100 Years of Baeyer–Villiger Oxidations

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In the present review, we report the discovery of the formation of esters and lactones by oxidation of ketones with a peroxide derivative, namely the Baeyer–Villiger reaction. This reaction was first reported by Adolf von Baeyer and Victor Villiger a century ago in 1899, just one year after the oxidant they used ($KHSO_5$) has been described. Furthermore, Baeyer and Villiger established the composition of this new inorganic peroxide and showed that its instability was the reason of a controversy between several European chemists between 1878 and 1893. For the first 50 years the mechanism of the Baeyer–Villiger reaction was a matter of debate. A side product, 1,2,4,5-tetraoxocyclohexane, was ruled out as an intermediate in the ester formation by Dilthey. Criegee postulated a nucleophilic attack of the oxidant on the carbonyl group. This mechanism was confirmed by von E. Doering by a labeling experiment with [^{18}O]benzophenone. The rearrangement step occurs with retention of the stereochemistry at the migrating center. The competitive migration and the rate-determining step are also discussed in this review.

The transformation of ketones into esters or of cyclic ketones into lactones by peracids was discovered as early as 1899 by Adolf von Baeyer[1] and Victor Villiger[2], when they were working on the ring cleavage of cyclic ketones (terpene derivatives).[3] On the treatment of menthone, carvomenthone, and camphor with a new oxidant without solvent for 24 h at room temperature, the corresponding lactones of menthone and carvomenthone were obtained in 40−50% yield and 15−20% of the starting material was reisolated (Scheme 1). For camphor, the mass balance was lower than 50%. Additionally, they mentioned that this new oxidation reaction works also with several small-ring ketones, but the corresponding lactones could not be isolated and no further experimental details were given.[3,4] The newly discovered oxidant that they employed was potassium monopersulfate ($KHSO_5$). Their attention was drawn to it by a publication of Caro the year before.

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The Discovery of Monopersulfuric Acid and the Exploration of its Composition

In 1898, Caro[5] detected a nitrobenzene odor in the oxidation of aniline with ammonium persulfate [$(NH_4)_2S_2O_8$] (persulfate stands for the symmetrical peroxodisulfate $S_2O_8^{2-}$).[6] This product had never been observed before − not with that oxidant nor with any other oxidizing agent. So he looked for an impurity in the ammonium persulfate and found out that the addition of ammonium or potassium persulfate to concentrated sulfuric acid produces an oxidant which converts aniline into nitrosobenzene. He concluded that the persulfate was protonated by sulfuric acid and then transformed into the "Nitrosobenzol liefernde Substanz" (nitrosobenzene producing substance; see Table 1 for a correlation between historical, mostly German names and current English ones of peroxide derivatives and peracids). Furthermore, he confirmed that electrolyzed sulfuric acid did not contain any persulfuric acid after two days but the "Nitrosobenzol liefernde Substanz".

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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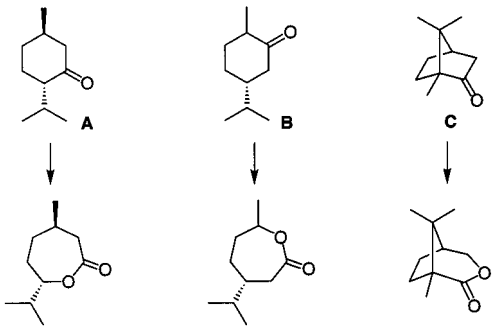
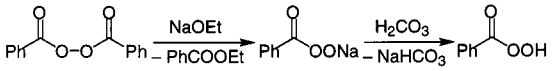


Scheme 1. Menthone (**A**), carvomenthone (**B**), and camphor (**C**) were transformed by Baeyer and Villiger to the corresponding lactones with $KHSO_5$ in 24 h at room temp.[3]

Baeyer and Villiger then reported the first preparation of this new oxidant and explored its composition. The "dry reagent" was prepared by adding 11 g (0.11 mol) of concentrated sulfuric acid to 10 g (0.037 mol) of a potassium persulfate powder in a mortar. After 10 min, 30 g (0.17 mol) of potassium sulfate was added and the mixture grated until a very dry powder was obtained. The salt had a composition of $KHSO_5 \cdot 7\ KHSO_4 \cdot 2\ K_2SO_4$ and was stable in the absence of humidity. Additionally, they prepared a solution of this reagent by addition of sulfuric acid and water which was used for the camphor oxidation.[7]

During their studies on the structure of Caro′s reagent, for which they suggested the formula $KHSO_5$ in their second publication,[8] they looked for comparable oxidants and discovered en passant the organic peracids.[9] Baeyer and Villiger treated dibenzoyl peroxide with sodium ethoxide and the sodium salt of perbenzoic acid precipitated as colorless powder (Scheme 2).[4]

The free perbenzoic acid (PBA) could be generated by protonating the salt with the very weak proton donor H_2CO_3. The "Monobenzoylwasserstoffsuperoxid" (monobenzoyl hydrogen peroxide or perbenzoic acid) showed identical reactivity as H_2SO_5, i.e. fast precipitation of black



Scheme 2. The first synthesis of an organic peracid by Baeyer and Villiger[4]

iodine from KI solution and crystallization of nitrosobenzene from an aqueous solution of aniline.[4] Due to chemical properties they preferred to formulate this oxidant as a peracid rather than as a dioxirane (Figure 1).[10,11]

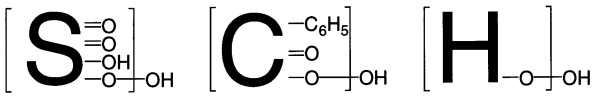


Figure 1. Formulas used by Baeyer and Villiger for the oxidants H_2SO_5, $PhCO_{3\ H,}$ and H_2O_2 (see ref.[10])

In analogy to the organic peracids, Baeyer and Villiger proposed for the Caro′s reagent a sulfur peroxide species as active oxidant (Figure 1). To prove the composition they tried to determine the ratio between active oxygen and sulfate. They recognized, sensitized by Caro′s work, that the main difficulty of this purpose was the transformation of persulfuric acid into monopersulfuric acid which then decomposed into hydrogen peroxide, i.e. all three different oxidants could be present at the same time. So they worked out an analytical protocol where hydrogen peroxide was titrated with a $KMnO_4$ solution, Caro′s acid estimated by titration with thiosulfate immediately after potassium iodide addition (the other two oxidants are by far slower in iodide oxidation), and persulfate by the same method but after a contact time of 12−24 hours with iodide and substraction of the amounts of the other two oxidants. With this protocol, Baeyer and Villiger were able to find a 1:1 ratio for H_2SO_4 to active O and consequently they proposed H_2SO_5 for the composition of Caro′s acid.[12] Furthermore, they were able to follow the kinetics of the decomposition of persulfuric acid. They showed that after 8 days already 6% of Caro′s acid was present in a solution of pure potassium

Table 1. Overview of the historical names of peroxides and peracids

Historical name	Used by	Formula	Current name
Persulfosäure	Caro	$H_2S_2O_8$	persulfuric acid
Ueberschwefelsäure	Baeyer and Villiger	$H_2S_2O_8$	persulfuric acid
Peroxydschwefelsäure	Baeyer and Villiger	$H_2S_2O_8$	persulfuric acid
Perschwefelsäure	Baeyer and Villiger	$H_2S_2O_8$	persulfuric acid
Kaliumpersulfat	Baeyer and Villiger	$K_2S_2O_8$	potassium persulfate
acide persulfurique	Berthelot	$H_2S_2O_8/H_2SO_5$	[a]
Sulfurylholoxid	Traube	H_2SO_5	monopersulfuric acid
Sulfurylhyperoxyd	Traube	H_2SO_5	monopersulfuric acid
Ueberschwefelsäure	Traube	H_2SO_5	monopersulfuric acid
die Nitrosobenzol liefernde Substanz[b]	Caro	H_2SO_5	monopersulfuric acid
Caro′sche Säure	Baeyer and Villiger	H_2SO_5	monopersulfuric acid
Sulfomonopersäure	Baeyer and Villiger	H_2SO_5	monopersulfuric acid
Monobenzoylwasserstoffsuperoxid[c]	Baeyer and Villiger	$PhCO_3H$	perbenzoic acid
Benzopersäure	Baeyer and Villiger	$PhCO_3H$	perbenzoic acid
Acetonsuperoxyd[d]	Baeyer and Villiger	$C_3H_6O_2$	dimethyldioxirane
Holoxyd	Traube	H_2O_2	hydrogen peroxide
Perhydrol	Dilthey et al.	H_2O_2	hydrogen peroxide

[a] Mixture of persulfuric acid and monopersulfuric acid. − [b] The nitrosobenzene producing substance. − [c] Monobenzoyl hydrogen peroxide. − [d] Only postulated, not synthesized.

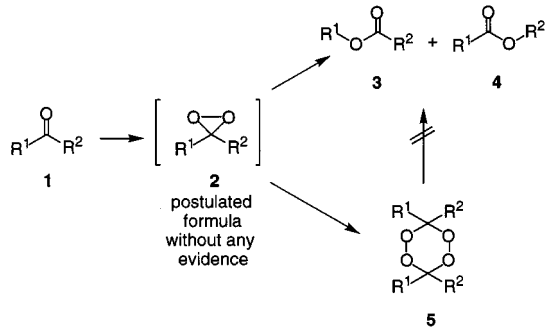
persulfate. The presence of sulfuric acid enhanced the rate of transformation. This acid-catalyzed decomposition of persulfuric acid to monopersulfuric acid was the origin of the troubles of Traube with Berthelot and Marshall when he first reported the discovery of H_2SO_5 (postulated as anhydride SO_4), before the description of the same compound by Caro. With their results in hand, Baeyer and Villiger found the solution of a controversy in literature between the three European chemists.[13]

Berthelot[14] was the first who recognized that the electrolysis of sulfuric acid did not produce hydrogen peroxide but an oxygen-rich compound of sulfur. He called it "acide persulfurique" and postulated a composition corresponding to $H_2S_2O_8$[15–17] which he could not prove because of the lack of a purification method.[18,19] Real evidence of the formation of a persulfuric acid during the electrolysis of sulfuric acid was provided by Marshall who electrolyzed alkali sulfates.[20] He was able to purify the substances by crystallization. In contrast, the attemps of Berthelot had to fail because he worked on an inseparable and variable mixture of persulfuric acid and monopersulfuric acid, as explained later by Baeyer and Villiger. Berthelot realized that he had a mixture of two substances, wrongly attributed to persulfuric acid and hydrogen peroxide. The former was supposed to form iodine rapidly with an aqueous KI solution whereas hydrogen peroxide was thought to do it slowly. When in 1891 Marshall isolated crystalline persulfates,[20] Berthelot thought he recognized the salts of his "acide persulfurique" because of the composition $K_2S_2O_8$.[21] However, he refused to admit that Marshall's substances liberated iodine only slowly which was in contradiction with his observation that "acide persulfurique" (in fact a mixture of $H_2S_2O_8$ and H_2SO_5, see Table 1) performed iodide oxidation very quickly.

Meanwhile in 1889, Traube analyzed the electrolyzed sulfuric acid with a new method.[22,23] He first removed the disturbing sulfate by precipitation with freshly prepared $Ba_3(PO_4)_2$. Then he determined the active oxygen content by titration and the sulfate content (after reduction) by precipitation with $BaCl_2$ and HCl. He found a 1:1 ratio of active oxygen to sulfate, so he concluded that this oxidant had a composition corresponding to H_2SO_5. He considered it as a peroxide and named it "Sulfurylholoxyd". In 1892 Traube became very upset when Berthelot[24] and Marshall[20] denied the existence of his "Sulfurylholoxyd" without having checked his results, since both persons had independently established the existence of persulfuric acid. At that time Traube was not able to work in the laboratory but nevertheless his results were fully reproduced by a co-worker.[25] In 1893, he repeated his experiments himself but this time he obtained a 1:2 ratio of active oxygen to sulfate, i.e. he analyzed a substance having the composition postulated by Marshall and Berthelot for "acide persulfurique".[26] Consequently, in one of his last publications, he withdrew the name "Sulfurylholoxyd". A decade later, Baeyer and Villiger provided the explanation for these contradictory results. The electrolyzed sulfuric acid solution was probably allowed to age for a certain period of time before the first experiments on oxygen titration, whereas the solution was freshly prepared for the second analytical assays. After the elimination of "Sulfurylholoxyd" from the literature, Caro had to re-discover the monopersulfuric acid which then was named "Caro's acid" by Baeyer and Villiger.

The Role of the Dimeric Peroxide Side Product

Baeyer and Villiger realized that the oxidation of ketones by Caro's acid was very similar to the Beckmann rearrangement. Besides of the ring cleavage of cyclic ketones, both reagents, hydroxylamine and Caro's acid, led to products with the same carbon skeleton.[27] Consequently, they postulated a dioxirane as intermediate (Scheme 3) as the Beckmann rearrangement was believed to proceed via an oxaziridine at the end of the last century. For mechanistic investigations they used acyclic aliphatic ketones. With acetone they did not find a rearrangement product, but they obtained crystals having an elemental analysis corresponding to $C_3H_6O_2$, "Acetonsuperoxyd" (dimethyldioxirane, cf. Table 1). The high melting point indicated a polymer structure rather than a monomer and later on they showed that this compound was 3,3,6,6-tetramethyl-1,2,4,5-tetraoxacyclohexane, formally the dimer of dimethyldioxirane.[4][8] They concluded that ketones reacted with Caro's acid to produce a primary oxidation product, a ketone plus one oxygen atom. For cyclic substrates, the latter compound rearranged to a lactone and for acyclic ones, dimerization or polymerization was observed (Scheme 3). In many cases a mixture of products was obtained. No explanation was found for the different chemoselectivities. It was therefore a challenge for the next investigators to solve this problem, i.e. to obtain a high ketone conversion with a high selectivity for the desired lactone product.

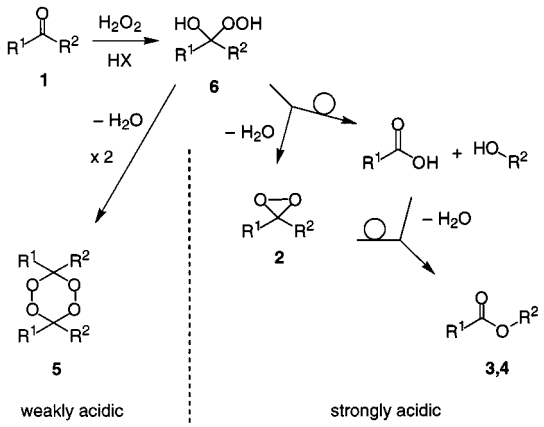


Scheme 3. The mechanism of the oxidation of ketones proposed by Baeyer and Villiger

In their study on the oxidation of 13- to 17-membered ring ketones, Ruzicka and Stoll investigated for the first time the influence of temperature (from room temperature to 65 °C) and solvent (petroleum ether or glacial acetic acid) on the product formation in the oxidation of ketones with $KHSO_5$.[28] Besides polymeric peroxides as by-products, they also observed a polyester resulting from the polymeri-

zation of the lactone as an additional problem. The best results were obtained in glacial acetic acid at a reaction temperature of 50−65°C. The only by-products were oligomers of the lactone, formed by trans-esterification caused by the acidity of the triple salt of $KHSO_5$. At lower temperatures polymeric peroxides were significant by-products. The same problems were observed by Robinson and Smith in the oxidation of cyclohexanone and cycloheptanone (suberone) with Caro′s acid.[29]

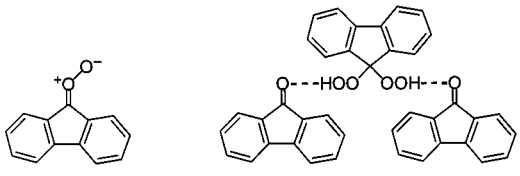
Dilthey, Inkel, and Stephan continued the investigation on the dimeric peroxides and figured out their role in the mechanism of the Baeyer−Villiger oxidation.[30] As oxidant they claimed to use an acidic solution of hydrogen peroxide. However, a closer look on the experimental details suggest a different interpretation. The oxidations were carried out in a solution of 25 g of 30% aqueous hydrogen peroxide, 20 g of concentrated sulfuric acid, and 50 g of acetic anhydride. Under these conditions, an in-situ formation of peracetic acid is very likely so that hydrogen peroxide should not be proposed as sole reagent in the Baeyer−Villiger reaction. By mixing the compounds in different amounts, they were able to optimize the yield of the formation of the dimeric peroxide **5**, to isolate the latter and to study its stability. For at least two different substrates (Scheme 3, benzophenone and cyclohexanone) they showed that the peroxide **5** could not be transformed to the product esters **3** and **4** (under heating and acidic conditions, decomposition of **5** into ketone and hydrogen peroxide was observed), indicating that **5** was not an intermediate in the Baeyer−Villiger rearrangement but a dead-end compound. These results were also in agreement with the observations of Robinson and Smith who obtained high yields of lactones and low ones of dimeric peroxides and vice versa.[29] Additionally, Dilthey and co-workers concluded the existence of a first oxidation product as proposed by Baeyer and Villiger, which then was transformed either into the dimeric peroxide or rearranged to the ester product. However, in contrast to Baeyer and Villiger, they did not propose the dioxirane as intermediate for both the peroxide and the rearrangement product, but the perhydrate **6** formed by nucleophilic addition of hydrogen peroxide to the ketone (Scheme 4). This perhydrate **6** should then dimerize under slightly acidic conditions with intermolecular water elimination. Under strongly acidic conditions, the water was assumed to be eliminated in an intramolecular manner to form the dioxirane **2** (Scheme 4), which would immediately rearrange to the ester/lactone product. Alternatively, Dilthey and co-worker suggested the rearrangement of the perhydrate itself under strongly acidic conditions to the free acid and an alcohol which then formed the ester and one water molecule (Scheme 4). Although the whole mechanistic problem was not solved, their work allowed the exclusion of dimeric peroxides as intermediates. Additionally, besides the dioxirane intermediate suggested by Baeyer and Villiger, a second possible compound was brought into the discussion which was formed by a nucleophilic addition to the C=O double bond, namely the perhydrate **6**.



Scheme 4. The mechanism of the formation of the dimeric peroxide and the cleavage products as suggested by Dilthey, Inckel, and Stephan[30]

The Wittig−Criegee Alternative Route for the Baeyer−Villiger Rearrangement: Synthesis of the Dihydroperoxy Derivative and Acid-Catalyzed Rearrangement of Its Diacetate

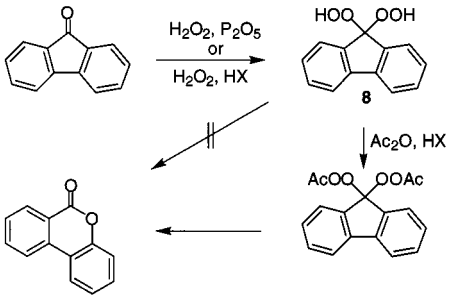
In 1940, Wittig[31] and Pieper introduced a new monomeric peroxide intermediate, the "Fluorenonoxoxyd" (**7**, fluorenone carbonyl oxide).[32] They treated fluorenone with an ether hydrogen peroxide solution in the presence of phosphorus pentoxide and obtained yellow crystals with a melting point of 108−108.5°C (for comparison: the melting point of fluorenone is 82−85°C). The cryoscopic determination of the molecular mass favored a monomeric peroxidic compound. The dioxirane structure was excluded by the grounds of the yellow color, which was attributed to a carbonyl bond not present in the dioxirane. So, the only remaining possible structure with a C=O double bond was the carbonyl oxide **7**. Upon addition of acetic anhydride and sulfuric acid, the oxidation conditions of Dilthey and his co-workers (cf. above),[30] Wittig and Pieper obtained the rearranged lactone in 20% yield and reisolated 60% of the fluorenone from the "carbonyl oxide". Also direct transformation of fluorenone to the corresponding lactone under Dilthey′s conditions was possible. Consequently, the carbonyl oxide became a reasonable intermediate for the Baeyer−Villiger oxidation.



However, nine years later Criegee[33] demonstrated by the means of chemical correlations, "daß das Fluorenonoxoxyd aus der Literatur zu streichen ist" (that the fluorenone carbonyl oxide has to be eliminated from literature).[34] Although he was able to reproduce all experimental details provided by Wittig concerning synthesis, physical

properties, elemental analysis, and molecular mass, Criegee found out that Wittig′s "Fluorenon-oxoxyd" consisted of a mixture of 2 molecules of fluorenone and 1 molecule of the 9,9-bis(hydroperoxy)fluorene (**8**). As first fact against a carbonyl oxide he obtained a vigorous evolution of oxygen from the reaction of the yellow crystals with $Pb(OAc)_4$, as expected when treating a hydroperoxide derivative with this oxidant. Furthermore, the content of active oxygen was only 2/3 of the amount calculated for a monomeric peroxide. The final fact and the end of the speculations on fluorenone carbonyl oxide (**7**) were obtained with the benzoylation of these yellow crystals giving 2 molecules of fluorenone and 1 molecule of benzoylated 9,9-bis(hydroperoxy)fluorene.

Having identified the structure of Wittig′s compound, Criegee investigated further its reactivity and its rearrangement ability. By thermal treatment he was not able to transform it into the Baeyer−Villiger rearrangement product (he observed only oligomeric peroxides). In contrast, the desired lactone was obtained upon the already mentioned treatment with $Pb(OAc)_4$ in a 25% yield. The rearrangement by treatment of the dihydroperoxide compound **8** with acetic anhydride, first carried out unknowingly by Wittig (Scheme 5), has been established to be of a broader scope by the French chemists Velluz, Amiard, Martel, and Warnant.[35] They synthesized several dihydroperoxy steroids and rearranged them to the corresponding lactones after acetylation.



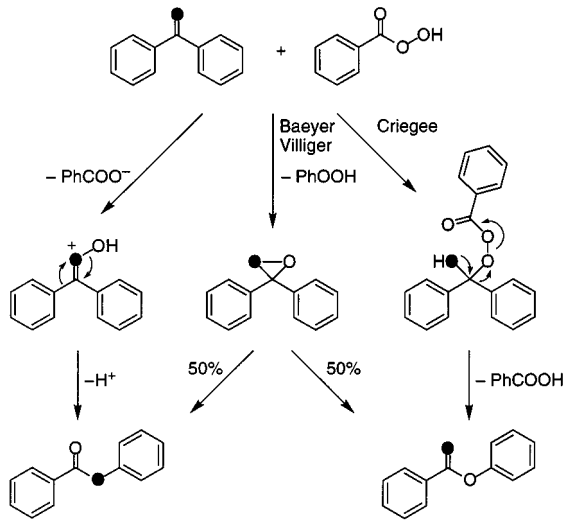
Scheme 5. Transformation of a cyclic ketone into a lactone with hydrogen peroxide/P_2O_5 followed by acid-catalyzed acetylation first carried out by Wittig,[32] who was unaware of the dihydroperoxide **8**, and explained later by Criegee[34]

Fifty years after the discovery of the Baeyer−Villiger oxidation, this rearrangement reaction was used in many steroid syntheses; among them 3-keto steroid derivatives,[36−41] 17-keto steroids,[42−44] sarsasapogenin,[45] and 20-keto pregnanes.[46−50] As very interesting substrates, α,β-unsaturated ketones were transformed to synthetically useful enol lactones.[51−53]

With the use of the organic peracids for the Baeyer−Villiger oxidation,[54,55] namely peracetic acid (PAA) and perbenzoic acid (PBA), more systematic explorations of the scope of this reaction have been investigated because of the better mass balances and higher conversions of the reactions in organic solution and reduced the acidity of the reagent. The mechanism of the rearrangement was clarified and the retention of configuration of the migrating carbon center demonstrated and thereby the intramolecularity of the rearrangement.

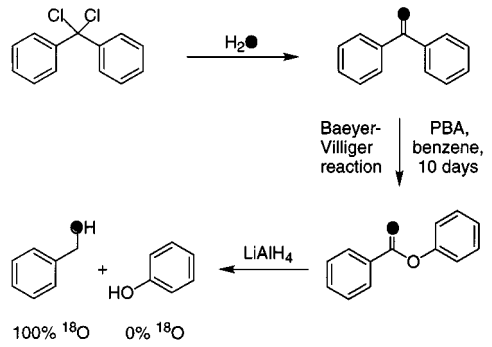
Exploration of the Mechanism of the Baeyer−Villiger Rearrangement

In 1953, Doering and Dorfman clarified the mechanism by performing a labeling experiment.[56] Three years before, Doering and Speers considered three different possible intermediates which had to be distinguished.[57] The first one was the already mentioned dioxirane suggested by Baeyer and Villiger (Scheme 3). The second hypothesis was the carbonyl oxide resulting of the transfer of an OH^+ species from the peracid onto the oxygen atom of the keto group (Scheme 6).[58] Although the carbonyl oxide is only a protonated form of a dioxirane isomer, in contrast to the latter, the transferred oxygen atom and the ketone oxygen atom are chemically not equivalent at any time of the reaction. This remark will be important later in the discussion on data obtained in labeling experiments. A third possible mechanism that they considered was related to the work of Criegee on the rearrangement of a decalin peroxyester. Criegee postulated a nucleophilic attack of the peracid onto the ketone in the Baeyer−Villiger oxidation to generate the so-called "Criegee intermediate" (Scheme 6).[59] Then, the carboxylic acid moiety acts as a leaving group and, in a quasi-concerted fashion, the C=O bond is formed again and one substituent migrates from the carbonyl carbon atom to the partially positively charged oxygen atom (six electrons are involved in this heterolytic cleavage of the peroxidic O−O bond).



Scheme 6. Position of the labeled oxygen atom of benzophenone after the Baeyer−Villiger oxidation depending on the reaction mechanism via the carbonyl oxide, via a dioxirane as suggested by Baeyer and Villiger[3] and via the Criegee intermediate, named after Criegee who postulated this reaction pathway[59]

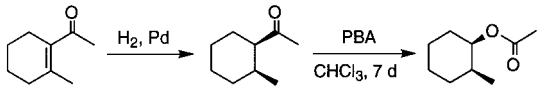
To distinguish between these three possible mechanisms for the Baeyer−Villiger rearrangement, Doering and Dorfman labeled the oxygen atom of benzophenone with ^{18}O.[56] If the reaction proceeded via the Criegee intermediate, the labeled oxygen atom would be found as carbonyl oxygen atom in the lactone (Scheme 6). If the carbonyl oxide played a role, the phenolic oxygen atom should be obtained completely labeled in the corresponding lactone. In the case of a dioxirane formation as suggested by Baeyer and Villiger, no preference would be observed, a statistical 50:50 distribution of the labeled oxygen atom would be expected (Scheme 6). As unequivocal probe for the mechanism of the Baeyer−Villiger oxidation, Doering synthesized the labeled benzophenone from dichlorodiphenylmethane with ^{18}O-enriched water (Scheme 7). Treatment of [^{18}O]benzophenone with perbenzoic acid in a benzene solution gave phenylbenzoate with an ^{18}O-carbonyl group. The position of labeling was determined by reducing the ester to phenol and benzyl alcohol with lithium aluminium hydride (Scheme 7). The resulting phenol contained no ^{18}O atom whereas the benzyl alcohol contained 93% of the labeled oxygen atom of the starting material indicating that the ^{18}O atom of benzophenone appeared exclusively in the carbonyl oxygen atom of phenyl benzoate. This isotope distribution was incompatible with mechanisms involving a dioxirane or a carbonyl oxide and is completely consistent with the "Criegee mechanism".[60]



Scheme 7. Reaction sequence used by Doering and Dorfman to establish the mechanism via Criegee's intermediate[56]

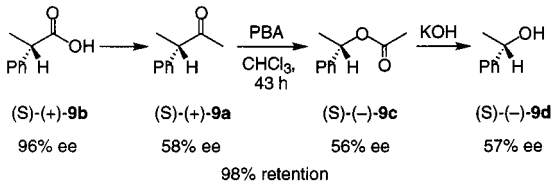
The Baeyer−Villiger Rearrangement Occurs with Retention of the Stereochemistry of the Migrating Group

In the middle of this century, enantiomeric analysis was restricted to the measurement of optical rotations and a limited number of non-natural enantiomerically pure compounds was available. The comparison with the stereochemistry of an adjacent asymmetric carbon center, i.e. the diastereoselectivity, was employed to obtain the first data on the stereoselectivity of the Baeyer−Villiger rearrangement. In 1950 Turner synthesized *cis*-1-acetyl-2-methylcyclohexane by Pd-catalyzed hydrogenation of 1-acetyl-2-methyl-1-cyclohexene (Scheme 8).[61] By treatment of the hydrogenated product with sodium ethoxide, the thermodynamically more stable *trans* diastereoisomer was obtained. Both *cis* and *trans* compounds were oxidized with perbenzoic acid (PBA) in chloroform for seven days (Scheme 8). Both products, *cis*- and *trans*-2-methylcyclohexyl acetate, were saponified directly, converted into the corresponding phthalates, and isolated in a 60% yield. The products were identified by mixing them with authentic samples of *cis*- and *trans*-2-methylcyclohexyl phthalate without depressing their melting point. Having established that the *cis*-methylcyclohexyl acetate was exclusively obtained from the *cis*-1-acetyl-2-methylcyclohexane in the Baeyer−Villiger oxidation with PBA and the *trans* diastereomer from the *trans*-configured ketone, Turner demonstrated that the rearrangement occured with retention of configuration at the migrating center by an intramolecular process. Simultaneously, Gallagher and Kritchevsky obtained similar results in studies on the stereochemistry of the 20-keto stereoid oxidation.[62]



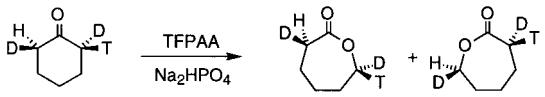
Scheme 8. First evidence for the retention of conformation of the migrating center with the help of an adjacent asymmetric carbon atom[61]

A few years later, Mislow and Brenner confirmed the stereoselectivity of the Baeyer−Villiger reaction by oxidizing the optically active 3-phenyl-2-butanone (**9a**, Scheme 9).[63] This ketone was prepared from the optically almost pure hydratropic acid (**9b**) with partial racemization. The ketone **9a** could be transformed into the corresponding ester **9c** by treatment with PBA without significant loss of stereochemistry; the ester **9c** was obtained with 98% of retention of configuration (Scheme 9). The optical activity of the (*S*)-(−)-phenylethanol **9d** obtained by saponification of **9c** confirmed also the retention of configuration at the chiral center during the Baeyer−Villiger reaction (Scheme 9).



Scheme 9. Reaction sequences to prove the retention of configuration of the migrating carbon atom with an optically active ketone[63]

In the 1980s, it was shown that the configuration also is retained in unsubstituted substrates such as cyclohexanone. The treatment of α-tritiated cyclohexanone by acetoacetate decarboxylase with D_2O gave an optically active, doubly labeled cyclohexanone which was converted into labeled caprolactone by a Baeyer−Villiger oxidation with trifluoroperacetic acid (TFPAA, Scheme 10).[64] The retention of the stereochemistry makes the Baeyer−Villiger reaction a useful tool for asymmetric synthesis. However, it should be noted that ketones and lactones epimerize easily.[65]



Scheme 10. Proof of retention of configuration at the migrating center by using an isotopically labeled cyclohexanone[64]

Competitive Migration − Rates and Selectivities

The first studies on the competitive migration of the substituents of unsymmetrical ketones were also carried out with organic peracids. From literature examples before 1950, Doering concluded a general preference in migration of secondary and tertiary susbstituents over a methyl group.[57] He suggested that groups bearing a positive charge at the migrating carbon atom will rearrange more rapidly during the peroxidic bond cleavage.[57] He verified this by analyzing the behavior of substituted benzophenones (Table 2).

The migration of substituents with an electron-donating group like MeO or Me in *para* position was found to be preferred over phenyl migration (entries 1 and 2, Table 2). Electron-withdrawing substituents (Cl, Br, and NO_2) favored the migration of the phenyl group (entries 4−6, Table 2). The order of the migrating ability of *p*-substituted aryl groups has been determined by Friess by kinetic measurements on the Baeyer−Villiger oxidation of the corresponding acetophenones with PBA as indicated in Figure 2.[66] However, these kinetics should be interpreted with caution. Also the nucleophilic attack on the carbonyl bond can be influenced by the substituents of the aromatic moiety, i.e. it is not possible to conclude in every case on the migration ability of the substituents by comparison of the reaction rates of two different compounds. This was demonstrated in the case of mesityl phenyl ketone (entry 7, Table 2).[57] This compound should react at least as fast as the unsubstituted benzophenone (there are no rate-retarding electron-withdrawing substituents), but after a reaction time of eight days, 92% of the starting material was recovered, instead of half of this amount in the benzophenone case (entry 3, Table 2). The *ortho* substitution of the aryl group makes the ketone almost inert with regard to the Baeyer−Villiger oxidation, i.e. the steric demand of these substituents prevent the nucleophilic attack of the peracid on the carbonyl group.

p-MeO-Ar > *p*-Me-Ar > Ph > *p*-Cl-Ar > *p*-Br-Ar > *p*-NO_2-Ar

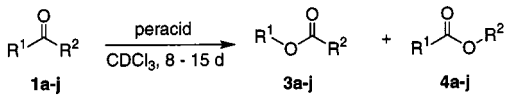
Figure 2. Migration ability of *p*-substituted aryl groups estimated from the selectivites and the reaction rates of the corresponding benzophenones[57] or from kinetic measurements of the corresponding acetophenones[66]

An additional problem for the investigations of migration preferences was exposed by Hawthorne.[67] He demonstrated that the peroxy acid used may have a large effect on the results obtained; cyclohexyl phenyl ketone gave a phenyl/cyclohexyl migration ratio of 1:9 with peroxyacetic acid (PAA), but 1:4 with trifluoroperacetic acid (TFPAA). In view of this, comparison of results employing different reagents cannot be made with precision.[68] Consequently, for preparative applications, the review by Krow in *Org. React.* should be consulted for comparative migration ability. Literature examples with more than 1000 references have been listed and a model compound can be found easily.[69] From extensive studies on the relative migration aptitude, the following order has been found (to be treated with the above-mentioned restriction): tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > cyclopentyl, cyclopropyl > methyl.[67,70−75] Since all groups migrate in preference to methyl it is evident that all methyl ketones will give predominantly or entirely acetate esters.

The Camphor Mystery

One of the first substrates employed in the transformation of cyclic ketones into lactones by Baeyer and Villiger in their first publication in 1899[3] − camphor − caused a lot of trouble in the 1950s and early 1960s. They isolated a product in which a methylene group migrated (Scheme 1) and not the tertiary bridgehead carbon atom. Then Doering and Speers realized that the product was not in agreement with their proposed rule on the migration

Table 2. Influence of electronic effects on the Baeyer−Villiger reaction using mono-*para*-substituted benzophenones and PAA[57]

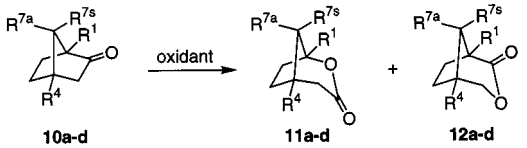


1a-j **3a-j** **4a-j**

Entry		Substrate R^1	R^2	r. t.[a] [d]	Conv.[b] [%]	Yield[c] [%]	Product distribution[d] **3/4**
1	**1a**	*p*-MeO-Ar	Ph	8	100	86	100:0
2	**1b**	*p*-Me-Ar	Ph	8	61	47	100:0
3	**1c**	Ph	Ph	8	54	45	−
4	**1d**	*p*-Cl-Ar	Ph	8	26	22	9:91
5	**1e**	*p*-Br-Ar	Ph	8	6	3	[e]
6	**1f**	*p*-O_2N-Ar	Ph	15	100	29	0:100
7	**1g**	mesityl	Ph	8	8	7	100:0

[a] Reaction time in days. − [b] Conversion, based on recovered ketone. − [c] Yield of isolated ester or of the saponification products. − [d] Product distribution normalized to 100. − [e] In favor of R^1 migration, but the low conversion did not allow the determination of the precise ratio.

Table 3. Influence of different substituents on the product distribution in the Baeyer–Villiger oxidation of 2-norbornanone



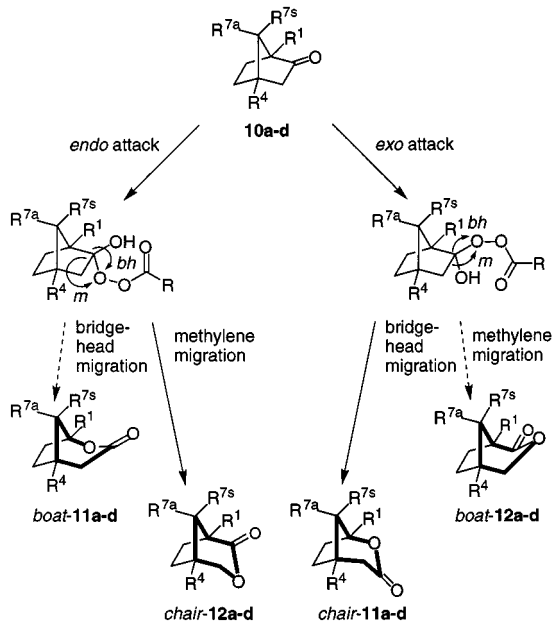
Entry		Substrate R^1	R^4	R^{7a}	R^{7s}	Oxidation	Yield [%]	Product distribution[a] **11/12**
1[b]	**10a**	H	H	H	H	28% PAA, NaOAc	88	100:0
2[b]	**10a**	H	H	H	H	40% PAA, HOAc, H_2SO_4	97	100:0
3[c]	**10a**	H	H	H	H	CF_3CO_3H, Na_2HPO_4	100	100:0
4[d]	**10b**	Me	H	H	H	40% PAA, buffer	42	100:0
5[e]	**10c**	Me	H	Me	Me	40% PAA in 40:60 H_2SO_4/HOAc	30	0:100
6[d]	**10c**	Me	H	Me	Me	PAA, NaOAc	[f]	75:25
7[d]	**10d**	Me	Me	Me	Me	40% PAA, NaOAc	94	0:100

[a] Product distribution normalized to 100. – [b] From ref.[79] – [c] From ref.[80] – [d] From ref.[77] – [e] From ref.[76] – [f] Yield not given.

ability (see above).[57] In a footnote, they attributed "the opposite behavior of camphor ... to the fact that the tertiary carbon is part of a bridgehead". Ten years later, Sauers published a series of articles on this camphor puzzle. In 1959, he demonstrated that the methylene migration product **12c** (Table 3) was not the only product, i.e. the selectivity was no longer 100:0 making the problem less dramatic.[76] Already Baeyer and Villiger, who isolated around 30% of the lactone **12c**, obtained a second unknown product which analyzed as $C_{10}H_{16}O_4$. Sauers employed milder conditions with peracetic acid (PAA), buffer and a longer reaction time (14 days) instead of Caro′s acid in sulfuric acid and obtained 82% of the bridgehead migration product **11c**. With a more careful analysis two years later, he found a ratio for the lactones **11c** and **12c** of 75:25, but still in favor of the bridgehead migration product (entry 6, Table 3).[77] Having the regioisomer **11c** in hand he found that it was not stable under strongly acidic conditions and rearranged to another lactone. Without buffer he observed a mixture of lactones[76] and in presence of the strong sulfuric acid he obtained only the regioisomer **12c** in 30% yield (entry 5, Table 3).[76]

These were the first results of different product selectivities with a change of the acidity in the Baeyer–Villiger reaction. Consequently, he thought that the Criegee mechanism must be modified when operating in strongly acidic solution.[76] He postulated a protonation of the Criegee intermediate (Scheme 6) prior to its decomposition. The leaving acid derivative would be transformed into a better leaving group which is obtained in its protonated neutral form. This would shift the transition state of the rearrangement towards an earlier stage with consequent de-emphasis of the importance of electronic stabilization of the migrating group. Furthermore, he ended with the conclusion that "alternate explanations for the formation of α-campholide [lactone **12c**] are no longer applicable although they may contribute to the various forces involved". With the "alternate explanations" he referred to a model suggested by Murray, Johnson, Pederson, and Ott. They proposed that the subsequent course of reaction is affected both by electronic and steric factors.[78] In general, they agreed with Doering and Speers[57] that in most cases the migrating group was that one better able to accommodate a positive charge, i.e. the more substituted group. However, particularly in polycyclic fused systems, they estimated steric effects to be important. Consequently, they had a closer look at the geometry of the transition state of the rearrangement of the Criegee intermediate to the products. Upon an *endo* attack (less hindered in the camphor case, cf. Scheme 11, left hand side), the bridgehead migration (bh) would proceed through a boat-like transition state with the least movement of atoms in space whereas methylene migration (m) would involve a chair conformation which should be lower in energy. With this model Murray and co-workers could at least rationalize why the methylene migration was able to compete with the migration of the higher substituted carbon atom at the bridgehead.

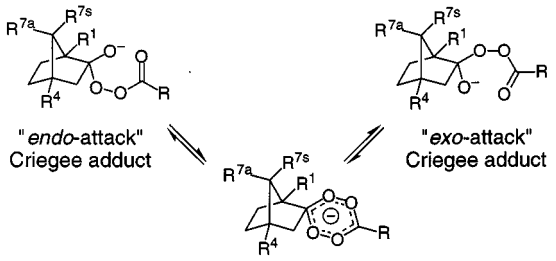
Oxidations of norcamphor **10a** (R^{7a} = R^{7s} = H) by Meinwald and Frauenglass supported the boat/chair model and were in contradiction to the modified mechanism of Sauers in strongly acidic solution.[79] The product distribution was similar in buffered conditions (entry 1, Table 3) or in strongly acidic medium (entry 2, Table 3). The only regioisomer observed by Meinwald and Frauenglass was the lactone **11a** resulting from a bridgehead migration. If acid catalysis played a role in the transition state and in the product distribution, the latter should be in favor of lactone **12a** analogous to the observations for substrate **10c** by Sauers (cf. entries 2 and 5, Table 3). The boat/chair model of Murray must be applied in this case. As the attack from the *exo* side was no more hindered by a methyl group (R^{7s} = H), it was now the sterically favored approach (Scheme 11, right-hand side) consequently changing the conditions of the rearrangement. In addition, the electronically favored migration of the bridgehead became favored for steric reasons since this rearrangement involved an energetically more stable chair conformation. Consequently, steric and electronic factors work synergically for substrate **10a** to give the lactone **11a** as exclusive regioisomer.



Scheme 11. Upon an *endo* attack onto a norbornanone derivative **10** (left-hand side of the Scheme) methylene migration (m) is favored over bridgehead migration (bh) leading mainly to lactone **12** because the transition state proceeds via an energetically more favored chair configuration with the least movement of atoms in space instead of a boat form; in the case of the formation of the Criegee intermediate by an *exo* attack (right-hand side), bridgehead migration leads to lactone **11** as preferred product; this steric explanation was introduced by Murray, Johnson, Pederson, and Ott (see Table 3 for substituents of **10a–d**)[78]

Rassat and Ourisson confirmed the preference of bridgehead migration in norcamphor.[80] They employed buffered conditions (trifluoroperacetic acid and Na_2HPO_4) and obtained the "normal" Baeyer–Villiger product **11a** (entry 3, Table 3). However, they did not pay attention to the change of the attack of the carbonyl group introduced by the smaller steric demand of a proton versus a methyl group as R^{7s} in camphor when they compared their results with those of Sauers under buffered conditions (cf. entries 3 and 6, Table 3). So, they obtained similar results and tried to rationalize them in relation to the ones observed for camphor under acidic conditions (entry 5, Table 3). They proposed a rearrangement of the Criegee adduct formed by an initial *endo* attack to the addition product resulting from an *exo* attack, namely from the "*endo*-attack" to the "*exo*-attack" adduct as shown in Scheme 12 (such a proposal can now be considered as being a sigmatropic rearrangement). Then, the chair transition state is favored and the *chair*-**11a** product is obtained. However, Meinwald′s and Frauenglass′ results disprove the proposal because under strongly acidic conditions, where the rearrangement should not be possible, the same product is obtained for norcamphor as in buffered conditions (entry 2, Table 3).

In his second publication on the oxidation of norbornanone derivatives in 1961, Sauers investigated as additional substrates 1-methylnorcamphor (**10b**) and epicamphor (**10d**).[77] In this article, he finally admitted that steric effects could compete successfully with electronic effects in controlling the outcome of the Baeyer–Villiger reaction, in complete contradiction with his own mechanistic proposals claimed in his previous publication. For a substrate without methyl group as R^{7s} such as ketone **10b**, he obtained lactone **11b** resulting from a bridgehead migration (entry 4, Table 3). Ketone **10d** was transformed into lactone **12d** by methylene migration (entry 7, Table 3). These results were analogous to the cases of norcamphor (*exo* attack) and camphor (*endo* attack) and fitted perfectly with the boat/chair theory in terms of product selectivity. Later, he tried to correlate roughly the amount of the "wrong" lactone and the size of the R^{7s} substitutent.[81] Assuming that the order of increasing size was chlorine < bromine < methyl, Sauers observed an increase in the percent of methylene migration 53% < 71% < 100%. However, the halogenated compounds seemed to be oxidized under buffered conditions whereas the camphor results were obtained under acidic conditions.



Scheme 12. Rearrangement of the Criegee intermediate under buffered conditions postulated by Rassat and Ourisson in the norcamphor oxidation by a peracid ($R^1 = R^4 = R^{7a} = R^{7s} = H$, $R = CF_3$)[80]

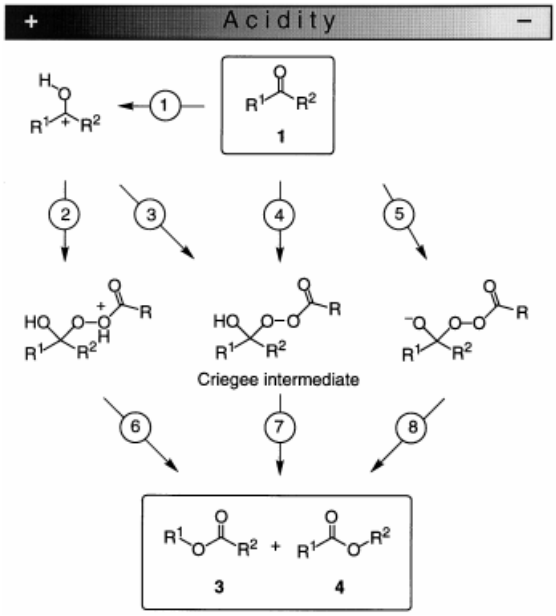
Finally, it can be concluded that all results on the Baeyer–Villiger oxidation of norbornanone derivatives can be rationalized with the boat/chair model for the transition-state geometry. Changes under strongly acidic conditions may be due to protonation of the carbonyl group and conformational changes in the substrate (Figure 3). For the left structure an *exo* attack would be sterically easier than for the unprotonated carbonyl group. In fact, a rate enhancement was also observed under acid catalysis (14 days for entry 6 of Table 3 versus 5 days for entry 5). Protonation of the carbonyl group has been observed by Hawthorne with very strong acids like trifluoroperacetic acid.[82]

Figure 3. Two possible epimers after protonation of a norbornanone derivative

The Kinetics of the Baeyer–Villiger Reaction and the Rate-Determining Step

Additional data have been obtained on the kinetics of the Baeyer–Villiger reaction. In fact, there are so many factors which can influence the transition state of the reaction that small changes in the reaction conditions or the reactants

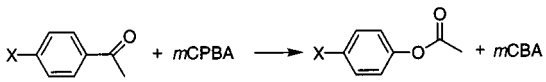
may lead to different results. This has already been reported for the product selectivity and the migration ability; however, it is even more pronounced in the kinetics and the rate-determining step of the Baeyer–Villiger rearrangement. In 1951, Friess and Soloway postulated that the formation of the Criegee intermediate (Scheme 13, step 4) was slow and constituted the rate-determining step.[66]



Scheme 13. Possible reaction mechanisms of the Baeyer–Villiger oxidation depending on the acidity of the reaction medium (decreasing from left to right)

In contrast, Hawthorne and Emmons did not consider the formation of the Criegee intermediate as rate-determining (Scheme 13, step 4), but its rearrangement (step 7, Scheme 13).[82] Their results were confirmed by Simamura and co-workers studying the reaction rates of various benzophenones with perbenzoic acid.[83] Isotopic labeling experiments were not definite and could be interpreted for both rate-determining migration and rate-determining addition. The authors of the original work on the ^{14}C labeling of the migrating carbon atom, Palmer and Fry, postulated that "the present isotope effect results [see Table 4] lead unambiguously to the conclusion that the present reaction is concerted. No isotope effect would be expected for rate-determining formation of [the Criegee intermediate (step 4, Scheme 13)] ... since those steps do not involve significant alternation of the bonding at the labeling position."[84] In 1993, Krow just considered the value for the *p*-methoxyacetophenone which has a negligible carbon isotope effect $k^{12}/k^{14} = 0.998$ (entry 1, Table 4) and concluded that "the absence of an isotope effect is consistent with the rate-controlling addition of peracid to the ketone carbonyl."[69] Actually, the data of Table 4 show nicely the change of the rate-determining step from addition to migration with a change of substituents. In the case of *p*-methoxyacetophenone, the migrating substituent had a rather good migration ability due to its electron-donating substituent in *para* position. The addition was rate-determining and no isotope effect was observed (entry 1, Table 4). In contrast, the electron-withdrawing CN substituent in *para* position lowers the migration ability of the aryl substituent and the rearrangement step became slower and decisive. Consequently, an isotope effect of $k^{12}/k^{14} = 1.084$ was obtained (entry 5, Table 4). This is a convincing example that there is no simple law for the kinetics of the Baeyer–Villiger oxidation since different substituents, even far away from the reaction center, are able to modify the kinetics of the reaction. Data on the secondary deuterium isotope effect that favor the migration as rate-determining step have been collected.[85]

Table 4. Rates and ^{14}C kinetic isotope effects for the oxidation of *para*-substituted [1-^{14}C]acetophenones with *meta*-chloroperbenzoic acid in chloroform at 32°C[84]



Entry	X	$k \times 10^3$	k^{12}/k^{14} Ester	k^{12}/k^{14} Ketone
1	CH_3O	40.3	0.998	0.998
2	CH_3	19.1	1.032	1.033
3	H	4.53	1.048	1.048
4	Cl	3.39	1.049	1.052
5	CN	0.50	1.084	1.085

One problem concerning the kinetics of the Baeyer–Villiger reaction was addressed by Friess and Soloway. They observed a general acid catalysis with weak acids.[55][66] This had a crucial consequence for the comparison of results on the kinetics of the Baeyer–Villiger reaction taken from different publications. A comparison was impossible because acid is a by-product in a variable amount in peracid synthesis and was not removed prior to the use of the peracid since it was considered as being negligible. Furthermore, under certain conditions (in acetonitrile/1,2-dichloroethane solution), Hawthorne and Emmons observed a pronounced acid catalysis with trifluoroperacetic acid (TFPAA).[82] The by-product from peracid reduction, trifluoroacetic acid, enhanced the reaction rate as required for an autocatalytic reaction. An additional fact in favor of the acid catalysis was obtained by Rassat and Ourisson.[80] They reported a rate-retarding effect when employing TFPAA in the presence of Na_2HPO_4, i.e. when the acidity of the medium was reduced. A very convincing example was provided by Doering and Speers.[57] Using 13 vol-% of concentrated sulfuric acid as solvent, they were able to speed up the oxidation of benzophenone from eight days in pure acetic acid to only half an hour. Unfortunately, the acid catalysis was more complicated than a simple first-order dependence because the catalytic action of sulfuric acid went through a maximum depending on the structure of the ketone being oxidized.[57,86] All these examples demonstrate that statements on the kinetics of the Baeyer–Villiger reaction should take in account the acidity of the reaction solution. Reports on kinetics without the exact amount and the type of acid present in the reaction are useless.

Besides of the acid catalysis, heterogeneous bicarbonate as base also accelerated Baeyer−Villiger oxidations with *meta*-chloroperbenzoic acid (*m*CPBA) in dichloromethane, the rate was approximately doubled.[87] This was rationalized by the removal of the hydroxy proton in the Criegee intermediate. The deprotonated adduct was supposed to rearrange more easily than the neutral one (step 8 versus step 7, Scheme 13).[88] The rate acceleration was probably not caused by increased nucleophilicity through deprotonation of the peracid. As Baeyer and Villiger reported the protonation of the sodium salt of PBA with H_2CO_3 to obtain PBA and $NaHCO_3$,[4] the back reaction should be disfavored for PBA and in the same manner for *m*CPBA. The pK_a values for *m*CPBA and PBA of 7.60 and 7.78 (at 25°C), respectively, are in the same range.[89] A general disadvantage of the basic medium was the enhanced decomposition of the peracids to the corresponding acids.[89]

Besides of the amount of acid present in the reaction mixture, the substrate itself with its substitution pattern and its geometry has a huge influence on the reaction rate. It has already been mentioned that, for example, the *ortho* substituents of mesityl phenyl ketone are able to block the nucleophilic attack on the carbonyl group (entry 7, Table 2).[57] However, an aryl substituent at the carbonyl carbon atom alone has a rate-retarding effect. This is evident when comparing the reactivity of acetophenone (**1h**), cyclohexyl methyl ketone (**1i**) and cyclohexyl phenyl ketone (**1j**) with PBA (Table 5).[54,90,91] For the methyl-substituted ketones **1h** and **1i**, as already mentioned, the migration of the other more substituted group gives the corresponding acetates **3h** and **3i** (entries 1 and 2, Table 5). The reaction rates for these two ketones are very different. The conversion of the aliphatic compound **1i** is faster than of the aromatic one **1h** (Figure 4).

Table 5. Influence of an aromatic substitution of the ketone on the product distribution of the Baeyer−Villiger oxidation with PBA after 10 days reaction time

Entry	Substrate			Yield[a]	Product distribution[b]
		R^1	R^2	[%]	**3/4**
1	**1h**	Ph	Me	63	100:0
2	**1i**	cyclohexyl	Me	67	100:0
3	**1j**	cyclohexyl	Ph	85	84:16

[a] For the susbtrates **1h** and **1i** based on the converted ketone; conversion is not given;[54] for substrate **1j**, yield of isolated material.[91] − [b] Product distribution normalized to 100.

The intramolecular competition of the migration ability of the phenyl group and the cyclohexane substituent in ketone **1j** indicated that the cyclohexyl group migrated preferentially over the phenyl group and the ester of benzoic acid **3j** is obtained as main product (entry 3, Table 5). Since the same substituent is migrating in the substrates **1i** and **1j**, the transition state should be very similar in terms of energy and similar reaction rates are expected. However, Figure 4 shows that the oxidation of ketone **1j** proceeds significantly slower than that of ketone **1i** in which the carbonyl group

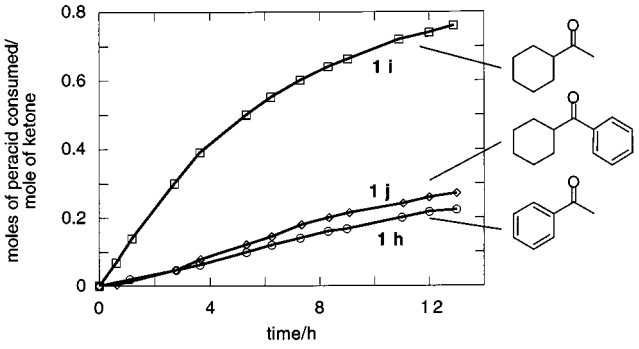


Figure 4. Reaction rates of the Baeyer−Villiger Oxidation for the ketones **1h−j** and perbenzoic acid from reference[91]

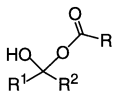
is not conjugated with an aromatic substituent. The reaction rate for ketone **1j** was rather in the same range as for acetophenone (**1h**). This indicates clearly that the conjugation of the carbonyl group with an aromatic substituent significantly decreases the reactivity of the ketone towards the Baeyer−Villiger oxidation. Consequently, qualitative conclusions on the reaction rates based on the migration ability of the migrating substituents are not correct. This example also contradicts the postulation that the rearrangement of the Criegee intermediate is rate-determining (step 7, Scheme 13). If so, the reaction rates would be in the same range for substrates **1i** and **1j**, because the decisive factor should be the nature of the migrating substituent, which in these two cases is the same. The rate-retarding effect of the phenyl group could not be explained. The different reactivities of aromatic and aliphatic ketones also became obvious by comparing reaction times qualitatively. Cyclohexanone is completely oxidized within 6.5 h with peracetic acid[92] or with perbenzoic acid[55] whereas for acetophenone and perbenzoic acid 10 days are necessary;[66] for benzophenone and peracetic acid 8 days.[57]

As clearly demonstrated above, the acid plays a role in the kinetics of the Baeyer−Villiger oxidation. Focusing on the acid strength some logical connections become obvious. Hawthorne and Emmons worked with deactivated aromatic ketones and trifluoroperacetic acid (TFPAA) when they found that the rearrangement step was rate-determining and not the addition step. In the same article they reported the protonation of the ketone by trifluoroacetic acid (TFAA), a by-product of the peracid synthesis and also a by-product of the Baeyer−Villiger oxidation. Consequently, they did not form the Criegee intermediate from the neutral ketone (step 4, Scheme 13), but after protonation (step 1) from the activated carbocation (step 3). This step should be by far faster than when from a neutral ketone (step 4) and the rearrangement became rate-determining. Alternatively, due to the strongly acidic medium, the reaction may proceed through a protonated Criegee intermediate (steps 2 and 6, Scheme 13; the indicated position of the proton is arbitrary; protonation of the carbonyl group is also reasonable). The activation by protonation of the ketone seemed to be important for the reactivity of TFPAA. Sager and Duckworth explained the enhanced reaction rates by the fact that strong acids are better leaving groups than weak

ones and should speed up the reaction.[93] However, a rate-retarding effect under buffered conditions as observed by Rassat and Ourisson can only be rationalized by a decreased acid catalysis and not by the nature of the leaving group.[80]

The results of Hawthorne and Emmons concerning the rate-determining step have been confirmed completely by Simamura and co-workers.[83] As oxidant they employed perbenzoic acid in dichloroacetic acid as solvent. This acid had also been shown to protonate all investigated substituted benzophenones. Consequently, the rate of the addition is increased and their "observation strongly suggested that the formation of the isomeric esters from the adduct was the rate-determining step in the Baeyer−Villiger reaction, at least under the present experimental conditions in agreement with Hawthorne and Emmons′ conclusion".[83]

Whereas the effect of strong acids (trifluoroperacetic acid, dichloroperacetic acid, or sulfuric acid) and the influence of base (Na_2HPO_4) on trifluoroperacetic acid is easy to rationalize by activation of the ketone by protonation, the action of weak acids such as benzoic acid or acetic acid is difficult to explain. Additionally, the reports in literature are contradictory. Acceleration by acid catalysis has been reported,[55,66] but also rate-enhancement under buffered conditions.[87] In contrast to the anions of strong acids, a deprotonated weak acid should tend to add to the carbonyl compound to form the adduct **13**. The formation will compete with the addition of the peracid and will inhibit the Baeyer−Villiger reaction. By employing heterogeneous bicarbonate, the acid but not the peracid is deprotonated. The acid anion is less soluble and precipitates, so the formation of rate-retarding adduct **13** is avoided. The rate enhancement by bicarbonate addition is only observed when using *m*CPBA in a non-hydrogen-bonding solvent like $CHCl_3$ or CH_2Cl_2.



13

In summary, it is clear that in the Baeyer−Villiger reaction several steps can be rate-determining depending on the reaction conditions and the substrate itself and "under the present experimental conditions" should be added to all statements on kinetic studies performed on the Baeyer−Villiger reaction.

Further Interesting Aspects

During one century of Baeyer−Villiger oxidation, the reaction has been used in the preparation of many different organic molecules. Many examples are collected in the recent review of Krow.[69] Polycyclic substrates showed often an abnormal selectivity for the migration step in the Baeyer−Villiger rearrangement which was influenced by many different factors. The reactivity of these substrates has also been reviewed by Krow.[94] Noyori has postulated stereoelectronic conditions for the transition state based on remote substituent influences.[95,96] An interesting oxidant for the Baeyer−Villiger reaction, bis(trimethylsilyl)monoperoxysulfate, has been introduced by Adam.[97] As shown in labeling experiments, the reaction proceeded via the dioxirane.[98] Theoretical models have been reported in the literature,[99] as well as ab-initio and semi-empirical studies of the rearrangement.[100] Metal-catalyzed Baeyer−Villiger oxidations have been recently reviewed by Strukul[101] (the work of Bolm[102] on the asymmetric version with a chiral Cu complex has been discussed in this review). It should be noted that the Baeyer−Villiger reaction is easily performed by enzymes such as flavin-dependent peroxygenases. This aspect has been reviewed by Walsh,[103] Alphand and Furstoss,[104,105] and Roberts and Wan.[106] Many cyclic ketones are oxidized by the cyclohexanone oxygenase isolated from the bacteria *Acinetobacter* NCIB 9871,[107−109] or by modified yeast[110] as well as by microorganisms.[111−112]

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[5] For a biography of Heinrich Caro see: A. Bernthsen, *Angew. Chem.* **1911**, *24*, 1059−1064.
[6] H. Caro, *Angew. Chem.* **1898**, 845−846.
[7] The triple salt is now commercially available (commercial names: Caroat®, Curox®, Oxone®) with a higher content of active oxygen and the following composition: 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. It became very popular with the discovery of the dioxirane formation with ketones and the oxidation power of the latter. However, the oxidant "$KHSO_5$" is also one of the best oxygen atom donors with metal catalysts for the generation of high-valent metal-oxo species. For a review see: B. Meunier, *New J. Chem.* **1992**, *16*, 203−211.
[8] A. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 124−126.
[9] A very curious point in the series of the publications of Baeyer and Villiger on peracids and ketone oxidation is that they also discovered the organic peracids and compared them with Caro′s acid but they never carried out the reaction that one now has in mind when talking about the Baeyer−Villiger reaction, namely the oxidation of a ketone with an organic peracid.
[10] A. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1569−1585.
[11] One of these chemical properties was the reaction with benzoyl chloride to form the symmetrical benzoyl peroxide.
[12] The sulfate was removed before starting the analysis by precipitation with $Ba_3(PO_4)_2$. After reduction of $H_2S_2O_8$ and H_2SO_5, the newly formed sulfate was determined quantitavely by means of the same method. This analysis was optimized by Traube; cf. ref.[22,23]
[13] The work of Richarz should also be cited here. However, to discuss it in details would be too great a diversion; he reported the electrochemical formation of persulfuric acid and hydrogen peroxide: F. Richarz, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 1669−1674.
[14] For a biography of Marcelin Berthelot see: G. Bredig, *Angew. Chem.* **1907**, *20*, 689−694.

[15] Berthelot described first the persulfuric acid as being an anhydride. He obtained it by subjecting a well-cooled mixture of sulfurous anhydride and oxygen to the "silent discharge" in an ozone tube. However, the product of this reaction was not stable in solution.
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