Baeyer–Villiger Oxidations with Hydrogen Peroxide in Fluorinated Alcohols: Lactone Formation by a Nonclassical Mechanism**

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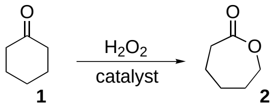
The Baeyer–Villiger oxidation of ketones to esters or lactones is of high synthetic utility.[1,2] In the vast majority of cases, peracids such as 3-chloroperbenzoic acid have been employed as the source of oxygen. Hydrogen peroxide as oxidant clearly offers a number of advantages, in particular the lack of a by-product (except for water). Strained ketones such as cyclobutanones have long been known to afford γ-butyrolactones rapidly and in high yield when treated with alkaline hydrogen peroxide.[3] On the other hand, the Baeyer–Villiger oxidation of nonstrained ketones such as cyclohexanone (**1**) to ε-caprolactone (**2**) with H_2O_2 is much more difficult to achieve [Eq. (1)]. Until recently, highly concentrated hydrogen peroxide, long reaction times and/or heterogeneous[4] or homogeneous catalysts such as transition metal complexes,[5,6] arsonic[7] and seleninic acids[8,9] were required for satisfactory conversions. In contrast, we recently reported that in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent, the Baeyer–Villiger oxidation of **1** to **2** proceeds smoothly and efficiently in the presence of Brønsted acid catalysts such as *para*-toluenesulfonic acid.[10,11] With the aim of developing a generally applicable method for the Baeyer–Villiger oxidation of nonstrained ketones with hydrogen peroxide, we investigated the mechanism of this remarkably simple process. As it turned out, the formation of **2** from **1** proceeds in a two-step fashion, via a distinct, isolable intermediate, formed initially from the ketone and H_2O_2. This intermediate was unambiguously identified as the bisperoxide 7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane. In the second step, the cation-stabilizing solvent HFIP allows the hitherto unknown acid-catalyzed rearrangement of this tetroxane to give two equivalents of the product lactone.



(1)

A first hint to the formation/decay of a reaction intermediate came from the observation that at temperatures of about 30 °C, ketones such as **1**, 2-methylcyclohexanone, or cyclopentanone were consumed rapidly, but the formation of the product lactones lagged behind. Furthermore, it was surprising to see that camphor—a well-known substrate of the Baeyer–Villiger oxidation with peracids—was not significantly consumed.[1,2,13] These results clearly indicated that a mechanism different from the classical peracid-induced Baeyer–Villiger oxidation may be operative. To gain further insight, we performed the oxidation of **1** in [D$_2$]HFIP and monitored the reaction by ^{13}C NMR spectroscopy (Figure 1).

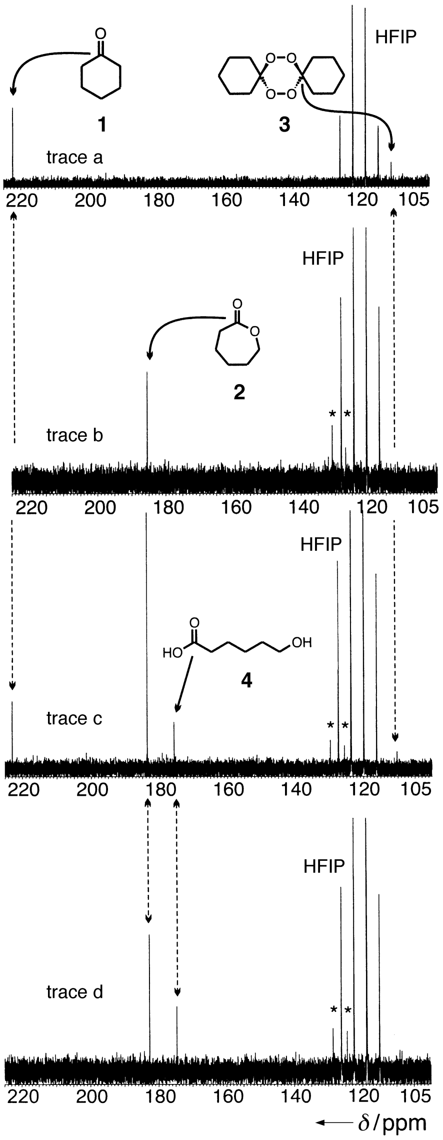


Figure 1. In situ NMR-monitoring of the Baeyer–Villiger oxidation of **1** with hydrogen peroxide in [D$_2$]HFIP (*:signals of *p*-TsOH). See text for details.

At 55 °C, treatment of **1** with 1.3 equivalents of 50 % aqueous hydrogen peroxide and one crystal of *p*-toluenesulfonic acid resulted in smooth conversion, and **2** was formed in 71 % yield. ε-Hydroxycaproic acid (**4**) was formed as a side product (29 %, Figure 1, trace d). However, when **1** was treated with H_2O_2 in the absence of acid at room temperature, it was cleanly converted within minutes to a single product which was *not* **2**. Instead, this material showed a characteristic ^{13}C NMR peak at $\delta = 110$ ppm, indicative of an acetal-like structure (Figure 1, trace a). When the reaction was repeated in nondeuterated HFIP on larger scale, this primary product

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could be isolated in significant quantities: Upon application of mild vacuum (0.2 Torr), the compound deposited on a condenser in the form of colorless crystals. The X-ray analysis of this material enabled us to unambiguously assign the spiro-bisperoxide structure **3** (Figure 2, Eq. (2)).[14,15] Clearly, the NMR spectroscopic data of isolated **3** were identical to those obtained by combining **1** with hydrogen peroxide in HFIP in situ (see above).

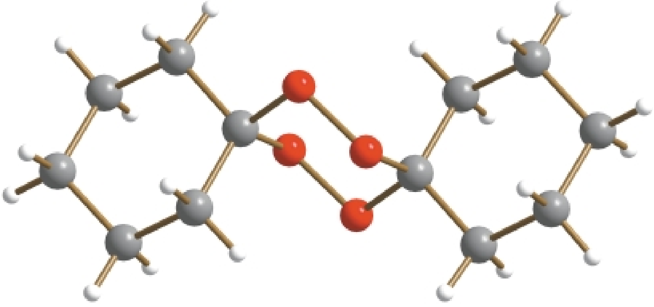
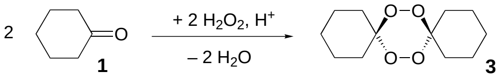


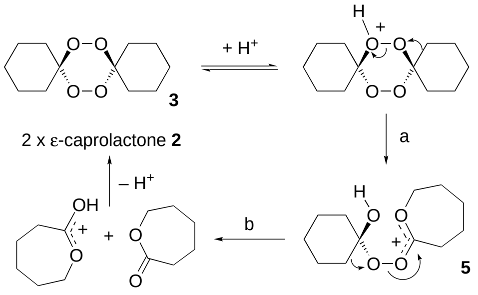
Figure 2. X-ray crystal structure of **3**.



(2)

Treatment of isolated **3** in HFIP with catalytic amounts of strong acids (such as *p*-TsOH) resulted in rapid and quantitative rearrangement to **2**. For example, monitoring of a solution of isolated **3** in dry [D$_2$]HFIP by ^{13}C NMR spectroscopy showed complete conversion within seconds (with evolution of heat; Figure 1, trace b). Upon addition of water to the HFIP solvent, the rearrangement becomes increasingly slow, and **4** becomes more and more prominent as a side product (Figure 1, trace c). The time course of the reaction (not shown) indicated that **4** is *not* formed by subsequent hydrolysis of **2**, but that these two compounds are formed *in parallel*. In line with the above results, anhydrous urea-hydrogen peroxide clathrate as oxidant cleanly afforded **2** and only traces of **4** (monitoring by NMR spectroscopy, not shown). When cyclopentanone was treated with hydrogen peroxide in HFIP, the formation of the analogous spiro-bisperoxide was indicated by the appearance of a new resonance signal at $\delta = 124.58$ ppm. Camphor did *not* afford a detectable adduct with H_2O_2. Thus, the overall activity pattern of ketones in the Baeyer–Villiger oxidation with hydrogen peroxide in HFIP is determined by the reactivity/unreactivity in the initial step, that is peroxide formation [Eq. (2)].

We interpret our experimental observations based on the mechanism shown in Scheme 1. Upon protonation, **3** rearranges to the lactonium cation **5** (step a, Scheme 1). Fragmentation of cation **5** with concomitant rearrangement of the second six-membered ring affords two equivalents of **2** (step b, Scheme 1). Interestingly, the cyclohexyl spiro-bisperoxide **3** was isolated and characterized as early as 1940, in the course of a first attempt to perform the Baeyer–Villiger oxidation of **1** with hydrogen peroxide.[16] However, the authors were unable to transform the peroxide **3** to **2**, and they concluded correctly that **3** cannot be an intermediate in the Baeyer–Villiger oxidation with peracids, but represents a “dead end”.[16] Various other peroxidic adducts of **1** with hydrogen peroxide have been reported,[17–20] and a number of further attempts have been made to isomerize them to **2**. However, in standard organic solvents, acid or Lewis acid catalysis never afforded reasonable yields of lactone,[21–23] and thermolysis invariably gave rise to decomposition initiated by homolytic fission of the peroxide bond(s).[24–26]



Scheme 1. Postulated mechanism for the rearrangement of **3** to **2**.

What is the peculiar effect of HFIP that allows the long-sought rearrangement of the bisperoxide **3** to the lactone **2**? HFIP is well known to form strong hydrogen bonds to anions, thus stabilizing “naked” cations and radical cations.[27–29] Hence we conclude that HFIP 1) not only allows the formation of the protonated spiro-bisperoxide (Scheme 1), but also 2) enables this cation to rearrange by preventing competing intermolecular interception by nucleophiles. The vigor of the peroxide rearrangement in HFIP as compared to other solvents is impressively demonstrated by IR thermography (Figure 3): At identical peroxide and acid loadings, the reaction in dry HFIP gives rise to an immediate temperature increase of more than 20 °C, whereas the evolution of heat is much less pronounced in all other solvents. The reaction retarding effect of water is also clearly visible (wells nos. 1 and 2 from the top; Figure 3).

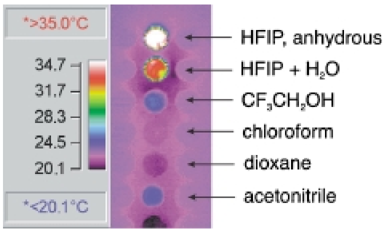
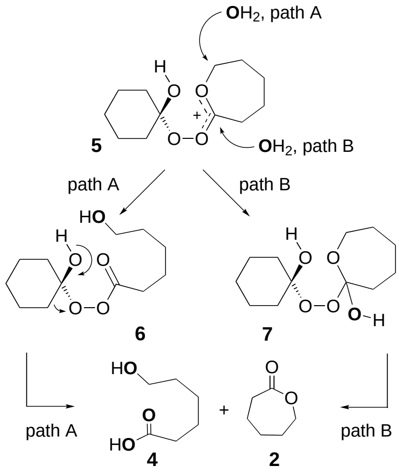


Figure 3. IR-thermographic solvent screening of the acid-catalyzed rearrangement of **3**.

Finally, the mechanism shall be addressed by which **4** is formed from **3**. In principle, addition of a water molecule to the seven-membered ring of the lactonium cation **5** may occur in two ways (Scheme 2): nucleophilic attack at the ε-carbon atom (path A, Scheme 2) gives rise to the ring-opened product **6** which in fact represents the Criegee-intermediate of a “normal” Baeyer–Villiger oxidation. The decay of this intermediate gives rise to **4** and one equivalent of **2**. Attack of



Scheme 2. Postulated reaction paths to **4** and **2**.

water at the acyl carbon atom of **5** (path B, Scheme 2) gives rise to the bishemiperhydrate **7** which may undergo cleavage to **4** and **2** in an analogous fashion. We reasoned that the use of ^{18}O-labeled water should allow a distinction between paths A and B: In the former case, the ^{18}O label should end up in the hydroxy function of **4**, whereas the latter mechanism should integrate the water-derived oxygen atom into the carboxyl group of **4** (Scheme 2). In fact, when the acid-catalyzed rearrangement of **3** was carried out in the presence of $^{18}OH_2$, GC-MS analysis revealed that 1) *one* oxygen atom of the product **4** was derived from $^{18}OH_2$, and that 2) this oxygen atom was part of the *carboxy* function. Consequently, path B (Scheme 2) appears to be the most reasonable mechanism for the formation of the by-product **4**. The latter result is in agreement with earlier studies on the mechanism of hydrolysis of orthoesters, structurally related to the intermediates **5** and **7** (Scheme 2).[30]

In summary, we have shown that the Baeyer–Villiger oxidation of ketones with hydrogen peroxide in HFIP proceeds by a novel mechanism, via spiro-bisperoxides as intermediates. Most importantly, the use of cation-stabilizing HFIP as the solvent opens a new reaction channel for 2,3,5,6-tetroxanes, that is a smooth protonation-induced rearrangement to lactones. In other solvents, this type of peroxide rearrangement does not occur to a significant extent. We could furthermore demonstrate that in the case of **1**, the by-product **4** is produced in parallel and not by subsequent hydrolysis of the main product **2**. Isotopic labeling experiments support the idea of an intermediate lactonium ion (**5**) as the branching point between rearrangement (leading to the lactone **2**) and interception by water (leading to **4**). Further work in this area will address the question of whether the use of fluorinated alcohols as solvent may allow other novel reaction modes of high-energy compounds such as peroxides.

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[14] Crystals suitable for X-ray structural analysis were obtained by recrystallization of **3** from methanol. Crystal data for **3**: $C_{12}H_{20}O_4$, $M_r = 228.28$, colorless platelet, $0.20 \times 0.20 \times 0.10$ mm, triclinic, $a = 5.7373(6)$, $b = 5.9759(7)$, $c = 9.3955(11)$ Å, $\alpha = 85.143(6)$, $\beta = 87.743(7)$, $\gamma = 62.874(5)°$, $V = 285.67(6)$ Å^3, space group $P\bar{1}$, $Z = 1$, $\rho_{calcd} = 1.327$ g cm^{-3}, $\mu = 0.098$ mm^{-1}, $T = 100$ K. A total of 3049 reflections were measured, 1593 unique, 114 parameters, final residuals were $R1 = 0.045$ and $\omega R2 = 0.095$ for 1037 observed reflections with $I > 2\sigma(I)$. Data were collected on a Nonius KappaCCD diffractometer ($2\theta_{max} = 60°$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), graphite monochromator, φ/ω scans. The structure was solved by using direct methods (G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997**), followed by full-matrix least-squares refinement (using all unique reflections) with anisotropic thermal parameters for C and O and isotropic parameters for H (G. M. Sheldrick, SHELXS-97, Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997**). CCDC-185714 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit @ccdc.cam.ac.uk).

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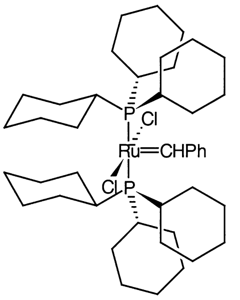
Ligand Rotation Distinguishes First- and Second-Generation Ruthenium Metathesis Catalysts**

Christian Adlhart and Peter Chen*

We report herein a combined quantum mechanical/molecular mechanics (QM/MM) study of the olefin-metathesis reaction catalyzed by ruthenium carbene complexes. The discovery and progressive improvement of Ru-based metathesis catalysts[1] makes an understanding of the mechanistic basis for the high activity and broad substrate tolerance of considerable theoretical as well as practical interest. The discovery of the "first-generation" metathesis catalysts $[(Cy_3P)_2(Cl)_2Ru{=}CHPh]$ (**1**, Cy = cyclohexyl) by Grubbs and co-workers,[2] of which **1** is representative, and the subsequent discovery of the "second-generation" catalysts **2** by the groups of Grubbs,[3] Nolan,[4] and Herrmann,[5] in which an *N*-heterocyclic carbene (NHC) ligand replaces one phosphane group in the first-generation systems, has spurred the synthesis of even more varied structural variants as well as extensive mechanistic work. Recently, Grubbs and co-workers presented an extensive in situ kinetic study[6] in which it was concluded that the origin of the greatly increased activity in the second-generation catalysts derived from a more favorable branching ratio for the partitioning of the active carbene complex, ($[(L)(Cl)_2Ru{=}CHR]$, L = Cy_3P or NHC), between entry into the catalytic cycle and rebinding of a phosphane. We have reported gas-phase mechanistic studies[7,8] with substituent and isotope effects aimed at identifying the rate-determining step as well as the role of preequilibria in determining catalyst activity.



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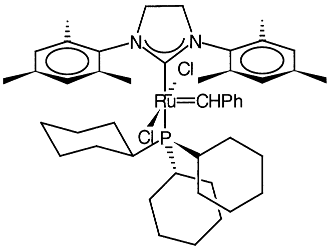

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This growing body of experimental work on metathesis catalysts makes a computational study timely, particularly given the recent successes of mixed quantum-mechanical/classical methods (QM/MM) that allow a reasonable treatment of large organometallic complexes with explicit inclusion of the full ligand set[9] with conformational flexibility. Our calculations show that the first-generation catalysts **1** have a high barrier in the middle of the reaction coordinate imposed by the necessity of rotation of the threefold symmetric phosphane ligand; a comparable barrier is absent in second-generation catalysts **2** because of the twofold symmetry of the NHC ligand. Depending on whether the metathesis reaction is exothermic, thermoneutral, or endothermic, the rate-determining step should therefore change.

Calculations were carried out on the metathesis reaction of both **1** and **2** using the IMOMM approach[10] implemented in the ADF2000.02 (ADF = Amsterdam Density Functional) package[11] on Quant-X Alpha (Compaq Unix Tru64 Unix 5.3) and AMD Athlon (Red Hat Linux 7.1) machines. The QM model was the $[(Me_3P)_2(Cl)_2Ru{=}CHPh]$ unit with hydrogen atoms as dummies for the carbon atoms of the actual complexes. The α values[12] were obtained by full DFT calculations on the QM model units and the full complexes. A triple-ζ basis set was used on ruthenium;[13] a polarized double-ζ basis set was used for all other elements. The $1s^22s^22p^63s^23p^63d^{10}$ electrons of the ruthenium atoms, the $1s^22s^22p^6$ electrons of the chlorine and phosphorus atoms, and the $1s^2$ electrons of the carbon atoms were treated within a frozen-core approximation. A set of auxiliary s, p, d, f, and g STO functions (STO = Slater orbital) centered on all nuclei was used to fit the molecular density and present Coulomb and exchange potentials accurately in each SCF cycle (SCF = self-consistent field).[13] The local density approximation by Vosko, Wilk, and Nusair,[14] and generalized gradient approximation were used with the BP86 functional.[15] Scalar relativistic corrections were added to the total energy.[16] Because all systems investigated showed a large HOMO–LUMO gap, a spin-restricted formalism could be employed throughout. For the MM part of the calculation, a modified sybyl/tripos 5.2 force field[17] was implemented.[18] In the course of comparing QM/MM to full DFT energies, we noticed that there was a systematic error that could be traced back to a double counting of MM interactions. Therefore the MM contribution to the hybrid DFT/MM energy has been removed, as most of this interaction is already taken into account by the imposed strain of the MM system on the DFT system. Validation against full DFT energies at full DFT-optimized structures show that the QM/MM energies simulate full DFT values to within 3–4 $kcal\,mol^{-1}$ in the worst case; the agreement is often much better. The conformational space,

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