Experimental Support for the Primary Stereoelectronic Effect Governing Baeyer−Villiger Oxidation and Criegee Rearrangement

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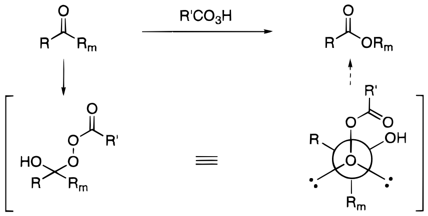
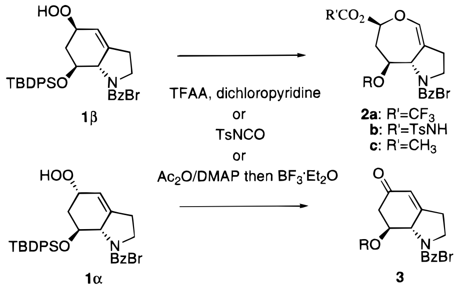
The Baeyer−Villiger reaction[1] has long been recognized as a powerful method for the preparation of esters and lactones. As a result, much research has been devoted to developing a variety of methods and conditions for the reaction, as well as to probing its scope.[2] Despite many investigations of the mechanism of Baeyer−Villiger oxidation, the factors controlling migratory aptitude are still not completely understood. While it is clear that electron density and, relatedly, steric bulk strongly influence migration ability (e.g., *t*-Bu > Ph ≈ *i*-Pr > Et > Me), the exact nature of this influence remains somewhat unclear.[3] Looking at the tetrahedral (Criegee) intermediate involved in the oxidation (Scheme 1), it is widely assumed that the group that migrates does so from a position anti-periplanar to the dissociating oxygen−oxygen bond of the peroxide.[4] According to FMO theory,[5] this orientation allows the best overlap of the $C-R_m$ σ bond with the O−O σ^* orbital. To the best of our knowledge, however, no solid experimental support exists for this *primary stereoelectronic effect*.[6] This lack of evidence has primarily been due to the difficulty in establishing a system with a defined conformation and a method to examine the relationship between conformation and migratory aptitude. To the best of our knowledge, the Criegee intermediate of the Baeyer−Villiger oxidation has never been intercepted, and consequently, no correlation can be made between the conformation of the labile peroxide bond and the migrating group. The investigation of Chandrasekhar[7] proceeded through a logical approach, attempting intramolecular Baeyer−Villiger oxidation, but lack of characterization of all the proposed intermediates leaves significant reservation as to the definitiveness of the evidence claimed and the conclusions drawn.

Since the Baeyer−Villiger reaction can be viewed as a subset of Criegee rearrangements, we realized an opportunity to examine this issue from the platform of our studies on the Criegee rearrangement of allylic hydroperoxides.[8] Our attention was initially drawn to this issue while investigating the use of the Criegee rearrangement to synthesize a model compound of the fungal metabolite aranotin.[9] During the course of those studies, we discovered an extraordinary dichotomy in the chemical behavior of two stereoisomeric allylic hydroperoxides: the *β*-peroxide **1***β* rearranged as expected with vinyl migration, without enone formation, under our three standard rearrangement conditions,[8] whereas the α-peroxide **1**α provided enone **3** exclusively under identical conditions (Scheme 2).[10]

Scheme 1



Scheme 2



This astonishing observation led us to speculate that a stereoelectronic effect, previously unrecognized in the Criegee rearrangement but of the same nature as that long assumed for the Baeyer−Villiger oxidation, was directing migratory aptitude in this case with marked absoluteness. Because substrates examined for Criegee rearrangement have already established the $R_m-C-O-O$ bond framework, we are much closer to defining the key conformational relationships present in the Criegee systems, relative to the typical Baeyer−Villiger intermediates derived from ketones. We became interested in the possibility of using crystal structural information as a tool for conformational insight and examining the correlation of this information with migratory aptitude. A search of the Cambridge X-ray crystallographic database revealed one structure of a synthetically available secondary allylic hydroperoxide **4**.[11] The X-ray structure indicates that the hydroperoxide O−O bond of **4** is oriented almost perfectly anti-periplanar to the neighboring $C-H_a$ bond (dihedral angle of 175.3°) (Figure 1). Assuming the X-ray structure reflects a preferred conformation of the hydroperoxide O−O bond, we anticipate that the stereoelectronic factor should dictate hydrogen migration under the conditions of Criegee rearrangement. On the other hand, our previous studies[8] have demonstrated that the reaction has an inherent general electronic bias for vinyl migration under our three prescribed rearrangement conditions. Thus, **4** is an excellent system to contrast the electronic effect with the conformational effect on the outcome of rearrangement.

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[1] Baeyer, A.; Villiger, V. *Chem. Ber.* **1899**, *32*, 3625.

[2] (a) Krow, G. R. *Org. React.* **1993**, *43*, 251. (b) Hassall, C. H. *Org. React.* **1957**, *9*, 73. (c) Plesnicar, B. In *Oxidation in Organic Chemistry*, Part C, Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; p 254.

[3] (a) Smith, P. A. S. *Molecular Rearrangements*; de Mayo, P., Ed.; Interscience: New York, 1963; Vol. I; p 577. (b) Gould, E. S. *Mechanism and Structure in Organic Chemistry*, Henry Holt and Company: New York, 1959; pp 629−634. (c) Waters, W. A. *Mechanisms of Oxidation of Organic Compounds*; Methuen and Company: London, 1964; pp 44−48.

[4] (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 313−314. (b) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, *21*, 2569 and 2573. (c) Noyori, R.; Sato, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2661. (d) Hawthorne, M. F.; Emmons, W. D.; McCallum, K. S. *J. Am. Chem. Soc.* **1958**, *80*, 6393.

[5] (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons: New York, 1976. (c) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.

[6] Since according to the assumed theory the migrating group is primarily determined by orientation relative to the oxygen−oxygen bond, we refer to this as the *primary* effect. A *secondary* stereoelectronic effect in the Baeyer−Villiger reaction would refer, for example, to the orientation of the α-hydroxyl oxygen's lone pairs relative to the migrating group. For examples and discussion, see refs 4a−c.

[7] (a) Chandrasekhar, S.; Roy, C. D. *Tetrahedron Lett.* **1987**, *28*, 6371. (b) Chandrasekhar, S.; Roy, C. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2141.

[8] Goodman, R. M.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 5125.

[9] Goodman, R. M. Ph.D. Thesis, Harvard University, May, 1998.

[10] Our earlier studies revealed that vinyl migration could reliably be induced by treating secondary allylic hydroperoxides with TsNCO, trifluoroacetic anhydride (TFAA)/2,6-dichloropyridine, or Ac_2O/DMAP followed by $BF_3 \cdot Et_2O$. On the other hand, enone derivatives could be generated selectively (via an E2 mechanism) in all cases only by acylating hydroperoxides in the presence of a large excess of base (e.g. Ac_2O and pyridine).

[11] Jefford, C. W.; Boukouvalas, J.; Jaggi, D.; Kohmoto, S.; Bernardinelli, G. *Helv. Chim. Acta* **1986**, *69*, 941. The authors thank Professor Jefford for providing experimental details and advice.

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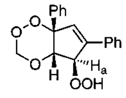


4

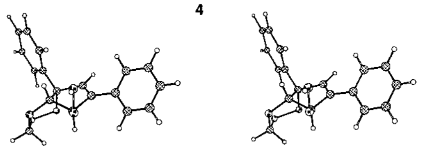
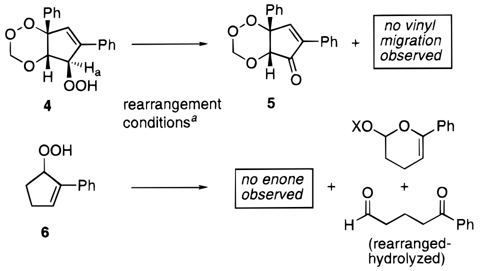


Figure 1. Stereoview of **4**, downloaded from the Cambridge crystallographic database.

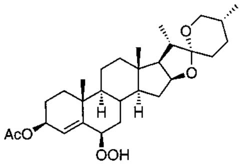
In fact, when **4**[11] was subjected to our rearrangement conditions, enone **5** was the exclusive product in each case (Scheme 3). As a control, phenyl-substituted hydroperoxide **6** was synthesized and subjected to the same reaction conditions to yield, in complete contrast to **4**, only products of vinyl migration with no traces of enone (^{1}H NMR). The steric congestion around H_a in **4** would seem to hinder the likelihood of E2 elimination,[8] implying that this is probably a case of *hydrogen migration* instead. This is additionally supported by the anomalous result that enone formation took place under Lewis acid conditions.

Scheme 3[a]



[a] TFAA, dichloropyridine (X = $COCF_3$); TsNCO (X = CONHTs); Ac_2O/DMAP then $BF_3 \cdot Et_2O$ (X = Ac).

Ideally, one would like to contrast the above results with a system whose X-ray structure indicates that the O−O bond of the peroxide is oriented anti-periplanar to a substituent other than hydrogen. Such a system was eventually discovered upon synthesis of the previously unknown diosgenin-derived hydroperoxide **7**; its X-ray structure shows a 162.3° dihedral angle between the O−O bond and the $\Delta^{4,5}$-olefin (Figure 2). In this case, the stereoelectronic factor should dictate a preference for vinyl migration under acylating conditions.



7

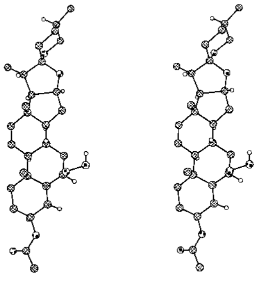
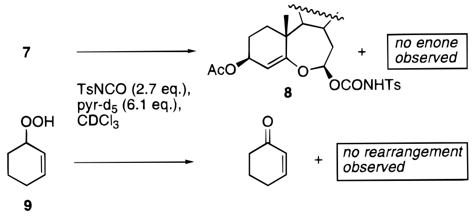


Figure 2. Stereoview of the X-ray structure of **7**.

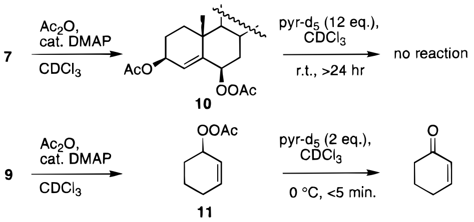
Indeed, when reacted with TsNCO, **7** rearranged cleanly to oxepin **8** (Scheme 4). More importantly, no enone was generated when **7** was subjected to TsNCO in the presence of excess pyridine—conditions which led exclusively to cyclohexenone in the case of cyclohexenyl hydroperoxide **9**. The extreme reluctance of this system to produce enone was most clearly demonstrated when the acyl-peroxide **10** was treated with pyridine (Scheme 5).[12] Whereas **11** rapidly eliminated to enone when treated with 2 equiv of pyridine at 0 °C, **10** remained unchanged even after 24 h at room temperature with 12 equiv of pyridine.

Scheme 4



We believe these results constitute the most compelling experimental support available for the primary stereoelectronic effect in Criegee rearrangements and Baeyer−Villiger oxidations. Hydroperoxides **4** and **7** display highly unusual reactivity patterns when subjected to our defined conditions for effecting Criegee rearrangement or, alternatively, elimination. We contend that their reactivities are best explained by considering the bond conformations revealed in their crystal structures; in both cases, the bond anti-periplanar to the dissociating peroxide bond is always and exclusively the bond that migrates, even when electronically disfavored from doing so.

Scheme 5



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Supporting Information Available: Experimental details and characterization data (4 pages). See any current masthead page for ordering information and Web access instructions.

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[12] Secondary hydroperoxides are known to eliminate to ketones upon exposure to weak base or simply over time; for example, see: Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880 and Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.