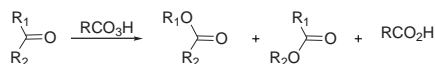


# Use of Theoretical Chemistry To Explain Baeyer–Villiger Oxidations of Methoxy Aromatic Aldehydes

N. Anoune, H. Hannachi, P. Lantéri, R. Longera, and C. Arnaud

Laboratoire de Chimiométrie et Synthèse Organique, CPE-Lyon, 43 Boulevard du 11 Novembre 1918, Villeurbanne Cedex F. 69622, France

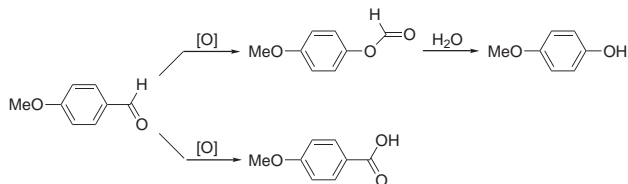
Students are taught that the Baeyer–Villiger reaction is an efficient way to transform ketones into esters using a peroxyacid as the oxidizing agent (1). The insertion of an oxygen into the  $Csp^2$ – $Csp^3$  bonds of ketones is explained by the migrations of alkyl groups during the rearrangement step:



The experimental study of the regioselectivity of the reaction constitutes an interesting project for advanced students. This is presented in two parts. A preliminary work consisting of the application of this reaction to *p*-methoxybenzaldehyde ( $R_1 = p\text{-CH}_3\text{O-C}_6\text{H}_4$  and  $R_2 = \text{H}$ ) uses monopersuccinic acid (PSA) as an alternative to *m*-chloroperoxybenzoic acid (mCPBA). The focus of the project is the oxidation of different polymethoxybenzaldehydes by PSA and the interpretation of the results using frontier MO theory.

The purpose of the preliminary work is to answer the following questions. Will the oxidation of *p*-methoxybenzaldehyde be achieved under the conditions of a Baeyer–Villiger reaction? If so, what will be the major product and what is the best peroxyacid for this reaction?

The oxidation of aromatic aldehydes into benzoic acids is well known. If the Baeyer–Villiger oxidation is the major pathway, the migration of the *p*-methoxyphenyl group (giving the formate) is more efficient than that of H (migrating as a hydride to give the carboxylic acid). This is a priori in good agreement with the strong electron density on the aromatic nucleus. Finally, the hydrolysis of the formate gives the phenol:



mCPBA is the most widely used peroxyacid, but a current tendency is to seek other peroxyacids that are equally efficient and less hazardous (explosions have been reported) (2). Monopersuccinic acid (PSA) may be used and it has the advantage of being water-soluble. The reactions were carried out at 55 °C in a biphasic medium ( $\text{CHCl}_3$ – $\text{H}_2\text{O}$ ) and the results obtained in 3 hours were comparable to those with mCPBA in  $\text{CH}_2\text{Cl}_2$  (3). In both cases the *p*-methoxyphenol is obtained in good yield (Table 1).

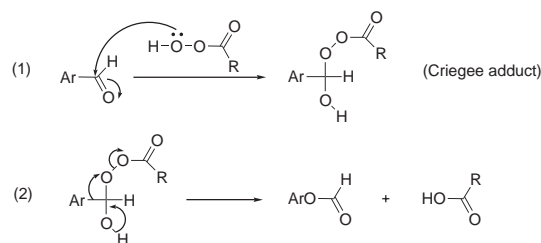
## Results and Discussion

The preliminary work having shown that the Baeyer–Villiger oxidation of a methoxybenzaldehyde could be achieved with PSA in a good yield, the most important part of the experimental section consists of an extension of this reaction to different polymethoxybenzaldehydes.

The experimental conditions chosen were PSA at 55 and 70 °C and PSA in basic medium at 82 °C.

### Oxidation with PSA at 55 and 70 °C

Formates were the major products at 55 °C (Table 2) and a gentle warming to 70 °C is sufficient to hydrolyze them into phenols in  $\text{CHCl}_3$ – $\text{H}_2\text{O}$  medium. From a mechanistic point of view, the synthesis of formates is explained in two steps:



If the second step is rate determining, as is usually the case in the Baeyer–Villiger rearrangement (4), the driving force in the migration of the aryl groups would be the electron density on the aromatic nucleus. Owing to the electron donating effects of  $\text{OCH}_3$  in the ortho and para positions, the reactivities for dimethoxy compounds should be  $2 > 1 > 3$ . In fact, however, the observed sequence is  $1 > 2 > 3$  (Table 2). This inversion may be explained if the first step in the mechanism is considered as rate determining when the dimethoxy compounds are oxidized with PSA at 55 °C.

Theoretical calculations (MOPAC/PM3 and Sybyl 6.01) were used to determine which factors are likely to explain the particular behavior of these dimethoxy compounds. The parameters able to intervene in the first step were HOMO (PSA)–LUMO (aldehydes) interactions, electronic densities on the carbons of the carbonyl groups in the aldehydes, and the energy of interaction between the peroxyacid and the aldehydes (Table 3). Students not familiar with MO calculations are advised to read a reference book (5).

The LUMOs of aldehydes have their highest orbital co-

Table 1. Oxidation of *p*-Methoxybenzaldehyde at 55 °C

Peroxy Acid	Medium	Time/h	Yield <i>p</i> -Methoxyphenol
mCPBA	$\text{CH}_2\text{Cl}_2$	5	92%
PSA	$\text{CHCl}_3$ – $\text{H}_2\text{O}$	3	93%

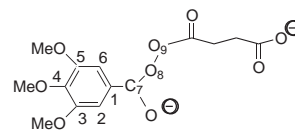
efficient on the carbons of the carbonyl groups. The HOMO of PSA has its highest coefficient on the hydroxylic oxygen. This supports the first step as a nucleophilic addition of PSA into the CHO group. The observed sequence of reactivities is in agreement with the calculated energies of interactions but not with HOMO–LUMO interactions. This discrepancy is not surprising because the energies of interactions are the calculated minima of the energies developed by the different systems of two reactants as these approach each other. This makes the energy of interactions a more appropriate parameter than frontier orbital interactions for understanding the first step.

#### Oxidation with PSA in Basic Medium (Table 4)

These results were more varied. The phenols were, as a rule, the major products, except for 2,4,6-trimethoxybenzaldehyde, **4**, for which the 2,6-dimethoxyquinone was the only product.

All the results in basic medium may be explained if the second step is rate determining. The calculated interactions between the HOMO of the migrating aryl groups and  $\sigma^*$  of the O–O bond in the Criegee intermediate were in good agreement with the observed experimental sequence (Table 5).

The particularly low conversion rate for the 3,4,5-trimethoxybenzaldehyde, **5**, may be explained with theoretical calculations: a dihedral angle C-1–C-7–O-8/C-7–O-8–O-9 of 180° (**6**, **7**) favors an easy migration of the aryl group towards oxygen O-8 (see structure below).



It has been found for compound **5** that a dihedral angle of 144° does not induce a high orbital coefficient on the aromatic carbon C-1 but does induce a high coefficient on the carbon C-4, making the migration more difficult. Successive optimizations on MOPAC/PM3 lead at best to this dihedral angle of 144°. The conformation of the molecule then has the methoxy group on C-4 lying in the plane of the aromatic ring and the two methyls of OCH<sub>3</sub> groups on C-3 and C-5 being disposed at a right angle to this plane, which minimizes the steric bulkiness. Theoretical calculations help us to understand the poor results in this reaction due to the deviation from 180 to 144° of the dihedral angle. Students should keep in mind that MO theory suffers some limitations. The barrier of interconversion of conformers may be low and the thermal energy of the reaction may overcome it. Without the knowledge of this last parameter, it is not possible to solve this problem.

#### Conclusions

The experimental part of the project consists in the application of the Baeyer–Villiger oxidation to various polymethoxybenzaldehydes, using PSA, an efficient peroxyacid in a biphasic medium (CHCl<sub>3</sub>–H<sub>2</sub>O). One of the primary reasons for this article is to show advanced students that frontier MO theory can help to explain the results. At 55 °C, the observed sequence of reactivity for dimethoxybenzaldehydes is in agreement with the first step as rate determining, the energy of interactions then being a better parameter than HOMO–LUMO interactions. This is not the same in basic medium at 82 °C where the interactions between HOMO of the aryl groups and  $\sigma^*$  of O–O bonds are in accord with the second step determining rate. The low conversion for 3,4,5-trimethoxybenzaldehyde may be explained by a deviation of a dihedral angle in the transition state during the Baeyer–Villiger rearrangement.

#### Experimental Procedures

##### Preparation of Monopersuccinic Acid (PSA) (**8**)

**CAUTION:** This preparation must be carried out under a hood. All glassware must be passivated in 10% HNO<sub>3</sub> and 10% H<sub>2</sub>O<sub>2</sub> for 24 h before use.

Succinic anhydride (25 g, 0.25 mol) and 82.5 mg of an aqueous solution of diethylenetriamine pentaacetic acid, a quencher of metallic ions sold as Versenex 80, are warmed in 250 mL of CH<sub>2</sub>Cl<sub>2</sub> at 35 °C until complete solution. H<sub>2</sub>O<sub>2</sub> (70%, 13.5 g) is added dropwise over a period of 15 min, while using a mechanical stirrer. Five minutes after the end of the addition of H<sub>2</sub>O<sub>2</sub>, 2.67 g of Na<sub>2</sub>CO<sub>3</sub> is added over 30 min at 35 °C, followed by 3.0 g of 96% H<sub>2</sub>SO<sub>4</sub>. Stirring is continued for 30 min at 35 °C. The solid is filtered, washed twice with CH<sub>2</sub>Cl<sub>2</sub>, and dried in a cold air stream.

**Table 2. Oxidation of Polymethoxybenzaldehydes**

Benzaldehyde	Conversion (%)	Products (%)	
		Formates	Other
<b>1:</b> 2,5-dimethoxy-	93	80	–
<b>7:</b> 4-methoxy-	93	–	93 (phenol)
<b>6:</b> 2-methoxy-	86	86	–
<b>2:</b> 2,4-dimethoxy-	86	82	–
<b>3:</b> 3,4-dimethoxy-	80	68	–
<b>4:</b> 2,4,6-trimethoxy-	66	60	–
<b>5:</b> 3,4,5-trimethoxy-	55	34	–
<b>8:</b> 3-methoxy-	98	–	98 (acid)

NOTE: The oxidizing acid was PSA (2 equiv). The reaction was carried out in CHCl<sub>3</sub>–H<sub>2</sub>O medium for 3 h at 55 °C.

**Table 3. Calculated Parameters in Interaction of PSA with Aldehydes**

Benzaldehyde	$E_{\text{LUMO}}/$ eV	$ \Delta E /$ eV <sup>a</sup>	Charge <sup>b</sup>	Interaction energy/ (kcal/mol)
<b>2:</b> 2,4-dimethoxy-	-6.010	6.061	0.378	34.700
<b>1:</b> 2,5-dimethoxy-	-6.388	5.683	0.404	33.770
<b>3:</b> 3,4-dimethoxy-	-5.733	6.338	0.378	34.960
<b>4:</b> 2,4,6-trimethoxy-	-6.420	5.650	0.366	35.243
<b>5:</b> 3,4,5-trimethoxy-	-6.374	5.697	0.367	36.412

<sup>a</sup> $\Delta E = E_{\text{HOMO(PSA)}} - E_{\text{LUMO(aldehydes)}} - E_{\text{HOMO(PSA)}} = -12.071$  eV.

<sup>b</sup>Electronic density on the carbonyl carbon.