

Decomposition Characteristics of Hypervalent Iodine Compounds Induced by X-Ray Core Excitation for the Development of X-Ray Activated Caged Compounds

We focused on a hypervalent iodine compound, 2-iodosobenzoic acid (IBA), as a candidate for the protecting group of X-ray-activated caged compounds. The decomposition reactions of IBA induced by X-ray irradiations around the iodine L_3 -edge region were investigated. Evidence showed that X-irradiations induced bond breakages around the hypervalent iodine atom. The associated decomposition rate depended on the X-ray energy. X-ray absorption spectral changes and desorbed molecular fragments confirmed a significant molecular decomposition induced by one of the iodine L-shell excitations. Our findings suggest that the hypervalent iodine compound could be a promising candidate for the design of novel X-ray-activated caged compounds.

Caged compounds are physiological signaling molecules that are biologically inactivated by the introduction of photo-removal protecting groups [1, 2]. The reactivation of caged compounds is possible through the removal of the protecting groups, thereby allowing for the temporal and spatial control of their biological activities via localized photoirradiation. Ultraviolet to near-infrared light are the most common methods for removing protecting groups from caged compounds, but their clinical applications are limited due to their low biological permeability [3]. Since X-rays, which can selectively excite atoms by photon energy, have high biological permeability and can selectively induce bond cleavage around the excited atoms, we attempted to develop X-ray activated caged compounds.

Hypervalent iodine compounds containing iodine atoms with more than eight electrons in the valence shell were selected as protecting groups for X-ray activated caged compounds. Iodine has a significant absorption cross-section for X-rays [4]. Furthermore, since hypervalent bonds are more easily broken than normal bonds, it is expected that X-irradiation will result in site-specific bond breakage around

the iodine atom. In this study, we investigated how X-rays decompose a hypervalent iodine compound, 2-iodosobenzoic acid (IBA; Fig 1(a)), as a potential protecting group for X-ray-activated caged compounds. We revealed that X-ray irradiation at particular resonance peaks could control the bond breakages around the hypervalent iodine atom [5].

The X-ray absorption spectrum of IBA exhibited four characteristic resonance absorption peaks as shown in Fig. 1(b). The DOS spectrum (Fig. 1(b)) well reproduced the first three peaks. The absorption peaks were assigned to $I 2p_{3/2} \rightarrow \sigma^*$ transitions of I-O and I-C (Fig. 1(c)), $I 2p_{3/2} \rightarrow \pi^*$ transitions of I-O and I-C (Fig. 1(d)), $I 2p_{3/2} \rightarrow \sigma^*$ transitions of I-O and I-C (Fig. 1(e)), and $I 2p_{3/2} \rightarrow \sigma^*$ transitions of I-O and I-C (Fig. 1(f)), from the lower energy side. Only the second peak was assigned as the π^* transitions.

The absorption spectra obtained before and after monochromatic X-ray irradiation were compared.

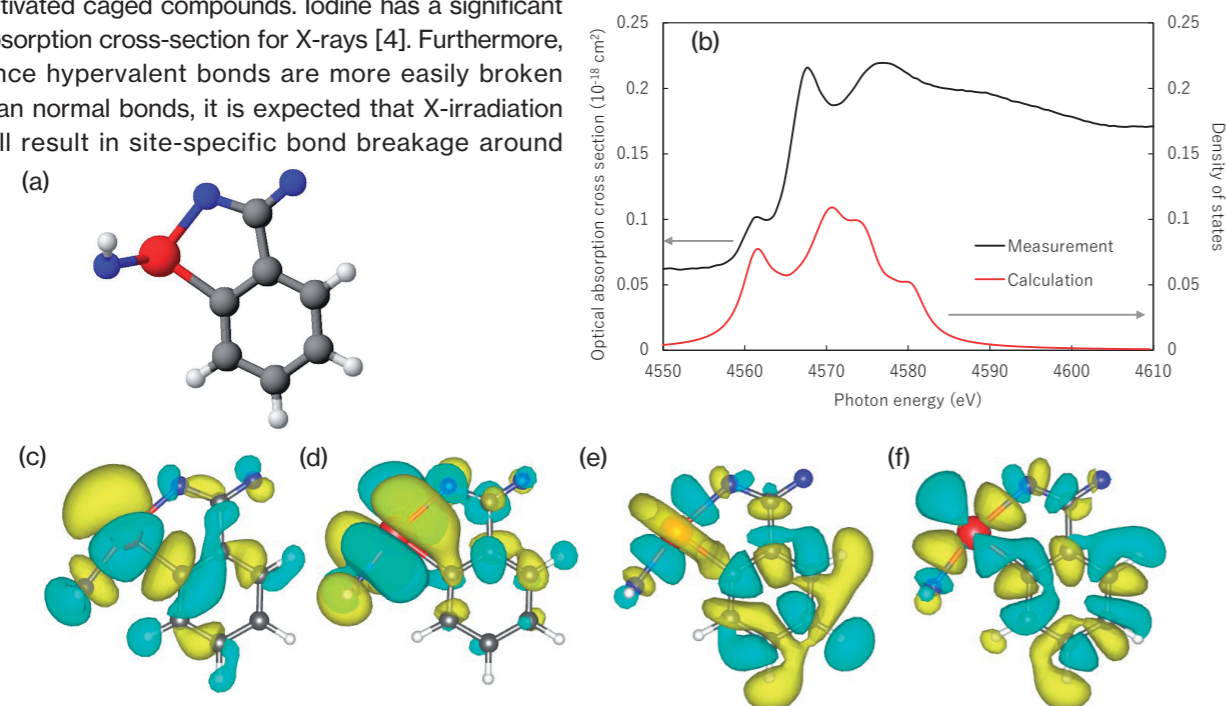


Figure 1 (a) The molecular structure of IBA. Gray : carbon, blue : oxygen, red : iodine. (b) X-ray absorption and DOS spectra of IBA in the iodine L_3 -edge energy region. (c-f) Calculated molecular orbitals of IBA in the final states assigned as the origins of resonance absorption peaks.

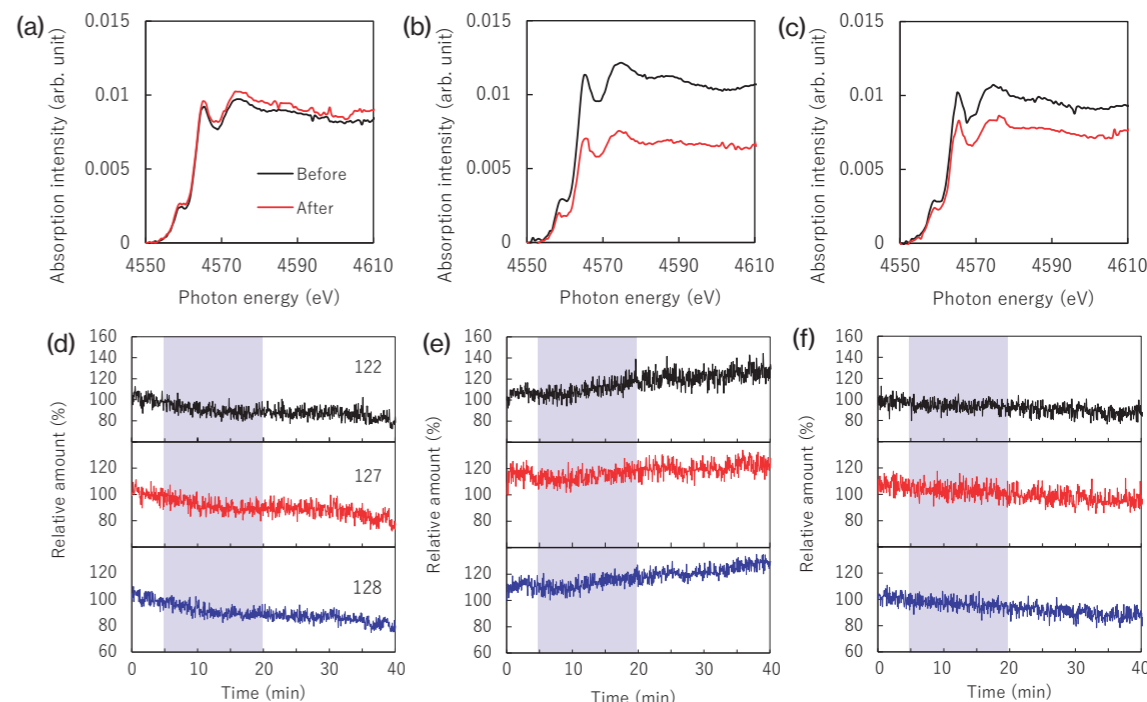


Figure 2 (a-c) Absorption spectral changes of IBA induced by monochromatic X-ray irradiation. (a) pre-edge; 4550 eV, (b) second peak; 4567.6 eV, and (c) post-edge; 4610 eV. (d-f) Time courses for the desorbed species with $m/Z = 122, 127$ and 128 . The light purple area corresponds to the irradiation period. (d) pre-edge, (e) second peak, and (f) post-edge.

No apparent spectral change was observed in the pre-edge energy irradiation (4550 eV; Fig. 2(a)). For the second absorption peak energy irradiation (4567.6 eV; Fig. 2(b)), the absorption intensity decreased significantly after irradiation, indicating that X-ray irradiation induced the decomposition of IBA. This may be attributed to the fact that the second absorption peak is only assigned to $I 2p_{3/2} \rightarrow \pi^*$ transitions of I-O and I-C (Fig. 1(d)). The absorption intensity exhibited a notable decline following post-edge irradiation (4610 eV, Fig. 2(c)). However, the decay rate was lower than that observed for irradiation with the second peak energy, despite similar absorption intensities for the two energies. These results indicate that the specific resonance excitation could efficiently induce the decomposition of IBA.

We focused on several desorbed species as candidates derived from IBA and measured their time courses with or without monochromatic X-ray irradiation using a quadrupole mass spectrometer. Fig. 2(d-f) shows the time courses for $m/Z = 122, 127$, and 128 , corresponding to the masses of C_6H_5COOH , I , and HI , respectively. The percentage of these species increased only when the sample was irradiated with an energy corresponding to the second absorption peak. The observed increases of the three species are evidence of desorption of iodine and other molecular fragments from the irradiated IBA. It indicates that the irradiation at the second absorption peak could induce efficient bond breakages around the hypervalent iodine atom of IBA.

Taken together, the irradiation corresponding to

the second resonance absorption peak at the iodine L_3 edge specifically induces bond cleavage at the hypervalent iodine atom. The observed higher decomposition rates than those by other X-ray energies indicate that the IBA molecule is a very promising protecting group for the design of novel X-ray activated caged compounds. These findings provide crucial insights into the activation mechanism of caged compounds by X-rays and may facilitate the development of compound activation techniques *in vivo* through inner-shell excitation.

REFERENCES

- [1] G. C. R. Ellis-Davies, *Nat. Methods* **4**, 8 (2007).
- [2] P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov and J. Wirz, *Chem. Rev.* **113**, 1 (2013).
- [3] T. Matsubara, T. Yanagida, N. Kawaguchi, T. Nakano, J. Yoshimoto, M. Sezaki, H. Takizawa, S. P. Tsunoda, S. Horigane, S. Ueda, S. Takemoto-Kimura, H. Kandori, A. Yamanaka and T. Yamashita, *Nat. Commun.* **12**, 4478 (2021).
- [4] C. T. Chantler, K. Olsen, R. A. Dragoset, J. Chang, A. R. Kishore, S. A. Kotochigova and D. S. Zucker, *J. Res. Natl. Inst. Stand. Technol.* (2005).
- [5] M. Ohara, Y. Izumi, H. Takakura, S. Enomoto, K. Fujii, A. Yokoya and M. Ogawa, *Radiat. Phys. Chem.* **216**, 111394 (2024).

BEAMLINE

BL-27B

M. Ohara¹, Y. Izumi¹, H. Takakura^{2,3}, S. Enomoto², K. Fujii¹, A. Yokoya¹, M. Ogawa² (¹QST, ²Hokkaido Univ., ³Kansai Medical Univ.)