

Photo-oxidative Fragmentation of Some α -Alkyl Substituted 4-Methoxybenzyl Alcohols and Methyl Ethers Sensitized by TiO₂

Enrico Baciocchi,^{a,*} Massimo Bietti,^{a,†} Marina I. Ferrero,^b Cesare Rol^{b,*} and Giovanni V. Sebastiani^{c,*}

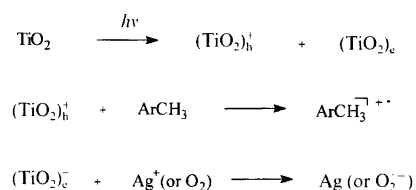
^aDipartimento di Chimica, Università 'La Sapienza', P.le A. Moro, 5 00185 Roma, Italy, ^bDipartimento di Chimica and ^cIstituto per le Tecnologie Chimiche, Facoltà di Ingegneria, Università di Perugia, 06100 Perugia, Italy

Dedicated to Professor Lennart Ebersson on the occasion of his 65th birthday

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The TiO₂-catalyzed photo-oxidation of some α -alkyl substituted 4-methoxybenzyl alcohols and ethers [4-MeOPhCH(OR)Y] has been investigated in MeCN, in the presence of Ag₂SO₄. When Y = *t*-Bu, the intermediate radical cation undergoes exclusive C _{α} -H bond cleavage (leading to the corresponding ketone) if R = Me, but predominantly C _{α} -C _{β} bond cleavage (leading to 4-MeOPhCHO) if R = H. The C _{α} -H bond cleavage path is also the major one when Y = *i*-Pr and R = H. For the substrates where Y = CH(OMe)Me or CH(OH)Me, exclusive C-C bond cleavage is observed when R is either H or Me. A similar situation holds when the photo-oxidations are carried out in the presence of oxygen, however a change in the outcome of the reaction has been observed for the substrates where R = Me and Y = *t*-Bu or CH(OMe)Me, which both form 4-MeOC₆H₄CO₂Me as the exclusive product. These results are interpreted on the basis of the structural effects on the fragmentation reactions of the intermediate radical cations, the stability of the formed carbon radicals and carbocations, as well as the possible reactions of the former with oxygen.

Photoinduced electron transfer reactions are one of the most useful tools to generate radical cations and to study their reactivity.¹ Generally, soluble sensitizers are used and the reactions are carried out under homogeneous conditions. The reduced form of the sensitizer, however, or in some case also the sensitizer itself, can intervene in the reactions following the electron transfer step, thus making the composition of the reaction products and the interpretation of the results more complex. This complication can be avoided by working under heterogeneous conditions with TiO₂ (a semiconductor) as the sensitizer. In this case, by the action of light on the TiO₂ crystal, a positive hole is generated together with an electron, as shown in Scheme 1. The positive hole can interact with adsorbed substrates having an oxidation potential < 2.3 V in MeCN^{2,3} to form a radical cation, whereas the photogenerated electron can be scavenged



Scheme 1.

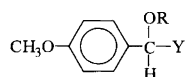
by O₂ or Ag⁺. Since the photocatalyst of course remains intact, the study of the reaction products deriving from the radical cation is significantly simplified, thus making it easier to obtain information on its chemical pathways. In addition, the role of absorption phenomena in this respect can also be investigated.

In this context, we recently studied the photo-oxidation of 1-aryl-2-propanols and their methyl ethers catalyzed by TiO₂ in MeCN. Useful information was obtained on the competition between C _{α} -H and C _{α} -C _{β} bond cleavage in the side-chain fragmentations of the radical cations of β -hydroxy and β -alkoxy-substituted alkylaromatics.⁴

* To whom correspondence should be addressed.

† Present address: Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma 'Tor Vergata'.

An extension of this work aimed also at determining the role of α -OH and α -OR groups in such a competition seemed of interest, especially in the light of recent results⁵ indicating that α -OH groups can favor the C–C bond cleavage path in aromatic radical cations as efficiently as β -OH groups. Thus, we have investigated the TiO₂-sensitized photo-oxidation of a number of α -substituted 4-methoxybenzyl alcohols and some of their methyl ethers (compounds 1–6), using Ag⁺ to scavenge the photogenerated electrons. The results of this investigation are reported in this paper.



	R	Y
1	CH ₃	C(CH ₃) ₃
2	H	C(CH ₃) ₃
3	H	CH(CH ₃)CH ₃
4	CH ₃	CH(OCH ₃)CH ₃
5	H	CH(OCH ₃)CH ₃
6	H	CH(OH)CH ₃

Results

A solution of 0.30 mmol of substrate in 25 ml of MeCN was subjected to external irradiation by a 500 W high-pressure mercury lamp, with Pyrex filter, in the presence of 130 mg of TiO₂ and 0.30 mmol of Ag₂SO₄, with gentle bubbling of N₂ or O₂. During the irradiation Ag was formed (presumably deposited on TiO₂).^{4,6,7} After irradiation, work-up of the reaction mixture was performed as usual (see Experimental) and the isolated products were characterized by spectroscopic methods and/or comparison with authentic specimens. Quantitative analysis of the reaction products and unchanged substrate was performed by ¹H NMR spectroscopy and by VPC in the presence of suitable internal standards. The material balance was generally satisfactory (in the range 85–95%).

The products obtained under nitrogen and the corres-

ponding yields are reported in Table 1. It is noteworthy that in the reaction of ether 1 only *tert*-butyl 4-methoxyphenyl ketone is formed, whereas the photo-oxidation of the corresponding alcohol 2 produces mainly anisaldehyde accompanied by very small amounts of ketone. With 3 (Y = *i*-Pr) the main product is again the corresponding ketone (together with a small amount of anisaldehyde). The reactions of 4, 5 and 6 form exclusively anisaldehyde, in yields which increase on going from 4 to 6.

The experiments carried out under oxygen exhibited similar efficiency to those under nitrogen. The products formed and their yields are reported in Table 2. In the reactions of 2, 5 and 6, the products were the same as under nitrogen; with 2, the aldehyde/ketone ratio is also practically the same. However, a different situation holds for the photo-oxidation of 1 and 4 in the presence of oxygen; both these compounds form methyl 4-methoxybenzoate as the exclusive reaction product, whereas, as shown in Table 1, under nitrogen, 1 and 4 form the corresponding ketone and anisaldehyde, respectively. A final observation is that the reactions in the presence of oxygen were much less efficient when carried out in the absence of Ag⁺, in line with previous observations.⁶

Discussion

Photo-oxidation in deaerated media. From the data in Table 1, it can be seen that when Y is *tert*-butyl (*t*-Bu) a quite drastically different situation arises depending on whether R is Me or H. In the former case (substrate 1), only formation of the ketone 4-MeOC₆H₄CO-*t*-Bu is observed, whereas in the second case (substrate 2) 4-MeOC₆H₄CHO is by far the main product and only small amounts of the ketone are formed. Anisaldehyde and 4-MeOC₆H₄CO-*i*-Pr are the products of the photo-oxidation of 3 (R = H, Y = *i*-Pr), with the latter predominant. In all the above reactions, the formation of the ketone can be rationalized by suggesting that the inter-

Table 1. Product yields in TiO₂-photosensitized oxidation of some α -substituted 4-methoxybenzyl alcohols and methyl ethers in deaerated CH₃CN, in the presence of Ag₂SO₄.^a

Substrate [R,Y]	t/min	Unchanged substrate	Products (%)	
			CH ₃ O-C ₆ H ₄ -CHO	CH ₃ O-C ₆ H ₄ -C(=O)-Y
1 [CH ₃ , C(CH ₃) ₃]	120	81	<0.5	10
2 [H, C(CH ₃) ₃]	15	58	27	2
	30	38	42	5
3 [H, CH(CH ₃) ₂]	30	67	4	18
4 [CH ₃ , CH(OCH ₃)CH ₃]	15	83	13	<0.5
5 [H, CH(OCH ₃)CH ₃]	15	51	41	<0.5
6 [H, CH(OH)CH ₃]	15 ^b	7	79	<0.5

^aThe average error is $\pm 10\%$ of the reported value. ^bIn the absence of TiO₂ no reaction is observed.

Table 2. Product yields in TiO₂-photosensitized oxidation of some α -substituted 4-methoxybenzyl alcohols and methyl ethers in CH₃CN, in the presence of Ag₂SO₄ and oxygen.^a

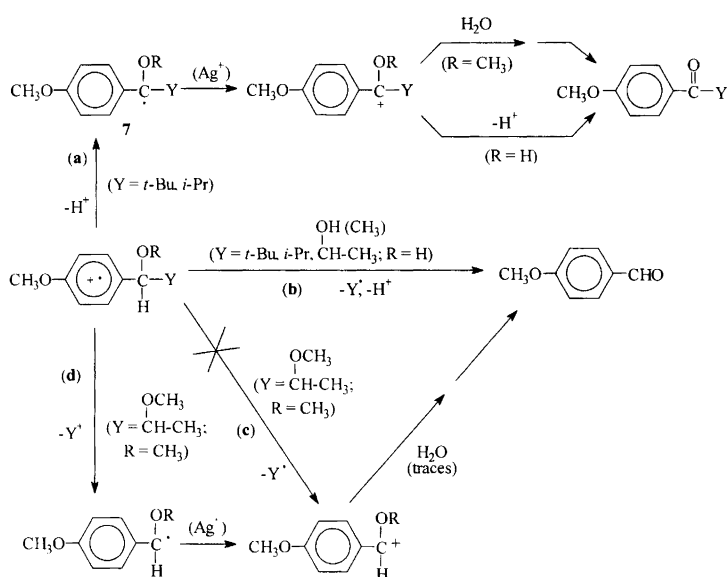
$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{C}(\text{OR})(\text{H})-\text{Y} \xrightarrow[\text{CH}_3\text{CN, O}_2]{\text{TiO}_2, \text{hv, Ag}_2\text{SO}_4} \text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CHO} + \text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{C}(\text{OCH}_3)=\text{O}$			
Substrate [R, Y]	t min	Unchanged substrate	Products (%)
1 [CH ₃ , C(CH ₃) ₃]	60	81	< 0.5
2 [H, C(CH ₃) ₃]	15	44	38
4 [CH ₃ , CH(OCH ₃)CH ₃]	15	77	< 0.5
	960	—	< 0.5
	1080 ^c	67	< 0.5
5 [H, CH(OCH ₃)CH ₃]	15	39	48
6 [H, CH(OH)CH ₃]	15 ^d	34	50
	15 ^e	47	38
	60	7	78 ^e

^aThe average error is $\pm 10\%$ of the reported value. ^b*tert*-Butyl 4-methoxyphenyl ketone. ^cWithout silver sulfate. ^dIn the absence of TiO₂ no reaction is observed. ^eAnisaldehyde (38%) and anisic acid (40%).

mediate radical cation undergoes a deprotonation process (Scheme 2, path **a**) to form a benzyl radical,⁸ which is oxidized (presumably by Ag⁺) directly to the ketone (in its protonated form) when R = H, or to the corresponding carbocation, when R = Me. The latter is then converted into ketone by reaction with adventitious water present in the medium. Deprotonation, however, is only a minor route for the intermediate radical cation **2**⁺ which, accordingly, undergoes nearly exclusively C–C bond cleavage (Scheme 2, path **b**), leading to anisaldehyde and the *t*-Bu radical. Clearly, the observation that the C–C bond cleavage route is completely absent in **1**⁺, where the OH group has been replaced by the MeO group, fully confirms recent results⁵ indicating the very important role of an α -OH group in favoring the cleavage of the C _{α} –C _{β} bond in alkylaromatic radical cations. The

interaction of a base with the O–H hydrogen was suggested to be important in the transition state of the C–C bond cleavage reaction. With a base as strong as OH[–], deprotonation to form a benzyloxy radical can be envisaged.^{5,9} In the present case, the radical cation is probably adsorbed onto the TiO₂ surface and the α -OH group may interact with the TiO₂ basic sites.¹⁰

The C–C bond pathway is much more important with **2**⁺ than with **3**⁺ (Y = *i*-Pr), where it is a minor route with respect to deprotonation, which is an expected result on the basis of the greater stability of the *tert*-butyl than of the isopropyl radical. A role played by stereoelectronic effects^{8,11} can also be envisaged. Accordingly, deprotonation should be a slower process with **2**⁺ than with **3**⁺ since the alignment of the C–H bond to be cleaved with the π -system (required to allow the intramolecular



Scheme 2.

electron transfer from the former to the latter), is made energetically more costly when Y is *t*-Bu than when it is *i*-Pr.

When Y is a hydroxy- or methoxy-substituted alkyl group (substrates 4–6), anisaldehyde is always the exclusive reaction product, when R is either H or Me. Clearly, the presence of an alkoxy or hydroxy group on both C_α and C_β makes the C–C bond cleavage the route most favored by the intermediate radical cation, which is in line with previous results as well as with theoretical calculations.^{5,12} The rationalization is that these groups weaken the C–C bond and moreover stabilize the positive charge which has to be transferred to the bond to be cleaved in the transition state of the cleavage process.¹¹ With 5⁺ and 6⁺ (R=H), the C–C bond cleavage should be assisted by the OH group⁵ (Scheme 2, path b). Such assistance is not possible for 4⁺ (R=Me) and both paths c (homolytic cleavage of the C–C bond) and d (heterolytic cleavage of the C–C bond) are therefore possible, with the former slightly favored thermodynamically [the E° value for the 4-MeOC₆H₄(OMe)CH⁺/4-MeOC₆H₄(OMe)CH· couple, –0.51 V (vs. SCE),¹³ is more negative than that for the Me(OMe)CH⁺/Me(OMe)CH·, –0.45 V].¹⁴ However, the drastically different behavior of 1⁺ (exclusive deprotonation) and 4⁺ (exclusive C–C bond cleavage) appears to support the heterolytic pathway. Accordingly, were the C–C bond of 4⁺ to cleave in a homolytic fashion it would be very difficult to explain why this path is completely absent in 1⁺, as similar stability can reasonably be predicted for the radicals Me(MeO)CH· and *t*-Bu·. In fact, heterolytic C–C bond cleavage is much more favored in 4⁺ than in 1⁺ since Me(MeO)CH⁺ (E° = –0.45 V) is much more stable than *t*-Bu⁺ (E° = 0.09 V).^{14,15} In addition, heterolytic breakage of the C–C bond in 4⁺, a conclusion confirmed by the results obtained in the presence of oxygen (*vide infra*), is also in line with the Maslak prediction of a lower intrinsic barrier for this type of rupture with respect to the homolytic one for the β-C–C bond in alkylaromatic radical cations.¹⁶

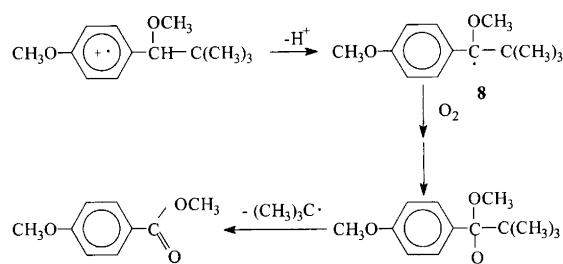
Photo-oxidation in the presence of oxygen. The data in Table 2 show that in all cases where R=H, the same products are obtained as those observed in deaerated MeCN. More significantly, in the photo-oxidation of 2, the aldehyde/ketone ratio is also practically the same as in the absence of oxygen, which indicates that oxygen does not modify the competition between the two pathways (C–H and C–C bond cleavage) available to the radical cation. This observation might suggest that the quite strong base O₂^{·-} is not formed, Ag⁺ being responsible, also in the presence of oxygen, for most of the scavenging of the photogenerated electrons.⁷ However, we should also consider that even though O₂^{·-} is formed, it might not influence the relative importance of the deprotonation pathway, since the deprotonation of the radical cation is probably carried out by the basic sites

present at the TiO₂ surface. Of course, the mechanisms described in Scheme 2 can also operate in the presence of oxygen, but another possibility is that the carbon radical 7 reacts with oxygen to form an α-hydroxy peroxy radical which is then converted into ketone.¹⁷

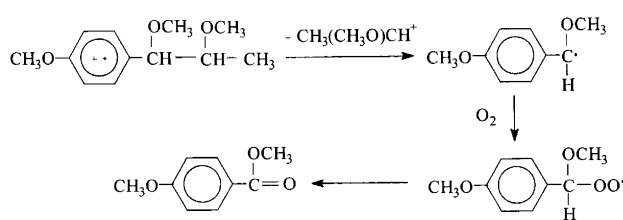
At variance with what is observed in the reactions of the substrates where R=H, oxygen plays an important role in the photo-oxidations of 1 and 4 (R=Me), which accordingly lead to the exclusive formation of methyl 4-methoxybenzoate, a product not observed when the same reactions were carried out under nitrogen. Since, as seen before, oxygen should not influence the type of cleavage (C–H or C–C bond cleavage) undergone by the radical cation, this result can reasonably be explained on the basis of the possible reactions between oxygen and the carbon radicals formed in the fragmentation process. Thus, deprotonation of 1⁺ leads to the carbon radical 8 (Scheme 3) which reacts with oxygen to form a tertiary peroxy radical. From the latter a benzyloxy radical can be produced, from which methyl 4-methoxybenzoate is formed by a β-fragmentation process.¹⁸ In 4⁺ the formation of the ester can be rationalized if the C–C bond cleavage takes place in a heterolytic fashion, as suggested before, leading to 4-MeOC₆H₄(OMe)CH· (Scheme 4). Reaction of this carbon radical with oxygen forms a secondary peroxy radical whose conversion into ester has already been proposed.¹⁹ On the other hand, a homolytic bond cleavage in 4⁺ can be excluded, since it would have led to anisaldehyde (Scheme 2, path c).

Experimental

¹H NMR spectra were run on a Bruker AC 200 (200 MHz) spectrometer, for solutions in CDCl₃. GCMS analyses were performed on a Hewlett–Packard 5890A gas chromatograph (SPB-1 and SPB-5 capillary columns, 30 m, 45–300 °C) coupled with a mass selective detector



Scheme 3.



Scheme 4.

5970 (70 eV). VPC analyses were carried out on an HP 5890 gas chromatograph using an SPB-5 capillary column (45–300 °C).

Materials. TiO₂ (anatase, dried at 110 °C), Ag₂SO₄, CH₃CN (HPLC grade) were commercial samples. 1-Methoxy-1-(4-methoxyphenyl)-2,2-dimethylpropane (**1**), 1-(4-methoxyphenyl)-2,2-dimethyl-1-propanol (**2**), 1-(4-methoxyphenyl)-1,2-dimethoxypropane (*erythro-threo* mixture) (**4**), 1-(4-methoxyphenyl)-2-methoxy-1-propanol (*erythro-threo* mixture) (**5**) and 1-(4-methoxyphenyl)-1,2-propanediol (*erythro-threo* mixture) (**6**) were available from a previous work.⁵ 1-(4-Methoxyphenyl)-2-methyl-1-propanol (**3**) was prepared by reaction of isopropyl magnesium bromide with 4-methoxybenzaldehyde in anhydrous tetrahydrofuran and purified by chromatography on a silica gel column (eluent petroleum ether–ethyl acetate 5:1), yield 65%. ¹H NMR (CDCl₃): δ 7.20 (d, *J*=11 Hz, 2 H, ArH), 6.85 (d, *J*=11 Hz, 2 H, ArH), 4.26 (d, *J*=6 Hz, 1 H, CH), 3.77 (s, 3 H, OCH₃), 1.91 (m, 1 H, CH), 1.87 (s, 1 H, OH), 0.98 (d, *J*=6 Hz, 3 H, CH₃), 0.75 (d, *J*=6 Hz, 3 H, CH₃).

Photochemical oxidation. Reactions were carried out by external irradiation (500 W high-pressure mercury lamp, Pyrex filter), with magnetic stirring and gentle N₂ bubbling, of an acetonitrile solution (25 ml) of the substrate (0.30 mmol), in the presence of TiO₂ (130 mg) and Ag₂SO₄ (0.30 mmol); the reactor was a cylindrical flask (Ø=1.6 cm, h=16 cm) equipped with a water cooling jacket and intensive condenser. After paper filtration of TiO₂, the reaction mixture was poured into water and extracted with ether. The analysis of the reaction products was performed by ¹H NMR spectroscopy in the presence of an internal standard (1,4-dimethoxybenzene or bibenzyl). The amount of unchanged substrate was determined, when possible, by ¹H NMR spectroscopy of the crude product or by VPC analysis of the reaction mixture before work-up, in the presence of an internal standard (1,4-dimethoxybenzene or bibenzyl). The material balance was always ≥85% based on the amount of starting substrate.

Reaction products. Products (isolated by column chromatography) were identified by comparison with authentic specimens or literature data. 4-Methoxybenzaldehyde, methyl 4-methoxybenzoate and 4-methoxybenzoic acid were commercial samples. *tert*-Butyl 4-methoxyphenyl

ketone was identified by comparison with literature data.²⁰

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