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Solvent Effect in the Free-Radical Oxidation and Electrophilic Ipso and Hydrogen Displacement of *p*-Methoxybenzyl Alcohol and *N*-(*p*-Methoxybenzyl)acetamide by Br_2

Anna Bravo,[*,†] Francesca Fontana,[‡] Barbara Dordi,[†] and Francesco Minisci[†]

Dipartimento di Chimica, Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy, and Dipartimento di Ingegneria, Università di Bergamo, viale Marconi 5, I-24044 Dalmine BG, Italy

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Introduction

Recently we have reported convenient, simple and highly selective methods under mild conditions (room temperature) for the oxidation of primary alcohols to aldehydes or esters, depending on the benzylic or aliphatic nature of the alcohol.[1,2] The reactions are based on the oxidation of the alcohol by H_2O_2 catalyzed by bromine or bromide ions in a two-phase system (eqs 1 and 2).

$$\text{Ar-CH}_2\text{OH} + \text{H}_2\text{O}_2 \xrightarrow[\text{or Br}^-]{\text{Br}_2} \text{Ar-CHO} + 2\,\text{H}_2\text{O} \qquad (1)$$

$$2\,\text{R-CH}_2\text{OH} + 2\,\text{H}_2\text{O}_2 \xrightarrow[\text{or Br}^-]{\text{Br}_2} \text{R-COOCH}_2\text{-R} + 4\,\text{H}_2\text{O} \qquad (2)$$

The reactions are promoted by ambient light, and the actual oxidant is Br_2, which operates by free-radical chain processes[1,2] in the organic phase (eqs 3−7); the formed HBr is continuously extracted by the aqueous phase and oxidized by H_2O_2 to Br_2 (eq 8), shifting the equilibrium of eq 3 to the right and making the process catalytic in bromine.

$$\text{Ar-CH}_2\text{OH} + \text{Br}^{\bullet} \rightleftharpoons \text{Ar-}\dot{\text{C}}\text{HOH} + \text{HBr} \qquad (3)$$

$$\text{Ar-}\dot{\text{C}}\text{HOH} + \text{Br}_2 \longrightarrow \text{Ar-CHO} + \text{HBr} + \text{Br}^{\bullet} \qquad (4)$$

$$\text{R-CHO} + \text{Br}^{\bullet} \longrightarrow \text{R-}\dot{\text{C}}\text{O} + \text{HBr} \qquad (5)$$

$$\text{R-}\dot{\text{C}}\text{O} + \text{Br}_2 \longrightarrow \text{R-COBr} + \text{Br}^{\bullet} \qquad (6)$$

$$\text{R-COBr} + \text{R-CH}_2\text{OH} \longrightarrow \text{R-COOCH}_2\text{-R} + \text{HBr} \qquad (7)$$

$$2\,\text{HBr} + \text{H}_2\text{O}_2 \longrightarrow \text{Br}_2 + 2\,\text{H}_2\text{O} \qquad (8)$$

Benzyl alcohols are much more reactive than the corresponding aromatic aldehydes toward hydrogen abstraction by $Br^{\bullet}$ (eq 3), so that the oxidation can be arrested with high selectivity to aldehydes (eqs 3 and 4). In contrast, aliphatic alcohols are much less reactive than the corresponding aldehydes, and the esters are obtained with high selectivity also at low conversion (eqs 5−7). This behavior has been ascribed to polar and enthalpic effects due to the different electronic configurations of the alkyl (π-type) and acyl (σ-type) radicals.[1−4]

Similar results and a similar mechanism are also involved in the bromine-catalyzed oxidation of *N*-benzylacetamides by H_2O_2 in a two-phase system[5] (eq 9).

$$\text{Ar-CH}_2\text{NHCOCH}_3 + \text{H}_2\text{O}_2 \xrightarrow[\text{or Br}^-]{\text{Br}_2} \text{Ar-CHO} + \text{CH}_3\text{CONH}_2 + 2\,\text{H}_2\text{O} \qquad (9)$$

Reaction 9 is slower than reaction 1 as a result of the faster reaction 3 compared to the analogous reaction with *N*-benzylacetamides.[5]

Since Br_2 is the actual oxidant, the same results of eqs 1, 2, and 9 were obtained by using stoichiometric amounts of Br_2 in the absence of H_2O_2 in a two-phase system;[1,2,5] the process is obviously much more expensive in this case.

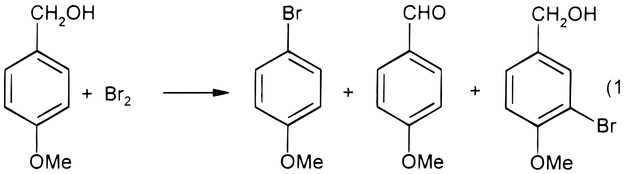
Attempts to utilize the bromine-catalyzed oxidation of *p*-methoxybenzyl alcohol or *N*-(*p*-methoxybenzyl)acetamide by H_2O_2 for the synthesis of *p*-anisaldehyde, a useful industrial intermediate, were unsuccessful; no substantial reaction took place.

Recently a much more complex catalytic system was reported,[6] involving methyltrioxorenium with Br^- as cocatalyst, which gives results similar to those of eqs 1 and 2 in the oxidation of primary alcohols by H_2O_2. Also, in this case *p*-methoxybenzyl alcohol was not oxidized, but *p*-methoxybenzyl bromide was the only reaction product. The mechanism of this catalysis was explained through hydride abstraction by bromine, but we believe that also this catalysis involves a hydrogen atom abstraction by $Br^{\bullet}$ according to the free-radical chains of eqs 3−8.

In attempts to explain the behavior of *p*-methoxybenzyl alcohol and acetamide, we have investigated the reaction of these substrates by Br_2 in a variety of solvents.

Results and Discussion

The reaction of *p*-methoxybenzyl alcohol with bromine by the typical procedure[1,2] to obtain aldehydes (H_2O/CH_2Cl_2 as solvent at room temperature) led to *p*-bromoanisole (**1**) as the main reaction product and to anisaldehyde (**2**) in low yields, with 3-bromo-4-methoxybenzyl alcohol (**3**) as a minor product (eq 10).



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[†] Politecnico di Milano.

[‡] Università di Bergamo.

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Scheme 1

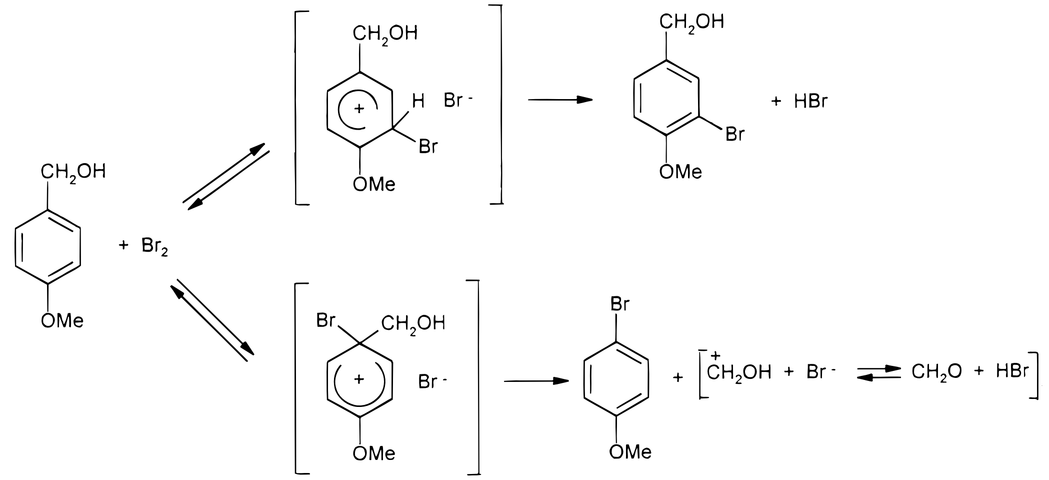

Table 1. Reaction of *p*-Methoxybenzyl Alcohol (1 mmol) with Br_2

		yields[a] (%)		
solvent	Br_2 (mmol)	**1**	**2**	**3**
n-hexane	0.8	16.3	21.3	3.9
n-hexane/H_2O 1:1	0.8	48.2	tr	6.3
CH_2Cl_2	0.8	38.1	4.4	4.4
CH_2Cl_2/H_2O 1:1	0.8	59.9	4.7	3.2
AcOEt	0.8	24.4	2.5	
AcOEt	1	28.6	0.7	
AcOEt/H_2O 1:1	1	70.7	1.6	
CH_3CN	0.8	42.5		
AcOH	0.8	36.9	1.8	
CH_3OH	1	75.5	1.2	
CH_3OH[b]	1	93.8	4.8	

[a] Yield based on reacted Br_2. [b] Irradiation by incandescent lamp.

Under the same conditions but in a homogeneous system (CH_2Cl_2 as solvent) the same products were obtained, but the yields of **1** were significantly lower. When the reaction was carried out in *n*-hexane, **2** was the main reaction product, but **1** was still significant. By using a different two-phase system (*n*-hexane/H_2O) the yields of **1** considerably increased, while **2** was obtained only in traces. The results with a variety of solvents are reported in Table 1. These results well explain why the bromine-catalyzed oxidation of *p*-methoxybenzyl alcohol by H_2O_2 is inhibited. The catalytic amount of Br_2 is consumed, and H_2O_2 cannot oxidize benzyl alcohol in the absence of the catalyst. The inertness of *p*-methoxybenzyl alcohol toward H_2O_2 in the absence of bromine has been verified by a blank experiment.

At least three competitive processes are clearly involved: the electrophilic ipso substitution of the $-CH_2OH$ group, the electrophilic ring bromination ortho to the methoxy group, and the free-radical oxidation of $-CH_2OH$ to $-CHO$.

The solvents affect both the ratio between electrophilic substitutions and free-radical oxidation [(**1** + **3**)/**2**] and the ratio between ipso and hydrogen displacement (**1**/**3**). Only in nonpolar solvents, such as *n*-hexane, the free-radical oxidation (eqs 3 and 4) prevails slightly over the electrophilic processes. This must be ascribed, in our opinion, to the influence of solvent effect on the electrophilic processes; on the other hand, the rate of the free-radical oxidation should be substantially unaffected by solvents. The solvent also influences the ratio between **1** and **3**; in polar solvents **3** was not formed. The fact is relevant because the two positions ortho to the methoxy group are free, and the ipso substitution (formation of **1**) is always greatly or exclusively prevailing over the normal ortho substitution (formation of **3**), considering that the bromination of anisole leads to the para isomer in great prevalence[7] (98.4%) but also to a minor amount of the ortho isomer (1.6%). A possible interpretation concerns the fact that the formation of the Wheland intermediates (Scheme 1) could be reversible and $^{+}CH_2OH$ is a better leaving group than proton under acid conditions (HBr is formed in the reaction); this would balance the unfavorable steric effect for the addition to give ipso substitution.

The electrophilic ipso substitution of activated benzyl alcohols is well-known,[8-15] but in the reaction of *p*-methoxybenzyl alcohol and Br_2 the evaluation of the normal ortho substitution was never reported, and formation of anisaldehyde (**2**) was carefully sought but not found.[14]

The reaction of *N*-(*p*-methoxybenzyl)acetamide with Br_2 led to similar results (eq 11). Moreover methyl 4-methoxybenzoate and methyl 3-bromo-4-methoxybenzoate were also formed when the reaction was carried out in methanol solution, and the rate of the free-radical processes was increased through irradiation by an incandescent light source. Clearly these last compounds were formed by further oxidation of **2** and **4**, according to the mechanism of eqs 5−7. The results are reported in Table 2. Also in this case three competitive processes can be recognized: free-radical oxidation, electrophilic

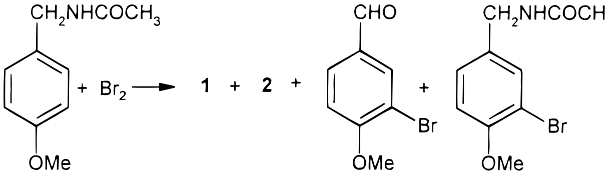

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Table 2. Reaction of *N*-(*p*-Methoxybenzyl)acetamide (1 mmol) with Br_2

solvent	Br_2 (mmol)	yields[a] (%) **1**	**2**	**4**	**5**
n-hexane	0.8	7.2			92.8
CH_2Cl_2	0.8	26.0			74.0
CH_2Cl_2/H_2O[b] 1:1	1	30.4		11.9	57.8
AcOEt	1	20.7			79.3
AcOEt[b]	1	26.1		4.7	69.2
AcOEt/H_2O 1:1	0.5	16.2	0.9		82.9
AcOEt/H_2O 1:1	1	16.3	0.7	0.4	82.8
AcOEt/H_2O[c] 1:1	2	28.2	0.7	6.5	63.8
CH_3CN	1	31.2			68.8
CH_3CN[b]	1	39.1	9.1	17.9	33.9
CH_3OH	1	11.3		5.5	83.2
CH_3OH[b,d]	1	13.2	12.3	9.6	56.2

[a] Yield based on reacted Br_2. [b] Irradiation by incandescent lamp. [c] 2,4-Dibromoanisole, formed by further bromination, was evaluated in **1**. [d] In addition, 6% of methyl 4-bromobenzoate and 2.1% of methyl 3-bromo-4-methoxybenzoate were also formed.

ring bromination, and ipso substitution, which is significant in all of the experiments of Table 2.

To the best of our knowledge it is the first time that ipso substitution of the $-CH_2NHCOR$ *group is observed in electrophilic aromatic substitutions.* This ipso substitution is somewhat less favorable than that of the $-CH_2OH$ group, and the ring bromination (formation of **5**) is generally prevailing. Two main factors are, in our opinion, responsible for this behavior according to the mechanism of Scheme 1: $^+CH_2OH$ is a better leaving group than $^+CH_2NHCOR$, which presents a larger steric hindrance for the electrophilic attack.

In this case, anisaldehyde (**2**) was formed in significant amount only when the reaction mixture was irradiated by an incandescent light source. This is due to the fact that hydrogen abstraction by $Br^{\bullet}$ from benzyl alcohols (eq 3) is faster than from N-benzylamides. This means that, in this latter case, a higher concentration of $Br^{\bullet}$ is necessary; we verified this assumption by competitive kinetics.[5]

The formation of **4** is also favored by the use of an incandescent light source, but in some solvents (CH_3OH, AcOEt/H_2O) ambient light is sufficient. In principle **4** could be formed either by electrophilic bromination of anisaldehyde (**2**) or by free-radical oxidation of **5**. The latter explanation seems more likely on the basis of the results obtained with an increasing amount of Br_2 in AcOEt/H_2O medium; the amount of **4** increases with the increased amount of Br_2. The introduction of bromine deactivates the aromatic ring of **5** toward further electrophilic bromination, but it has a negligible effect on the free-radical oxidation of the $-CH_2NHCOR$ group. Moreover, the electrophilic bromination of the aromatic ring is certainly faster for *N*-(*p*-methoxybenzyl)acetamide than for **2**.

Experimental Section

Experiments entailed the use of 8 mL of organic solvent, in which 1 mmol of *p*-methoxybenzyl alcohol or *N*(*p*-methoxybenzyl)acetamide were dissolved, and variable amounts of Br_2, as reported in Tables 1 and 2. In the case of the two-phase systems reported in these Tables, 8 mL of H_2O was also added. The solutions or heterogeneous mixtures were stirred at room temperature for 5 h. Where indicated the reaction medium was irradiated by an incandescent light source (Osram Halolux UV-stop 64479 230 V, 250 W). The reaction products dissolved in the organic phase were identified by GC−MS by comparison with authentic samples. The quantitative analysis was carried out by GLC with internal standards. The results of typical experiments with *p*-methoxybenzyl alcohol and *N*-(*p*-methoxybenzyl)-acetamide are reported in Tables 1 and 2, respectively.

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