A Novel and Highly Effective Halogenation of Alkanes with Halides on Oxidation with *m*-Chloroperbenzoic Acid: Looks Old, but New Reaction

Takahiko Kojima,* Hidenobu Matsuo, and Yoshihisa Matsuda
Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581

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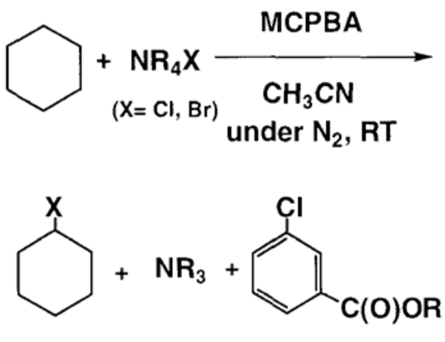
The combination of tetraalkylammonium halides (Cl^-, Br^-) and *m*-chloroperbenzoic acid in CH_3CN effectively halogenated alkanes accompanied by the formation of alkyl *m*-chlorobenzoate; for which the alkyl halides were formed via a non-photoinduced radical mechanism and the esters were derived from a non-radical process and concomitant with the formation of corresponding trialkylamine.

Halogenation reactions for saturated hydrocarbons have been an essential and versatile process in multistep organic syntheses toward functionalized compounds. In the case of radical halogenation, it usually requires heating at higher temperatures or photoirradiation for initiating radical processes. For instance, those reactions can be promoted by NBS/AIBN,[1] $SOCl_2/h\nu$ or benzoyl peroxide,[2] *t*-butyl hypochlorite/$h\nu$ or AIBN/heat,[3] tetraethylammonium chloride/benzoyl peroxide/heat,[4] and so on. Among those reactions, chlorination reactions of alkanes by tetraethylammonium chloride/benzoyl peroxide/heat was reported to give alkyl chloride in yield of up to 60% relative to the chloride source and a small amount of phenylchloride in CH_3CN.[4]

On the other hand, metal complexes can also participate in the alkane halogenation as observed in $Fe(TPA)X_2/TBHP$[5] and Mn(TPP)X/PhIO systems.[6] Especially, in the latter case, two-phase catalytic systems have been constructed by using aqueous NaX solution as halide source for adamantane halogenation. In the Mn(TPP)X/PhIO system, Brown and Hill proposed that Mn(V)(TPP)(O) abstracts hydrogen from the substrate to generate an alkyl radical; this halogenation is always accompanied by alcohol and ketone formation.

Besides those backgrounds mentioned above, if we could control the radical processes toward desired directions under mild conditions, it will allow us to have a strong and facile synthetic tool. We report here a highly effective halogenation of alkanes by the combination of tetraalkylammonium halides and *m*-chloroperbenzoic acid (MCPBA) in non-halogenated solvent, acetonitrile, at room temperature.



To a degassed acetonitrile solution (5 ml) of substrate and tetraethylammonium halide (0.5-1.5 mmol) or NaCl (0.5 mmol), MCPBA (1 mmol) was added as solids with stirring. After appropriate reaction time, quantification of products was done by GC with appropriate internal standards. Table 1 represents some reaction conditions employed and product distributions for halogenation reactions.

When cyclohexane was submitted as a substrate in the presence of 50 mol% of tetraethylammonium chloride (Et_4NCl) relative to MCPBA, the formation of chlorocyclohexane (CyCl) and ethyl *m*-chlorobenzoate (MCB-Et) was observed as main products in up to 35% and 20% yields relative to MCPBA added, respectively (CyCl was obtained in 70% yield based on NEt_4Cl added). The chlorination was accompanied by trace formation (ca.1% yields) of chlorobenzene (PhCl), cyclohexanol (CyOH), and cyclohexanone (CyO). Increasing the amount of NEt_4Cl up to 150 mol% relative to MCPBA raised the yields of CyCl and MCB-Et up to 50% and 38%, respectively; however, the yield of CyCl never went above 50%. The chlorination also proceeded to give comparable yield of CyCl in the presence of NaCl as a chlorine source in place of Et_4NCl without the formation of MCB-Et. This indicates that the ethyl group of MCB-Et is derived from Et_4NCl. In addition, the formation of $N(n\text{-}Bu)_3$ was confirmed by GC (not quantitated due to broadening of the signal) in the reaction using $N(n\text{-}Bu)_4Cl$. The same reaction conducted in the dark with Et_4NCl and similar stoichiometric formation of CyCl was also observed. This suggests that the halogenation described here is not a photoinduced reaction.

When toluene was used as a substrate, benzyl chloride ($PhCH_2Cl$) was obtained in 11% yield and MCB-Et in 11% yield. Trace formation of PhCl, benzyl alcohol, and benzaldehyde was observed in <0.1% yields. This indicates that the halogenation described here is applicable to benzyl positions.

Reactions using adamantane as a substrate gave some mechanistic insights into this halogenation. Changing alkyl groups of ammonium ions does not exert any influence to the 3°/2° selectivity of the reaction; those values were 7 for chlorination and 20 for bromination as shown in Table 1. Kinetic isotope effect was determined to be 4.7 for the chlorination and 2.3 for bromination by using a cyclohexane/cyclohexane-d_{12} (1/1) mixture as a substrate. These data indicate that the alkyl group of ammonium ion is not involved in the halogenation reaction nor the reactive species is derived directly from decomposition of MCPBA, but the halide is responsible for the reaction. At the beginning of the reaction, we observed that the solution turned to be pale yellow. Therefore, it is reasonable to anticipate the formation of Cl_2 or Br_2 in the course of the reaction. Moreover, addition of 2,6-di-*t*-butyl-4-methyl-phenol (BHT) quenched only the halogenation reaction; of our interest, the ester formation was not effected at all in the presence of BHT. This observation strongly suggests that the halogenation is a non-photoinduced radical reaction and the ester formation is not a radical process but ionic. To confirm that the halogen radical acts as a hydrogen abstraction reagent, adamantane was

Table 1. Product distribution for the halogenation using MCPBA in CH_3CN under N_2 at room temperature

Run	Substrate	Additive[a]	Reaction time	R-Cl or R-Br[b]	MCB-R[b]	3°/2° Ratio[c]
1	c-C_6H_{12}	Et_4NCl	5 min	33	26	
2	c-C_6H_{12}	Et_4NCl[d]	3 h	47	38	
3	c-C_6H_{12}	NaCl	22 h	17	none	
4	toluene	Et_4NCl	3 min	11	11	
5	adamantane	Me_4NCl	1 h	7.3 (1-Cl) 3.2 (2-Cl)	21	7
6	adamantane	Et_4NCl	1 h	8.5 (1-Cl) 3.5 (2-Cl)	21	7
7	c-C_6H_{12}	Et_4NBr	3 min	46	20	
8	adamantane	Me_4NBr	1 h	18.8 (1-Br) 3.1 (2-Br)	19	19
9	adamantane	n-Bu_4NBr	1 h	19.0 (1-Br) 2.8 (2-Br)	24	20

[a] 50 mol% relative to MCPBA was added. [b] Product yields(%) were determined by GC based on MCPBA added. [c] 3°/2° ratio = 3×[1-X]/[2-X]. [d] In this reaction, was used 100 mol% of Et_4NCl relative to MCPBA.

brominated by NBS/AIBN in CH_3CN under N_2 at room temperature. The reaction was much slower than that of our system, however, the 3°/2° ratio for the reaction was determined to be 20 and this is consistent with those observed for our system, indicating the bromination takes place via the formation of Br• as hydrogen abstracting species. The higher selectivity in bromination relative to the chlorination is due to the difference of bond energy formed; $\Delta H_{H\text{-}Cl} = 103$ kcal/mol and $\Delta H_{H\text{-}Br} = 87$ kcal/mol.[1] This suggests Cl• is more powerful than Br• in the hydrogen abstraction step and it is consistent with our results in the 3°/2° ratios of adamantane halogenation.

As for the oxidant, *t*-butyl hydroperoxide (TBHP) was examined for cyclohexane oxidation in place of MCPBA; however, only small amount of cyclohexanol (6% based on TBHP) and cyclohexanone (6%) was obtained and no chlorination was observed in the presence of NMe_4Cl. This can be due to the difference of redox potentials of both peroxides. In fact, Merényi and coworkers have reported that RC(O)OOH has a higher potential in 2-electron reduction than that of ROOH.[7] This argument is based on following claim: The formation of MCB-R and the absence of the formation of PhCl indicate that the O-O bond of MCPBA undergoes heterolysis to conduct 2-electron oxidation process rather than homolysis for 1-electron oxidation.

In conclusion, we discovered a facile and effective halogenation of alkanes by the combination of tetraalkylammonium halide and MCPBA in acetonitrile at ambient temperatures, accompanying a unique ester formation between *m*-chlorobenzoate and the alkyl group of tetraalkylammonium ions. The halogenation described here proceeds via oxidative formation of halide radicals which are responsible for the hydrogen abstraction from the alkanes. It may look like old-fashioned radical halogenation mentioned above, however, the reaction reported here exhibits distinct and attractive features in terms of the unique product distribution and mild reaction conditions. The reactions described here should have a versatile utility toward synthesis of functionalized hydrocarbons from abundant natural resources. In addition, considerable attention should be paid to the use of MCPBA toward metal-catalyzed oxidation in terms of halogenated product formation, if the reaction is conducted in the presence of halides which is metal-bound or not, even in a non-halogenated solvent.

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