Reactive Intermediates

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Interrupted Baeyer–Villiger Rearrangement: Building A Stereoelectronic Trap for the Criegee Intermediate

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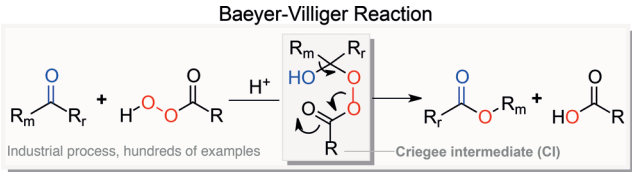
Abstract: *The instability of hydroxy peroxyesters, the elusive Criegee intermediates of the Baeyer–Villiger rearrangement, can be alleviated by selective deactivation of the stereoelectronic effects that promote the 1,2-alkyl shift. Stable cyclic Criegee intermediates constrained within a five-membered ring can be prepared by mild reduction of the respective hydroperoxy peroxyesters (β-hydroperoxy-β-peroxylactones) which were formed in high yields in reaction of β-ketoesters with $BF_3{\cdot}Et_2O/H_2O_2$.*

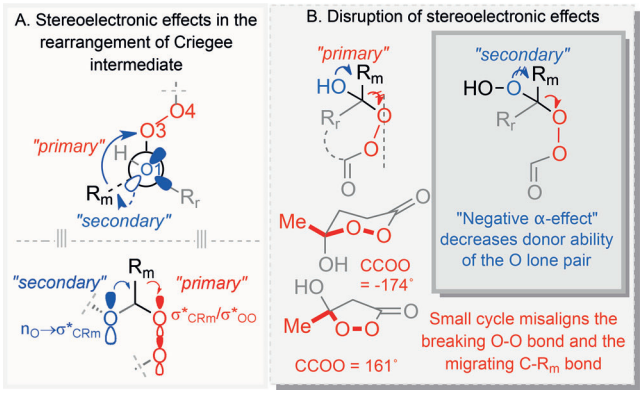
In 1899, Baeyer and Villiger reported a new reaction that could convert ketones into esters.[1] More than a century later, this transformation still continues to provide a valuable connection between these key organic functional groups (Scheme 1).[2] Furthermore, it displays a combination of stereoelectronic features that can be used to design stereo- and regioselective processes.[3]

It is generally accepted that the mechanism of the Baeyer–Villiger (BV) rearrangement involves a tetrahedral intermediate formed by the addition of a peroxyacid to the carbonyl group of a ketone (i.e., the Criegee intermediate, or the CI).[4] This high-energy oxygen-rich intermediate rearranges by a 1,2-alkyl shift that is assisted, among several factors, by exchange of a weak O–O bond[5] for a more stable C–O bond. A protected derivative of the CI [$CH_3C(O)OOC(CH_3)_2OCH_3$] was characterized by Griesbaum et al. using NMR and mass spectrometry data.[6] Anderson et al. reported ^{19}F NMR data and elemental analysis of $CF_3C(O)OOC(CF_3)_2ONa$[7] whereas Saito et al. described ^1H NMR and IR data of $PhC(O)OOC(CH_3)(CH_2Bn)OTBDS$.[8] In addition, a few examples disclose diverted reactivity where derivatives of the CI were trapped before rearranging.[9] However, the parent hydroxy version of the CI was never isolated and structurally characterized because of its fleeting stability and high reactivity. In this work, we will show that stereoelectronic restrictions can be used to block the 1,2-migration and allow preparation of stable versions of the Criegee intermediate for structural and mechanistic studies.



Scheme 1. General scheme for the Baeyer–Villiger reaction.

This oxygen-rich CI structure presents several stereoelectronic effects.[10] Previously, two such effects were suggested for the O1C2O3O4 unit directly involved in the transformation of the CI into the final product.[10,11] The key moieties include the *p*-type lone pair of O1, the breaking C2–R_m bond and the O3–O4 acceptor (Scheme 2 A). The "primary stereoelectronic effect" requires that the breaking O–O bond and the migrating C–R_m bond are anti-periplanar. The "secondary effect" is operative when the lone pair of the O1H group aligns with the breaking C–R_m bond.[12] When both effects are in play, an uninterrupted electron flow from the donor (O1) to the acceptor is ensured: donation from the



Scheme 2. A) Alternative representations of the two stereoelectronic effects for the 1,2-shift in CI. B) Strategies for weakening the primary and secondary stereoelectronic effects in the 1,2-alkyl shift.

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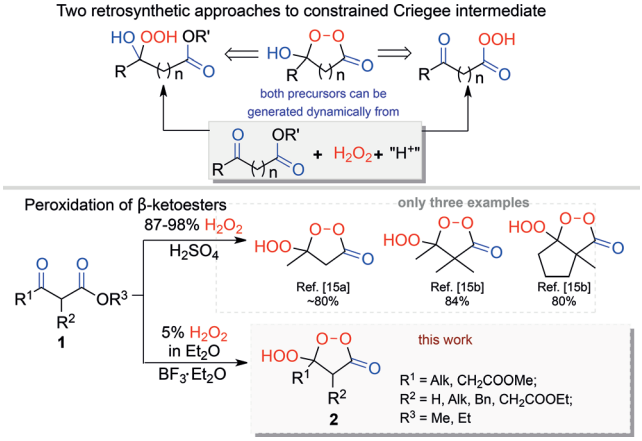
O1 lone pair assists in breaking the C–R_m bond by stabilizing the incipient cationic center as the R_m group moves to O3 and the O3–O4 bond breaks. As the result, the O1=C2 and R_m–O3 bonds are formed.

Based on these considerations, we decided to perturb this system of interconnected stereoelectronic interactions by creating a constrained cyclic version of the CI wherein the primary effect is reduced (Scheme 2B). Because containment within a six-membered ring does not stop the rearrangement,[13] we turned our attention to substrates with a rigid five-membered cycle. Additionally, we aimed to apply the recently discovered "negative" α-effect[14] for weakening the secondary effect.

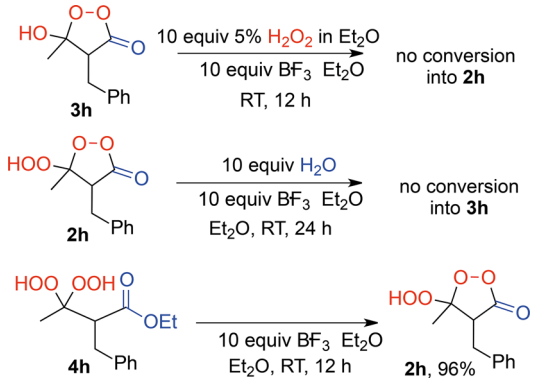
Indeed, our computational analysis revealed that the RCOO dihedral is distorted from anti-periplanarity in the five-membered peroxylactone (161°; Scheme 2) more than in the six-membered peroxylactone. This difference suggests that the five-membered ring may help in diverting the migrating bond from the stereoelectronically favorable alignment with the O–O moiety.

To study such systems experimentally, a synthetic approach to cyclic peroxylactones was needed. Although the cyclization of ketoesters in the presence of hydrogen peroxide appears straightforward, the earlier examples were limited in scope and required harsh reaction conditions (87–98% H_2O_2 in H_2SO_4).[15] To overcome these limitations, we developed a milder, more robust approach towards peroxylactonization by using Lewis acid catalysis in the presence of 5% H_2O_2 (Scheme 3). $BF_3{\cdot}Et_2O$ is particularly effective in assisting the transformation of β-ketoesters into the desired rigid five-membered peroxylactones. Furthermore, the two potential alternative directions for this process converge on the same product (Scheme 3).

The bisperoxides (**2**; hydroperoxy peroxylactones) formed under these reaction conditions represent a peroxy form of the CI, with an exocyclic OOH group instead of the OH moiety. We performed several control experiments for understanding the formation of **2** (Scheme 4). The β-hydroperoxy-β-peroxylactone **2h** does not equilibrate with the β-hydroxy-β-peroxylactone **3h** under these reaction conditions. In contrast, **2h** can be prepared in an almost quantitative yield



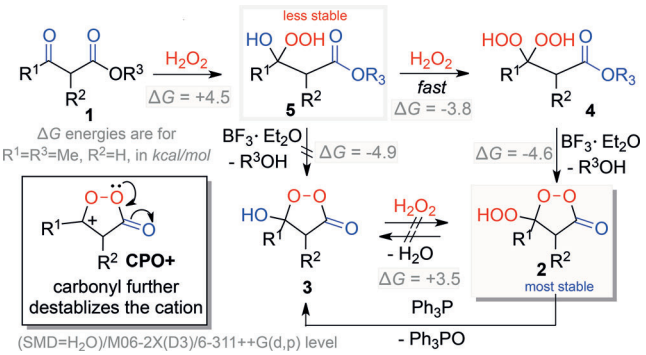
Scheme 3. The peroxidative cyclization of β-ketoesters.



Scheme 4. Control experiments show stability of endocyclic peroxylactones.

from an acyclic bis-hydroperoxide (**4h**; isolated as a minor product via peroxidation of ketoester **1** at a lower concentration of $BF_3{\cdot}Et_2O$). We suggest that low reactivity of these mono- and bisperoxides under acidic conditions stems from the inefficient stabilization of cationic center by an adjacent peroxide (i.e., the recently identified negative intramolecular α-effect).[14] Because peroxides are less capable of stabilizing cationic centers in comparison to ethers, peroxide chemistry allows synthetic access to functional groups that are unstable in their monooxygen incarnations as a result of transformations into oxacarbenium ions.

The suggested mechanism for the peroxylactonization is depicted in Scheme 5. The ketoester **1** is initially transformed into a mixed ketal (**5**) which further reacts with a second H_2O_2 molecule to form **4**. The observation that **3** does not transform

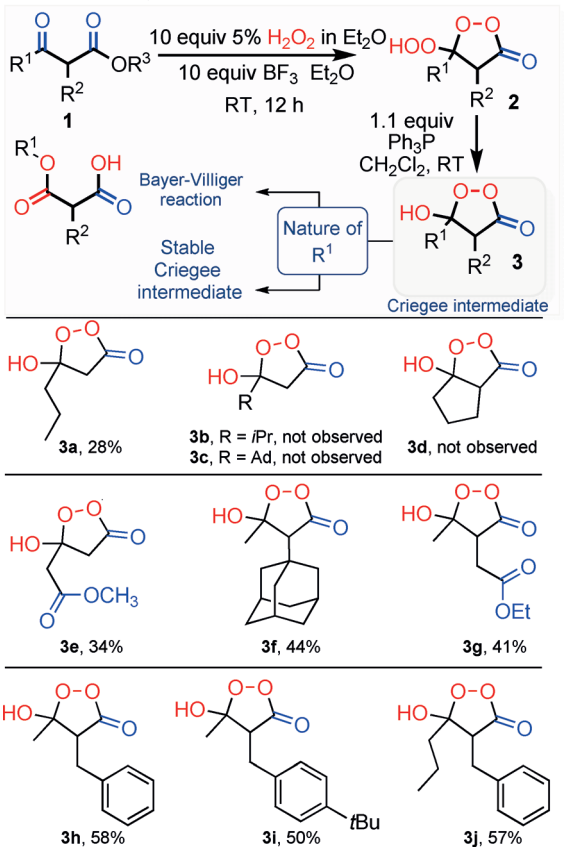


Scheme 5. Possible mechanism of CI synthesis and calculated free energies for the formation of the intermediate structures.

into **2** clearly shows that cyclization proceeds with **4** and not with **5**. Apparently, the cyclic peroxycarbenium ion **CPO** + is additionally destabilized by the carbonyl group. These results are fully consistent with the computed free energies of the intermediates. The addition of the first H_2O_2 molecule to the ketone is endergonic and the resulting unstable mixed monoperoxide is only a transient species. Apparently, formation of **4** is fast in the presence of excess H_2O_2. Subsequent cyclization provides **2**, the most stable species at this reaction hypersurface.

The remarkable stabilities of **2** allowed their isolation and full characterization. Furthermore, we found that the the exocyclic hydroperoxide moiety in **2** undergoes a clean mono-deoxygenation reaction with triphenyl phosphine. This breakthrough allowed us to prepare the classic form of the Criegee intermediates **3** under neutral conditions with a variety of substituents (Table 1). This finding opens the door for future mechanistic studies that can bypass the acid-catalyzed first step of the BV cascade. This potential is an exciting opportunity because the two steps can have similar activation barriers[16] and the rearrangement step is not always rate-limiting.[17]

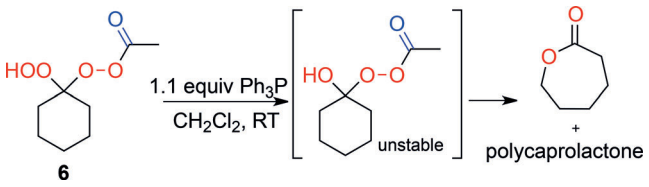
Table 1: Synthesis of the Criegee intermediates **3**.[a]



[a] Combined yields of the isolated products for the two steps.

The nature of the migrating substituent has a dramatic influence on the stability of the CIs **3a–j** (Table 1). Whereas the methyl derivatives **3f**,**g**,**h**,**i** are stable, the propyl-substituted compound **3a** was prepared in low yield and only with 90% purity according to ^{1}H NMR spectroscopy. Our attempts to isolate the isopropyl peroxide **3b**, formed by reduction of **2b** by flash chromatography on silica gel, led to its partial decomposition. Nevertheless, the characteristic signals of the C(O)OOC(R)$_2$OH group in both the ^{13}C NMR and HRMS spectra confirm the formation of **3b** (see the Supporting Information). In contrast, the compound **3c**, with a tertiary (adamantyl) substituent, was unavailable because the peroxide **2c** could not be isolated after peroxidation of **1c**. The strained peroxide **3d** was also not observed in reaction mixture after reduction of **2d** (see the Supporting Information). The presence of an acceptor ester group in **3e** increases stability of the β-hydroxy-β-peroxylactone and allows its isolation, albeit in a moderate yield. Substitution at the α-position does not compromise stability and the α-substituted-β-peroxylactones **3f–j** were obtained in 41–58% yields in two steps. These trends in reactivity are consistent with the migratory aptitudes of substituents in the BV rearrangement under acidic[2] and mildly basic conditions,[18] but different from the trends under strongly basic conditions.[19]

To test for the broad utility of the negative α-effect[14] as a new stereoelectronic strategy for the control of organic reactivity, we also prepared an acyclic model, the compound **6** (Scheme 6). It was known that α-alkoxy-peroxyesters undergo rearrangement in situ under acetylation reaction.[20] The peroxy derivative of the CI is sufficiently stable to be isolated.[21] However, once it is converted into the normal OH derivative by an in situ reaction with PPh_3, a fast BV rearrangement occurs.

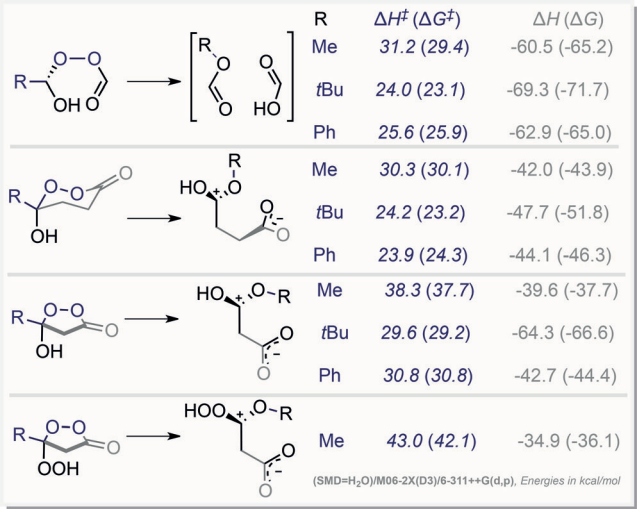


Scheme 6. Rearrangement of noncyclic CI can be triggered by PPh_3.

The computed activation barriers[22] suggest that the noncatalyzed BV migration of a methyl group is slowed by about 700,000 times (8.3 kcal mol^{-1} barrier increase) by inclusion of a peroxide moiety in a five-membered cycle (Scheme 7)! For the *t*Bu and Ph groups that are known to be more prone to migration, the difference in the barrier height is also significant (ca. 6 kcal mol^{-1}).

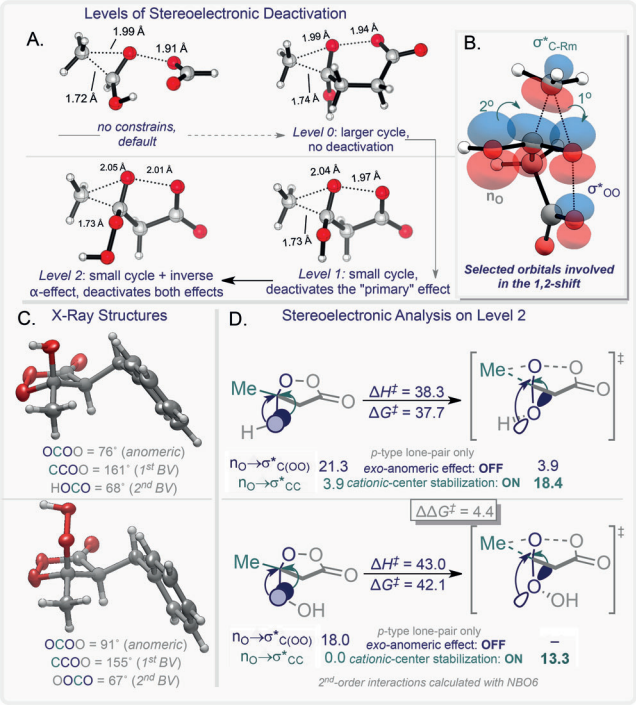
It is important to note that, unlike the acyclic CI, the cyclic peroxyester **3** cannot undergo the 1,2-alkyl shift with the simultaneous proton transfer that would avoid the formation of a zwitterionic intermediate.[23] The charge separation penalty is reflected in the approximately 30 kcal mol^{-1} lower exergonicity of the process. However, this penalty has little effect on the transition-state energy as illustrated by the 1,2-shifts in the analogous six-membered peroxylactones. The latter systems have activation barriers that are similar to the acyclic cases, despite having exergonicity similar to that for the five-membered cases. The rather high barriers (ca. 30 kcal mol^{-1} for the Me migration) suggest the importance of acid catalysis for these reactions. Furthermore, the change from the OH to OOH group imposes an additional protecting effect on the CI by adding an extra 4.4 kcal mol^{-1} penalty to the 1,2-shift free-energy barrier (Scheme 7, bottom).

Additional insights into the structure and reactivity of five-membered CIs were obtained from the combination of experimental X-ray data and computational analysis (Scheme 8).



Scheme 7. Computational analysis of the 1,2-shfit in acyclic and cyclic CIs.

The X-ray geometries reveal an interplay of *endo*- and *exo*-anomeric effects that define preferred conformations at the reaction center (see the Supporting Information). The *endo*-anomeric effect puts the OH pseudoaxial and helps the 1,2-shift by orienting the migrating group equatorially, so the latter aligns well with the breaking O–O bond. The *exo*-anomeric effect[24] aligns the *p*-type lone pair of the exocyclic oxygen center with the endocyclic C–O bond in the reactant. This interaction is lost in the TS where the lone pair reorients to align with the breaking C–C bond to the migrating group. As the exocyclic OH rotates, the *exo*-anomeric effect in the reactant is turned off in favor of stabilization of the cationic center in the TS. The TS for the 1,2-shift in the five-membered peroxylactones show noticeably longer R_m–O and O–O distances than the analogous TS for the less constrained analogues. The structural differences indicate the loss of C–O and O–O bonding interactions associated with the weakening of the accelerating stereoelectronic effects. The NBO analysis confirms that the donor ability of the OOH lone pairs is significantly lower than it is for the OH (the 3 and 5 kcal mol^{-1} differences in the reactant and TS, respectively).



Scheme 8. A) Levels of stereoelectronic deactivation illustrated with their correspondent transition states. B) Three (of the four) orbitals involved in the 1,2-shift for the "level 1" scenario. The $\sigma_{C\text{-}Rm}$ orbital is not shown. C) Key geometric parameters from the CI X-ray structures. D) Weakening of the secondary stereoelectronic effect of 1,2-Me shift of OOH versions of the trapped CIs. Energies in kcal mol^{-1}.

In summary, we disclosed two new strategies for stereoelectronic trapping of the elusive Criegee intermediate. Interruption and restarting of the Baeyer–Villiger cascade at an intermediate step opens the door for future detailed analysis of the effects of solvents, catalysts, and other additives on the key migration step that determines the regio- and stereoselectivity of the overall process. The paradoxical situation where a peroxide is more stable than its monooxygen counterpart illustrates the power of thinking about stereoelectronics in chemistry.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anomeric effects · Baeyer–Villiger reaction · peroxides · reactive intermediates · stereoelectronics

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Communications

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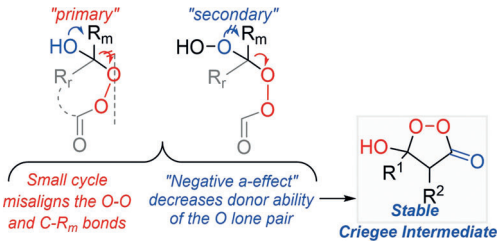

No longer elusive: The instability of hydroxy peroxyesters, the elusive Criegee intermediates of the Baeyer–Villiger rearrangement, can be alleviated by selective deactivation of the primary and secondary stereoelectronic effects that promote the 1,2-alkyl shift. Stable cyclic Criegee intermediates constrained within a five-membered ring can be prepared by mild reduction of the respective hydroperoxy peroxyesters.