

Ultrastrong Gravity-induced Unusual Reactivity in Radical Addition of Bromotrichloromethane to Ethyl Cinnamate

Yasuyuki Abe,¹ Tsuyoshi Sawada,¹ Makoto Takafuji,¹ Tsutomu Mashimo,^{2,3} Masao Ono,³ and Hirotaka Ihara^{*1,3}

¹Department of Applied Chemistry and Biochemistry, Kumamoto University, 2-39-1 Kurokami, Kumamoto 860-8555

²Shock Wave and Condensed Matter Research Center, Kumamoto University, 2-39-1 Kurokami, Kumamoto 860-8555

³Advanced Science Research Center, Japan Atomic Energy Agency, 2-4 Shirakata Shirane, Tokai, Naka-gun, Ibaraki 319-1195

(Received November 20, 2009; CL-091032; E-mail: ihara@kumamoto-u.ac.jp)

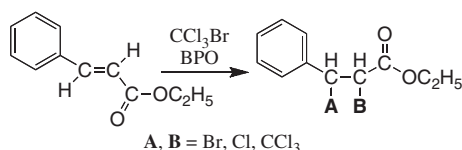
Radical addition of bromotrichloromethane to ethyl cinnamate was carried out under an ultrastrong gravitational field ($>2.5 \times 10^5$ G), and ethyl 3-chloro-3-phenyl-2-(trichloromethyl)propionate (**A**), ethyl 3-bromo-3-phenyl-2-(trichloromethyl)propionate (**B**), and ethyl 2-bromo-3-phenyl-3-(trichloromethyl)propionate (**C**) were isolated by reversed-phase HPLC. To date, there has been no report of the synthesis of **A** and **C** at 1 G, and this would be the first example of a selectivity change induced by ultrastrong gravity.

Radical addition reactions of alkenes are among the most fundamental reactions employed in organic synthesis and polymer synthesis. For achieving reactivity control,¹ many researchers have carried out radical additions in the presence of metal catalysts² or under extreme conditions such as high-pressure fields³ or high magnetic fields.⁴ The regio- and stereoselectivity of the cycloaddition of alkenes to heterocycles may change at high pressures, and this results in a decrease in the activation volumes.³ It has been reported that radical polymerization⁵ and photoreactions⁶ are accelerated in the presence of a magnetic field since intersystem crossing between the singlet and triplet states of a radical pair is facilitated by the applied magnetic field.⁴

In this communication, we report an unusual radical addition of alkenes in an ultrastrong gravitational field. This method is based on the fact that in addition reactions carried out under ultrastrong gravity, selective sedimentation of the reaction species occurs. Recently, we have reported that molecular-scaled graded materials can be obtained by the copolymerization of two monomers with different molecular weights.⁷

In this study, we selected bromotrichloromethane (BTCM), which is commonly used in radical addition reactions in the presence of an initiator,⁸ as the reactant. To examine the radical reactivity of the double bond, we selected ethyl cinnamate as the substrate because the phenyl group and carbonyl substituent in this compound influence the radical addition reaction via electrostatic effects or steric effects.^{9,10}

Radical addition was carried out using a mixture of ethyl cinnamate, BTCM, and benzoyl peroxide (BPO) (Scheme 1). The experiment was performed in an ultrastrong gravitational



Scheme 1.

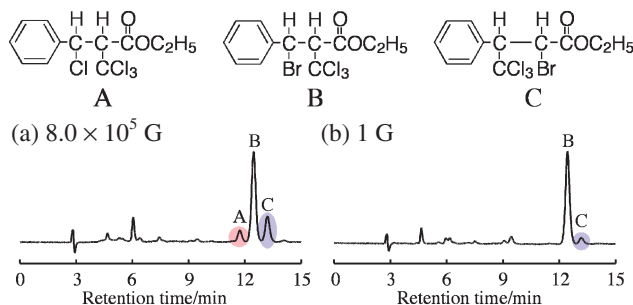


Figure 1. Chromatograms of the products obtained at (a) 8.0×10^5 G and (b) 1 G.

field in a newly developed ultracentrifuge.^{11,12} 150 μ L of the mixture (ethyl cinnamate:BTCM:BPO = 1:4:0.1)¹⁴ was sealed in a stainless steel capsule and exposed for 24 h at 80 °C to a gravitational field of 8.0×10^5 G generated by a centrifuge rotating at 1.43×10^5 rpm. The resultant mixtures were analyzed by reversed-phase HPLC.¹⁴ As shown in the chromatogram in Figure 1a, three peaks (**A**, **B**, and **C**) appeared at retention times of 11–14 min. Since the HPLC fractions absorbed light of wavelength 220–250 nm, we confirmed that they contained the phenyl group. These fractions were isolated for further analysis by preparative HPLC. The total yield of **A**, **B**, and **C** was approximately 70–90% in all cases.

On the basis of ¹H NMR, H–H COSY, and high-resolution EI mass spectral data, the major product **B** was confirmed to be ethyl 3-bromo-3-phenyl-2-(trichloromethyl)propionate.¹⁴ Further, the melting point of **B** was confirmed to match that of the product synthesized at 1 G.⁹ The minor products **A** and **C** were identified to be ethyl 3-chloro-3-phenyl-2-(trichloromethyl)propionate and ethyl 2-bromo-3-phenyl-3-(trichloromethyl)propionate, respectively. To date, there has been no report of the synthesis of **A** and **C** at 1 G. The identification of **A** and **C** was carried out in the following manner. (1) The high-resolution FAB mass spectrum of **C** showed a peak at m/z 394.8987, corresponding to bromo- and trichloromethyl-substituted phenyl propionate (m/z 394.8984 for C₁₂H₁₂BrCl₃O₂Na). (2) The high-resolution FAB mass spectrum of **A** showed a peak at m/z 350.9471, corresponding to chloro- and trichloromethyl-substituted phenyl propionate (m/z 350.9489 for C₁₂H₁₂Cl₄O₂Na). (3) The presence of ethoxyl and ethylene groups in compounds **A** and **C** was also confirmed from their respective ¹H NMR and H–H COSY spectra;¹⁴ thus, **C** was confirmed to be a regioisomer of **B**. (4) The similarity in the chemical shifts observed in the spectra of **A** and **B** suggested that **A** was a 3-chloro-2-trichloromethyl adduct.

To investigate the influence of gravity on the product ratio, the above-mentioned radical addition was carried out at different

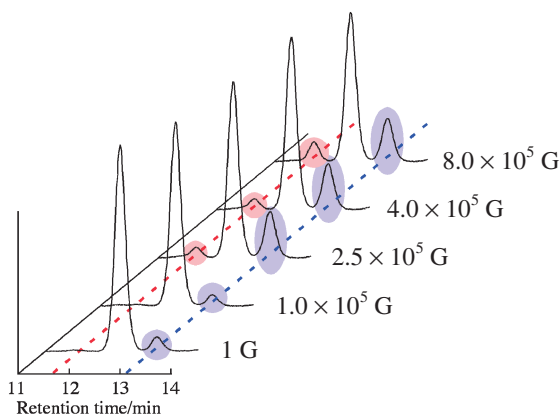


Figure 2. Chromatograms of the products obtained at various gravitational fields.

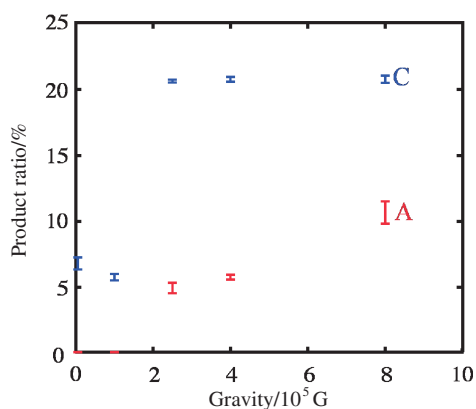


Figure 3. Influence of gravitational field on chemo- and regioselectivity.

gravitational fields such as 1, 1.0×10^5 , 2.5×10^5 , 4.0×10^5 , and 8.0×10^5 G (Figure 2 and Figure 3).

It is clear that product **A** is obtained only at gravitational fields stronger than 2.5×10^5 G and that the product ratio of **C** increases remarkably when the gravitational field is stronger than 2.5×10^5 G. Therefore, we conclude that ultrastrong gravity induces the formation of **A** and **C**, which is an unusual phenomenon.

The mechanism underlying the formation of **B** can be explained as follows: BPO (radical initiator) reacts with a bromine atom to yield a trichloromethyl radical, which then attacks the α -carbon of ethyl cinnamate. Subsequently, the bromine atom in BTCM reacts with the β -carbon of the ethyl cinnamate radical to afford **B**. In this reaction, a small amount of **C**, which is a regioisomer of **B**, is formed as the by-product (Figure 1b). Under normal conditions, this mechanism is considered to be reasonably accurate.

When the addition reaction was carried out in an ultrastrong gravitational field, the product ratio of **A** and **C** increased. We assumed that the formation of **A** depended on the selective molecular sedimentation caused by the ultrastrong gravity. The separation of ethyl cinnamate from BTCM by this selective molecular sedimentation could possibly interrupt the reaction of the bromine atoms in BTCM with the β -carbon of ethyl cinnamate. Although we could not identify the exact source of

the chlorine atoms in **A**, we expected that the second addition of the ethyl cinnamate radical to a chlorine atom would afford **A** instead of the bromo adduct **B**.

Under the ultrastrong gravity, a high-pressure of 10^4 Pa is generated; this leads to a decrease in the number of molecular degrees of freedom and an increase in the formation of regioisomer **C**. Although the above-mentioned pressure is not too high, it affects the regioselectivity of the first radical addition reaction, as in the case of the topochemical reaction.¹³ Regioisomer **C** is formed in a large amount because the activation volume associated with the radical addition to the β -position of ethyl cinnamate is less than that associated with the addition to the α -position.

In conclusion, we report the first example of a chemo- and regioselectivity change in a radical addition reaction carried out in an ultrastrong gravitational field. By carrying out the reaction in an ultrastrong gravitational field, we could obtain two new compounds **A** and **C**. There is no notable change in the observed selectivity, and the detailed mechanism of the formation of **A** and **C** remains to be clarified. Nevertheless, the unique results of this study encourage us to use the proposed radical addition method in polymer chemistry and for the synthesis of novel organic compounds.

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology and the Kumamoto University Global COE Program of the Global Initiative Center for Pulsed Power Engineering.

References and Notes

- I. Ryu, N. Sonoda, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050.
- a) O.-Y. Lee, K.-L. Law, C.-Y. Ho, D. Yang, *J. Org. Chem.* **2008**, *73*, 8829. b) A. S. Dneprovskii, A. A. Ermoshkin, A. N. Kasatochkin, V. P. Boyarskii, *Russ. J. Org. Chem.* **2003**, *39*, 933.
- K. Matsumoto, M. Kaneko, H. Katsura, N. Hayashi, T. Uchida, R. M. Acheson, *Heterocycles* **1998**, *47*, 1135.
- H. Hayashi, S. Nagakura, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 322.
- M. Imoto, K. Nomoto, *Makromol. Chem., Rapid Commun.* **1981**, *2*, 703.
- Y. Sakaguchi, H. Hayashi, *J. Phys. Chem.* **1984**, *88*, 1437.
- H. Ihara, Y. Abe, A. Miyamoto, M. Nishihara, M. Takafuji, M. Ono, S. Okayasu, T. Mashimo, *Chem. Lett.* **2008**, *37*, 200.
- a) M. S. Kharasch, O. Reinmuth, W. H. Urry, *J. Am. Chem. Soc.* **1947**, *69*, 1105. b) M. S. Kharasch, M. Sage, *J. Org. Chem.* **1949**, *14*, 537.
- R. L. Huang, *J. Chem. Soc.* **1956**, 1749.
- A. Ghosez-Giese, B. Giese, *ACS Symp. Ser.* **1998**, *685*, 50.
- T. Mashimo, X. Huang, T. Osakabe, M. Ono, M. Nishihara, H. Ihara, M. Sueyoshi, K. Shibasaki, S. Shibasaki, N. Mori, *Rev. Sci. Instrum.* **2003**, *74*, 160.
- An ultracentrifuge apparatus has been designed by T. Mashimo of Kumamoto University and developed at the Japan Atomic Energy Agency (JAEA). This ultracentrifuge can generate ultrastrong gravitational fields stronger than 1 MG at a constant temperature within $\pm 2^\circ\text{C}$.
- M. Nishio, *Tetrahedron* **2005**, *61*, 6923.
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.