

9.4 T and 7.05 T Magnetic Fields Accelerate a Radical Oxidation Reaction with a Hypervalent (*tert*-Butylperoxy)iodane

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Strong magnetic fields produced by NMR spectrometers (300 and 400 MHz) accelerate the radical oxidation of isochroman with a hypervalent (*tert*-butylperoxy)iodane.

There has been increasing public concern regarding the adverse effects on human health of the environmental electromagnetic field emitted from, e.g., high-voltage electric wire that produces an oscillating magnetic field (MF). The anxiety was stimulated by scientific reports such as that notifying a higher ratio of infant leukemia even at the MF level of 4 μ T (tesla).¹ However, very little is known as to whether a static magnetic field is harmful or otherwise to human health. The biological system depends on intricate actions of enzymes, which are in turn based on fundamental organic reactions. It should, therefore, be essential to have sufficient knowledge of magnetic field effects (MFE) on basic organic reactions in order to understand their mode of actions against or for the life system.

While the MFE on photochemical reactions involving high-energy transition states has been relatively well documented,² the MFE on thermal reactions has been less frequently reported, and some of the MFE experiments on ordinary chemical reactions were found to lack in reproducibility.^{3,4}

We have reported two examples of MFE on radical reactions, one on tributyltin hydride reduction of halides⁵ and the other on autooxidation of linoleic acid.⁶ The reproducibility of the results, however, was poor, and it was needed to repeat the reactions until statistically satisfactory results were obtained (six and three years were necessary for the respective cases). In this article, we report remarkable MFE on the radical oxidation of a benzyl ether with a hypervalent iodane reagent (1).

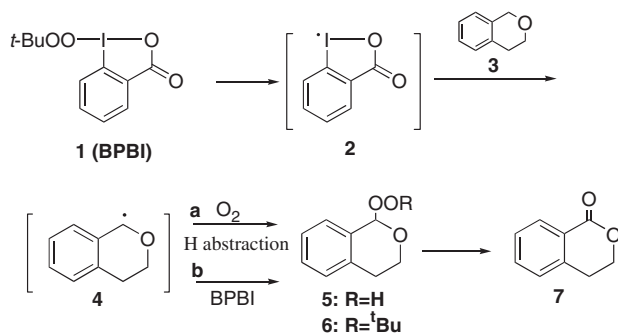
In the present study, the superconductive magnets of 400 and 300 MHz NMR spectrometers were used. They generate strong (9.4 and 7.05 T, respectively) and extremely stable MF

(<0.004 ppm = <3–4 $\times 10^{-8}$ T).

Hypervalent 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one (1) (BPBI) (commercially available) produces an iodine-centered radical (2), which can abstract a benzyl hydrogen affording a benzoic ester through a series of reactions as exemplified by conversion of isochroman (3) into 1-isochromanone (7) (92% yield in the presence of K₂CO₃) (Scheme 1).⁷ We selected this reaction for the MFE experiment for the convenience of HPLC.

Isochroman (3) (0.20 mmol) and 1 (0.44 mmol) were added to ethyl acetate (5 mL) containing 50 μ L of an ethyl acetate solution of coumarin (70 mM) (as an internal standard for HPLC). After stirring for 20 min, 0.4-mL portions of the mixture (a suspension containing a small amount of powdery 2-iodobenzoic acid) were delivered into four 5-mm NMR tubes. Each tube was capped and tightly sealed with PTFE seal tape. Two tubes were set in the probes of JEOL-JNM-AL300 (300 MHz; 7.05 T) and JEOL-GSX400 (400 MHz; 9.4 T) spectrometers (the samples were designated S_{7.05T} and S_{9.4T}, respectively), and the other two tubes (S_{0T}) were immersed in a water bath. Prior to the experiments, the temperature of the NMR probes and the water bath was adjusted at 30 °C by checking with a thermocouple (Yokogawa 2455 and SATO SK-1250MC).⁸ The spinner and transmitter for the pulses and lock signals of the spectrometers were turned off. The tubes in the water bath were covered with aluminum foil to shield them from light. The reaction course was followed by HPLC (Mightysil® Si60, hexane:ethyl acetate = 4:1, UV detector at 286 nm). The concentration (μ M) of the product 7 was calculated by the ratio of the peak intensities of 7 and the internal standard (coumarin).

Figure 1 shows that the slopes of the straight lines observed for the samples under strong MF (S_{9.4T} and S_{7.05T}) are steeper than those in a water bath (S_{0T}), which means that the radical oxidation is remarkably accelerated by 7.05- and 9.4-T MF. An in-



Scheme 1. Oxidation of isochroman (3) into 1-isochromanone (7) with hypervalent iodane BPBI (1). The benzyl radical (4) can afford a hydroperoxide (5) (route a) and *t*-butyl peroxide (6) (route b), both of which produce 7, as proposed by Ochiai.⁷

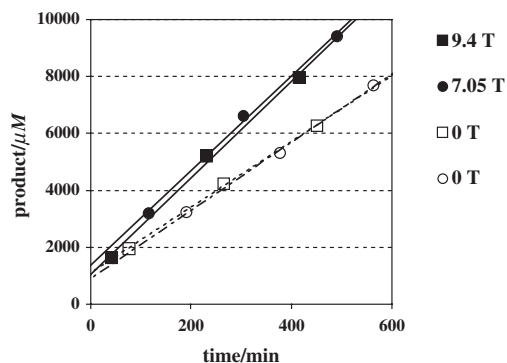


Figure 1. The reaction course of the oxidation of isochroman (3) with BPBI (1). Dark square: S_{9.4T}, dark circle: S_{7.05T}, blank square and blank circle: S_{0T}.

dex $K_{MF/0T} = S_{MF}/S_{0T}$ (S: $\mu\text{M}/t$) was introduced to show MFE. In the present case, $K_{9.4T/0T} = 1.44$ and $K_{7.05T/0T} = 1.41$.

The same experiments were repeated several times and averages of the indices $K_{MF/0T}$ were calculated as shown in Figure 2, which also includes the result obtained in the experiments under 0.4 T MF (neodymium magnet).

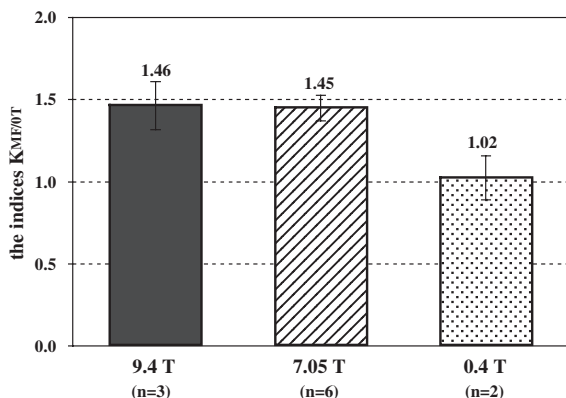


Figure 2. The indices $K_{MF/0T}$ obtained by the experiments using 400 MHz (9.4 T), 300 MHz (7.05 T) NMR spectrometers and a neodymium magnet (0.4 T).

It is clear that 9.4-T and 7.05-T MF increase the reaction rate in the range of 45–46% while 0.4-T MF does not affect the reaction rate.

The same experiments were performed in benzene instead of ethyl acetate, affording $K_{9.4T/0T} = 2.14$ ($n = 1$) and $K_{7.05T/0T} = 2.12 \pm 0.005$ ($n = 2$).

To further confirm the MFE, a ‘cross-experiment’ was introduced: A freshly prepared mixture of **3** and BPBI in ethyl acetate was delivered into two NMR tubes, one ($S_{7.05T \rightarrow 0T}$) of which was set in the 300 MHz NMR probe (30 °C) and the other ($S_{0T \rightarrow 7.05T}$) immersed in a water bath (30 °C). After 4 h, the samples were exchanged with each other. The reaction course was monitored by taking out a small portion (ca. 10 μL) of the mixture every 30 min, which was subjected to HPLC analysis (Figure 3). It is also obvious from this experiment that 7.05-T MF accelerates the oxidation.

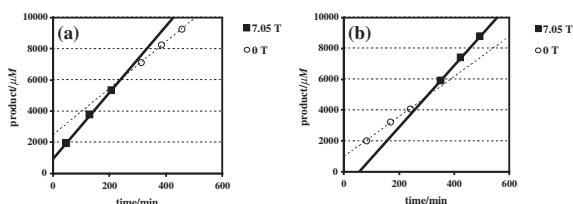


Figure 3. (a) The reaction course of the sample, 7.05 T $\rightarrow$ 0 T. (b) The reaction course of the sample, 0 T $\rightarrow$ 7.05 T.

The MFE observed in this study may be interpreted by the Δg mechanism of radical pair mechanism.⁹ Since the present radical oxidation is a thermal reaction, homolysis of **1** proceeds through a *singlet radical pair*, which either recombines to form **1**, diffuses to radical **2** and *tert*-butylperoxide radical, or converts to a *triplet radical pair* by intersystem crossing (ISC) (Figure 4). The triplet radical pair can no more recombine to **1** (Pauli theory) and easily releases **2** and the peroxide radical. In case where the

Δg mechanism is applicable, ISC predominates in the presence of a magnetic field. Consequently, increase of the concentration of **2** results in acceleration of the reaction rate.

There is a possibility that the present MFE is caused by increase of oxygen partial pressure.¹⁰

It should be emphasized that the reproducibility of the MFE in this study is good enough to perform the experiments under various conditions.

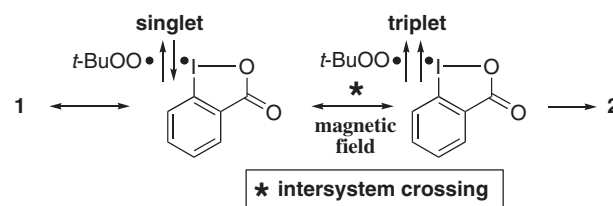


Figure 4. Intersystem crossing mechanism to interpret the acceleration of the radical oxidation of isochroman (**1**) to 1-isochromanone (**7**).

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References and Notes

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