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Secondary sonochemical effect on Mo-catalyzed bromination of aromatic compounds

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ABSTRACT

The Molybdate-catalyzed bromination of various aromatic compounds in the presence of KBr/H_2O_2 in an aqueous/chloroform biphasic system occurred under ultrasonic irradiation, whereas the reaction did not take place under conventional mechanical stirring (1400 rpm). The sonochemical activation was found to be of secondary effect, attributed to lowering pH by sonolysis of $CHCl_3$–H_2O solvents mixture.

1. Introduction

Halogenated aromatic compounds are a useful class of intermediates in synthetic organic chemistry. In particular, brominated aromatic compounds are widely used in the manufacture of several special chemical products among antibacterials, disinfectants, pharmaceuticals, agrochemicals [1]. In addition, they also play an important role in the design of metal catalyzed coupling reactions [2]. Various synthetic routes have thus been reported in the literature through the last century. The most commonly used reagent remains molecular bromine associated to various acidic co-catalysts such as Lewis acids or zeolites [3]. Nevertheless, all of them exhibit also several major drawbacks such as toxicity, corrosion, hazard and pollutant to the environment. In the nowadays necessity of developing sustainable organic synthetic routes, efforts were focused on the development of greener methods under milder conditions to afford bromoarenes. Therefore, in the recent years, several methodologies involving milder brominating reagents, among *N*-bromosuccinimide (NBS) [4], NBS/Brönsted acids (H_2SO_4, CF_3COOH, PTSA, etc.) [5], NBS/SiO_2 [6], HBr/DMSO [7], $KBrO_3$ [8] or KBr/H_2O_2/Oxone [9] were developed. Nevertheless, these methodologies still suffer major drawbacks such as hazard and toxicity of the prepared reagents, use of organic solvents and poor atom efficiency leading subsequently to the production of large amounts of toxic wastes. More recently, Singhal et al. developed an interesting alternative route by using a solid organic ammonium tribromide, the *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) as a brominating agent in the presence of 30% hydrogen peroxide at room temperature in methanol [10]. Various bromoarenes were afforded in excellent yields in very short times but the use of methanol, the nature and the used amount of the catalyst may postpone a further development.

In the late 90s, Conte et al. reported an interesting catalytic method of bromination of aromatic compounds by KBr, H_2O_2, and Na_2MoO_4 envisaged in a manner similar to the bio-halogenation performed by haloperoxidase enzymes [11,12]. This bromination is based on bromide salt oxidation to bromonium- or hypobromite-like species ("Br^+") by hydrogen peroxide. The reaction system is Br-atom efficient because of the use of bromide Br^- for the bromination, in contrast to the bromination by bromine Br_2 which utilizes only 50% of the available halogen with the other half forming HBr waste [13]. The proposed mechanism is composed of reaction steps involving a consumption of H_2O_2 and a catalytic use of Mo-complex enabling the formation of the "Br^+" moieties (BrOH, Br_2, Br_3^-) in a $H_2O/CHCl_3$ biphasic medium [11,14], which is illustrated in Scheme 1.

Even if the concept, in terms of Green Chemistry goals, remains attractive the reaction under vigorous stirring (1000 rpm) affords only low to moderate yields (56–65%) in 4 h. Moreover, up to

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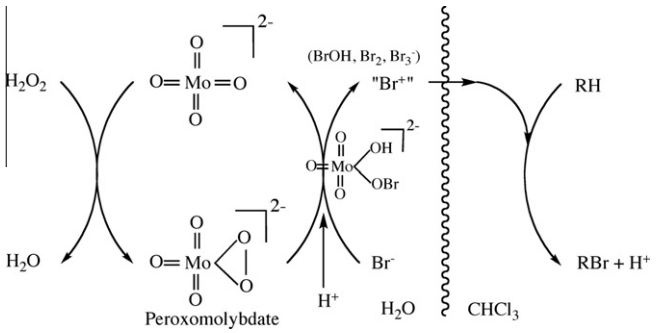


Scheme 1. Plausible mechanism for the molybdate-catalyzed bromination of aromatic compounds.

50 mol% of catalyst Na_2MoO_4 and additional H_2O_2 are necessary. Ultrasonic irradiation was thus expected to improve this bromination reaction through the synergism of its both chemical and physical effects, since ultrasound on the one hand produces H_2O_2 via the sonolysis of water and on the second enhances heterogeneous reactions [15].

2. Experimental

In a flat bottom reaction flask, 0.1 mmol of substrate, 0.1 mmol of H_2O_2, 0.126 mmol of KBr, and 0.005 mmol of $(NH_4)_6Mo_7O_{24}$ were mixed in a 5 mL H_2O/1 mL $CHCl_3$ solvent. Then the solution was submitted to ultrasound in a 36.6 or 480 kHz thermo-controlled ultrasonic bath at 0.2 W/mL acoustic intensity [16] for 1 or 2 h at 20 °C. Runs under conventional mechanical stirring at 1400 rpm were also carried out for comparison. Organic materials were separated into $CHCl_3$ phase and analyzed by GC using the internal standard method.

3. Results and discussion

Results obtained under both conventional and non conventional activation methods are summarized in Table 1.

In 2 h under stirring conditions, the bromination of phenol did not occur at all, whereas under ultrasonic conditions, bromophenol was obtained at 71% and 81% yield at, respectively 36.6 and 480 kHz. Anisole and acetanilide were also brominated efficiently in 4 h under sonication. Ultrasound is decisive to initiate the reaction, but the difference of frequencies of ultrasound irradiated doesn't make a large difference. When the reaction was carried out with no addition of H_2O_2, yields were low at both frequencies. Although the sono-production of H_2O_2 was expected under sonication, the low-yield of H_2O_2 was not enough to carry out the reaction. Thus, H_2O_2 had to be added.

In order to elucidate the mechanism of the ultrasonic activation, it was firstly confirmed that molybdate was doubtless involved in the reaction mechanism [11]. In its absence only 10% of bromophenol at 36.6 kHz and 16% at 480 kHz were obtained as shown in Table 2.

That is, the uncatalyzed bromination with Br^- and H_2O_2 under our experimental conditions does not work out. In our study, 5 mol% of molybdate gave the best results. Also, the selectivity of *o*- and *p*- isomers in the reaction in the absence of molybdate was slightly different from those in the presence of molybdate. The $H_2O/CHCl_3$ ratio of the solvents system also affected sensibly the yield as shown in Table 3. Moreover, in the absence of $CHCl_3$, the reaction did not proceed at all. Although the biphasic conditions are important, the solvent ratio does not affect significantly the yield.

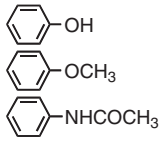
Our initial hypothesis was that ultrasound may accelerate the decomposition of the "peroxomolybdate-hypobromite" intermediate to accelerate cycling of the catalyst. According to the best of our knowledge, there is yet no report on the sono-activation of homogeneous catalysis, although there are many reports on the sono-activation of solid catalysis and on sonolysis of materials [17]. If it is so in our case, the fact must be very interesting.

Additionally, the difference of the initial pHs between Conte's reaction and ours, respectively 1.1 and 4.6, incited us to investigate further in this direction. Several experiments under both mechanical stirring and ultrasonic irradiation were carried out at the same pH, Table 4.

As shown in Table 4, the reaction under mechanical stirring did not occur without adjusting pH prior to the reaction. By lowering the initial pH of 4.6 to 1.3 by addition of $HClO_4$, the reaction afforded 44% of bromophenol in 1 h under stirring conditions emphasizing that the acidic conditions are required in this reaction system [11,13].

Thus, these results led us to envisage that the ultrasonic activation does come perhaps not from the decomposition of the homogeneous catalyst but from the homolytic decomposition of

Table 1
Bromination of aromatic substrates with H_2O_2 and KBr, catalyzed by $(NH_4)_6Mo_7O_{24}$ in a two phase system[a].

Substrate	Time (h)	Yield %[b] (*o*: *p* ratio)		
		Stirring (1400 rpm)	U.S. (36.6 kHz)	U.S. (480 kHz)
	2	0	71 (26:74)	81 (27:73)
	2	–	17 (32:68)[c]	15 (33:67)[c]
	4	0	96 (4:96)	75 (4:96)
	4	0	92 (0:100)	100 (0:100)

[a] Substrate 0.1 mmol, H_2O_2 0.1 mmol, KBr 0.126 mmol, $(NH_4)_6Mo_7O_{24}$ 0.005 mmol, Solvent: $CHCl_3$ 1 mL + H_2O 5 mL, Temp.: 20 °C.
[b] Determined by GC (internal standard: dodecane).
[c] Without H_2O_2.

Table 2
Bromination of phenol with various amounts of catalyst $(NH_4)_6Mo_7O_{24}$[a].

	Yield of bromophenol %[b] (*o*: *p* ratio) $(NH_4)_6Mo_7O_{24}$(mol%)[c]			
Frequency (kHz)	50	10	5	0
36.6	59 (26:74)	79 (26:74)	87 (25:75)	10 (39:61)
480	57 (25:75)	75 (25:75)	78 (25:75)	16 (35:65)

[a] Phenol 0.1 mmol, H_2O_2 0.1 mmol, KBr 0.126 mmol. Solvent: $CHCl_3$ 5 mL + H_2O 5 mL, Time: 2 h, Temp.: 20 °C.
[b] Determined by GC (internal standard: dodecane).
[c] mol% to phenol.

Table 3
Dependency of bromination of phenol on the solvent ratio $H_2O/CHCl_3$[a].

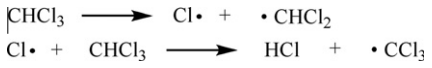
	Yield of bromophenol %[b] (*o*: *p* ratio) H_2O (mL)/$CHCl_3$ (mL)				
Frequency (kHz)	5.0/5.0	5.0/2.0	5.0/1.0	5.0/0.5	5.0/0.0
36.6	87 (25:75)	77 (24:76)	71 (26:74)[c]	58 (26:74)[d]	0
480	78 (25:75)	76 (25:75)	81 (27:73)	70 (27:73)	0

[a] Phenol 0.1 mmol, H_2O_2 0.1 mmol, KBr 0.126 mmol, $(NH_4)_6Mo_7O_{24}$ 0.005 mmol, Time: 2 h, Temp.: 20 °C.
[b] Determined by GC (internal standard: dodecane).
[c] 7.5% of dibromophenol was detected.
[d] 15% of dibromophenol was detected.

Table 4
Effect of the initial pH on the bromination of phenol[a].

	Yield of bromophenol %[b] (*o*: *p* ratio)	
	pH 4.6[c]	pH 1.3[d]
Stirring (1400 rpm)	0	44 (24: 76)
U. S. (480 kHz)	48 (24:76)	68 (24:76)

[a] Phenol 0.1 mmol, H_2O_2 0.1 mmol, KBr 0.126 mmol, $(NH_4)_6Mo_7O_{24}$ 0.005 mmol, Solvent: H_2O 5 mL + $CHCl_3$ 1 mL, Time: 1 h, Temp.: 20 °C.
[b] Determined by GC (internal standard: dodecane).
[c] An initial pH without $HClO_4$.
[d] An initial pH with 0.37 mmol of $HClO_4$.



Scheme 2. Radical decomposition of chloroform under ultrasonic irradiation.

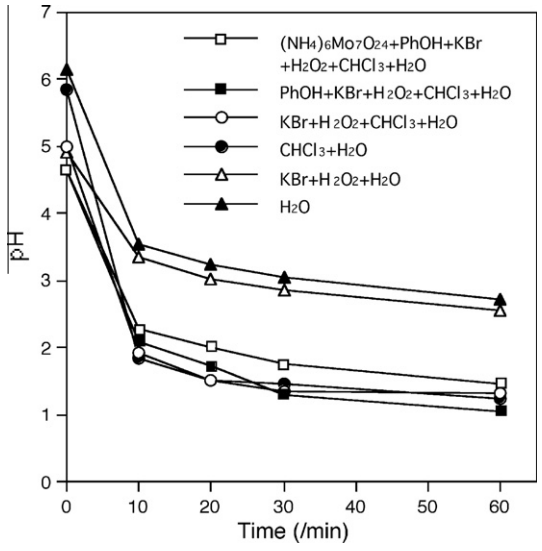


Fig. 1. pH change of various mixtures by 480 kHz sonication at 20 °C. $(NH_4)_6Mo_7O_{24}$ 0.005 mmol, Ph OH 0.1 mmol, KBr 0.126 mmol, H_2O_2 0.1 mmol, $CHCl_3$ 1 mL, H_2O 5 mL.

chloroform, which led to the formation of acidic species, lowering subsequently the value of the initial pH. In fact, the decrease of pH of aqueous chloroform solution by sonication was reported as the production of HCl or other acidic species [18–20] and interpreted as follows, Scheme 2.

Ultrasound may subsequently enhance the catalytic reaction through an indirect sonochemical effect brought by the sonolysis of $CHCl_3$–H_2O. This sort of sonochemical effect can be found in literatures. For examples, the rearrangement of ionone by *in situ* sonochemically generated hydrogen bromide from $CHBr_3$ [21] and cleavages of silyl ethers by *in situ* sonochemically generated hydrogen chloride from CCl_4/CH_3OH [22].

As these last results highlighted the importance of the pH values, we decided to study in more details its variation by carrying out several experiments under ultrasonic irradiation with different kinds of solutions; results are displayed here below, Fig. 1.

Whatever the solutions submitted to ultrasonic irradiation, they all suffered a more or less pronounced decrease in pH value. pH of the reaction solution became 2.0 from 4.6 in 20 min. H_2O itself and KBr/H_2O_2 in H_2O became respectively pH 3.3 and 3.0, in 20 min under 480 kHz sonication. When $CHCl_3$ is present in the solution, pH suffers a drastic decrease to become 1.5–1.9 within the same time.

Table 5
pH change[a] and bromination of phenol[b] in various solvent system.

Solvent system	pH[a]	Phenol[c]	Bromophenol[d] (*o*: *p* ratio)
CH_2Cl_2/H_2O	2.17	61	22 (26:74)
$CHCl_3/H_2O$	1.24	3	81 (27:73)
CCl_4/H_2O	1.36	0	2.2 (0:100)[e]

[a] A mixture of chlorinated methane 5 mL and H_2O 5 mL was sonicated at 480 kHz, 20 °C for 1 h.
[b] A mixture of phenol 0.1 mmol, H_2O_2 0.1 mmol, KBr 0.126 mmol, $(NH_4)_6Mo_7O_{24}$ 0.005 mmol in H_2O 5 mL + chlorinated methane 1 mL was sonicated at 480 kHz, 20 °C for 1 h.
[c] Recovered phenol.
[d] Determined by GC (internal standard: dodecane).
[e] 14 % of dibromophenol was detected.

As the reaction smoothly takes place at pH below two [13], one of the main reason of the acceleration of the reaction under ultrasound might be the lowering of pH by homolytic cleavage of $CHCl_3$.

When CCl_4 was used instead of $CHCl_3$, a little amount of bromophenol was obtained although all phenol was consumed as shown in Table 5. It may be because in aqueous solution of CCl_4 phenol and halogenated phenol are easily degraded by sonication [23]. On the other hand, CH_2Cl_2 did not work well, since the vapor pressure of CH_2Cl_2 is too high to sonolyze solvents as shown here below, Table 5.

Thus, the activation mechanism of the Mo-catalyzed bromination by ultrasound can be attributed to the secondary indirect sonochemical effect, that is the lowering of pH by sonolysis of $CHCl_3$–H_2O solvents. A strategic use of the secondary sonochemical effect such as *in situ* lowering pH by sonolysis should be taken into account in the application of ultrasound. However, the acceleration of the cycling of the catalyst by the sonolysis of the "peroxomolybdate-hypobromite" intermediate cannot be ruled out yet. Work is under progress to clarify this point.

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