In addition, we have rationalized the relationship between the acid-mediated radical formation from ketones and hydroperoxides and the Baeyer–Villiger oxidation. Both reactions proceed via Criegee adducts, but the electronic effects of the peroxides determine the ensuing pathways: peracids prefer the Baeyer–Villiger oxidation, hydroperoxides the radical formation, while for hydrogen peroxide, both are similarly accessible.

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