Regioselectivity control of radiation-induced reaction: electron beam-induced Fries rearrangement of sulfonamide within a β-cyclodextrin inclusion complex†

Jun Kato,*[a] Hiroyuki Kakehata,[a] Yasunari Maekawa[b] and Takashi Yamashita[a]

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EB (electron beam) irradiation of sulfonamide within a β-cyclodextrin (β-CD) inclusion complex in the solid state induced the solvent-free Fries rearrangement, which proceeded at a shorter reaction time with reversed regioselectivity by inclusion into the β-CD, compared with that of sulfonamide crystals; the β-CD as a restricted nanospace had a large effect on the reactivity and regioselectivity of the solvent-free EB-Fries rearrangement.

Due to the ability of EB (electron beam) to directly write nanometer-scale patterns, it has attracted a great deal of attention as a promising tool for nanolithography as well as future nanodevice fabrication in a variety of fields.[1] The development of new EB-sensitive polymeric materials for these applications should be possible *via* novel EB-induced reactions. Radiation-induced reactions are generally complicated and not selective, however, due to secondary reactions.[2] Thus, we have investigated *selective* EB-induced reactions[3,4] of useful organic molecules in the crystalline state and their application to EB-sensitive polymers.[5] One of the most interesting results is that the EB-sensitivity of sulfonic acid derivatives is much higher than that of the corresponding carboxylic acid derivatives; especially, the EB-induced Fries rearrangement of arylsulfonamides which preferentially yields aromatic amines.[4] This reaction can be applied to novel EB-reactive polymers[5,6] for nanolithography and nanofabrication not only because reactive functional groups are transformed selectively with the EB reaction but also because the EB reaction can modify the properties of the material from acidic to basic.

β-Cyclodextrin (β-CD) has a cyclic repeated structure consisting of seven glucose units. The cavity size and the inner hydrophobicity are suitable for encapsulating within it a variety of smaller molecules such as aromatic compounds.[7,8] The improvement of the reaction rate and selectivity with β-CD inclusion complexes has been reported in a number of thermal and photochemical reactions.[8,9] The complex formation with β-CD could alter product distribution in the photochemical Fries rearrangement.[10] These characteristics arise from the geometrical constraint of the guest molecules on inclusion into the β-CD. Therefore, we expected that an EB-induced reaction in a nanoscale cavity of β-CD, in which the motions of guest molecules are constrained, could result in different reactivity (sensitivity and selectivity) from that observed in the crystalline state. In this communication, the solvent-free EB-induced reaction of the inclusion complex of sulfonamide in β-CD was investigated, compared with that of the sulfonamide crystals themselves.

The β-cyclodextrin inclusion complex of BSA (BSA/β-CD) was prepared by precipitation from a mixture of a saturated aqueous solution of β-CD as a host compound and equimolar amounts of benzenesulfonanilide (BSA) as a guest compound. The precipitate was filtered off and dried *in vacuo* to yield an inclusion complex BSA/β-CD as a white powder in 91% yield. The formation of BSA/β-CD was confirmed with ^{1}H NMR in D_2O. The H-5 proton[11] inside of β-CD underwent a significant high-field shift upon complexation (Fig. S1†), while the chemical shifts of H-1, H-2, and H-4 protons outside of β-CD were not affected by complexation. The high-field shift of the inner proton must be due to a ring current effect of the aromatic rings of the guest molecule. This result indicates the inclusion of the guest molecule (BSA) into the β-CD cavity. The inclusion complex consists of BSA and β-CD in a 1 : 1 ratio; evidence for which is given by the peak area ratio of all protons of the BSA moiety to the H-1 proton of the β-CD moiety in the ^{1}H NMR spectrum in DMSO-d_6.

Solvent-free EB-induced reaction of the 1 : 1 inclusion complex BSA/β-CD was carried out as follows. A white powder of BSA/β-CD (0.12 g) was placed in a stainless plate (18 × 10 × 4 mm), which was covered with a Kapton film. The samples were irradiated on a water-cooled copper plate with EB (acceleration voltage: 1 MeV, beam current: 1 mA) at a dose rate of 2.9 kGy s^{-1}, using a cascade type electron accelerator (Dynamitron).

After EB irradiation of 0.10–10 MGy (0.054–5.4 mC cm^{-2}) in dose, the reaction products were extracted with chloroform from within β-CD, and the extracts were analyzed by GC and GC-MS. In the solvent-free EB-induced reaction of the BSA/β-CD inclusion complex, BSA as a guest molecule was completely consumed before reaching a dose of 5 MGy, while the conversion of BSA crystal itself under the EB reaction conditions was 28% even at the same dose (Fig. 1). This result indicates that the BSA/β-CD complex has a much higher EB-sensitivity than the BSA crystal itself, and that the EB-induced reaction of BSA was promoted by inclusion into the β-CD.

The products were identified by GC-MS as previously.[4] This reaction yielded the Fries rearrangement products (*ortho*- and

[a]*Department of Pure and Applied Chemistry, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba, 278-8510, Japan. E-mail: kato@rs.noda.tus.ac.jp; Fax: +81 4 7123 9890; Tel: +81 4 7124 1501*
[b]*Conducting Polymer Materials Group, Quantum Beam Science Directorate, Japan Atomic Energy Agency (JAEA), 1233 Watanuki, Takasaki, Gunma, 370-1292, Japan*

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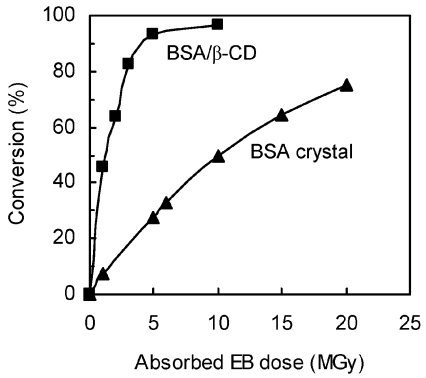


Fig. 1 Conversions of benzenesulfonanilide (BSA) in the crystalline state and the β-CD inclusion complex (BSA/β-CD) under EB irradiation (1 MeV, 1 mA).

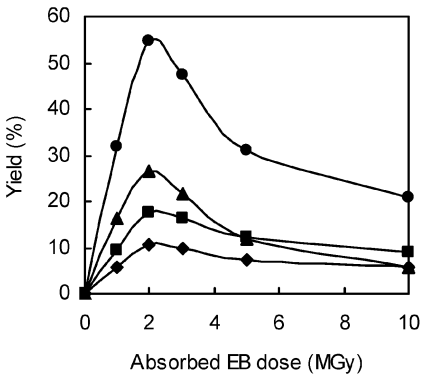
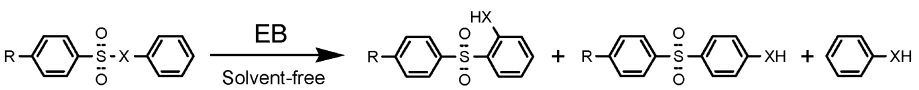


Fig. 2 Yields of each amine converted from benzenesulfonanilide (BSA) within the β-CD inclusion complex plotted as a function of the absorbed EB dose: *o*- and *p*-Fries products (◆ and ■, respectively), aniline (▲), and the total of them (●).

para-form) and aniline. No trace of the *meta*-form could be detected. As shown in Fig. 2, the combined yield of the three amines based on the amount of BSA as BSA/β-CD reached its maximum value of 55% with 2 MGy, then gradually decreased to 21% at 10 MGy as secondary reactions proceeded. The change in the X-ray diffraction patterns of BSA/β-CD during EB irradiation indicated that the β-CD skeleton of BSA/β-CD had higher EB-stability than β-CD itself and was maintained up to 2 MGy, but gradually deteriorated with further irradiation (Fig. S2†), which roughly corresponds to the result shown in Fig. 2. Accordingly, EB irradiation of BSA/β-CD induced the Fries rearrangement under a constrained environment with a dose of up to 2 MGy to give three amines in a high proportion of 86% (55% combined yield of amines to 64% conversion) at a dose of 2 MGy (Fig. 2 and Table S1†). Throughout the reaction, the *ortho* : *para* ratio of *ca.* 1 : 1.7 was maintained.

The product distribution in the reaction mixture after EB irradiation (1 MGy) is shown in Table 1. In every case, the EB-sensitivity of the guest molecules in β-CD increased about one order of magnitude over that in the crystals. Although active species are nonselectively produced for a variety of common substrates by ionization/excitation in the primary process of radiation reactions,[2] in this system, from the results mentioned above, it appears that EB acts selectively on the guest (BSA) first and then on the host (β-CD) to start deterioration of the β-CD skeleton. It has been reported that addition of aromatic hydrocarbons such as benzene can reduce radiation damage of aliphatic ones such as cyclohexane owing to energy and charge transfers.[2,12] The significantly high EB-sensitivity of the guest molecules and high EB-stability of the host molecules with the solid BSA/β-CD complexes may be due to the effect of β-CD as an EB-antenna, which transfers the energy from the host to the guest following ionization/excitation. In addition, the *para*-product was predominantly formed in the EB-induced Fries rearrangement of BSA/β-CD contrary to that of BSA crystals. The reversed regioselectivity (*ortho*/*para*) must have been achieved by inclusion of BSA into the β-CD. However, in the reaction of the guest compounds with a tolyl group such as *p*-toluenesulfonanilide (TSA) and phenyl *p*-toluenesulfonate (PTS), the proportion of the *para*-product became only slightly larger in comparison with the EB reaction in the crystalline state. We could also observe more cage–escape product, aniline or phenol, in the β-CD complex compared with the EB reaction in the crystalline state. This is probably due to the existence of hydrogens in the β-CD cavity to be abstracted by anilino radicals under high-energy radiation,

Table 1 Product distribution upon the EB-Fries rearrangement of sulfonic acid derivatives within β-CD inclusion complexes[a]



BSA : R=H, X=NH
TSA : R=Me, X=NH
PTS : R = Me, X=O

o-Fries *p*-Fries PhXH

Substrate	Conv.[b] (%)	EB-products[c] (%)			*ortho* : *para*	Proportion of amines (%)
		o-Fries	*p*-Fries	PhXH		
BSA/β-CD	46	12.9	20.9	36.2	1 : 1.6	70
BSA crystals	7.5	24.0	6.7	N.D.[d]	3.4 : 1	31
TSA/β-CD	70	5.3	6.1	18.5	1 : 1.2	30
TSA crystals	9.7	13.4	6.2	10.3	2.2 : 1	30
PTS/β-CD	74	7.8	4.6	17.2	1.7 : 1	30[e]
PTS crystals	7.1	7.0	N.D.[d]	<4	—	<11[e]

[a] Determined by GC. [b] Conversion after EB irradiation for 5.75 min (1 MGy). [c] Calculated on the consumed sulfonic acid derivatives. [d] Not detected. [e] Proportion of ArOHs.

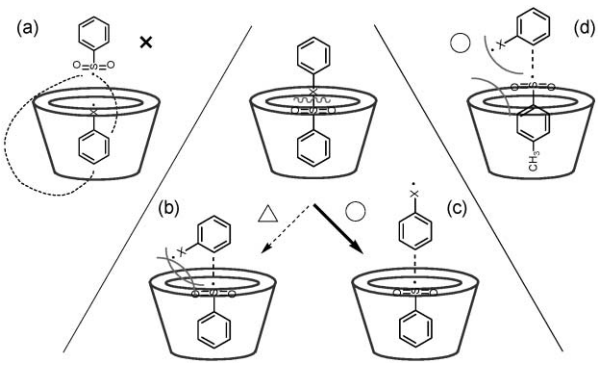


Fig. 3 Proposed mechanism of the EB-Fries rearrangement of sulfonamide and sulfonate within β-CD inclusion complexes: (a)–(c) BSA/β-CD, (d) TSA/β-CD and PTS/β-CD.

which aids the escape of anilino radicals from the cage of β-CD. These results show that β-CD as a restricted nanospace has a large effect on the EB-Fries rearrangement, suggesting that other EB-induced reactions could also be controlled by appropriate choice of reaction spaces.

The proposed mechanism of the EB-Fries rearrangement of β-CD inclusion complexes is shown in Fig. 3. This reaction proceeds through two radicals generated by the homolytic cleavage at the S–X bond *via* ionization/excitation by radiation, in analogy with the photo-Fries rearrangement. There are two possibilities for the directions of the guest molecules in the β-CD cavity; namely the aniline group (a) or the benzenesulfonyl group (b, c) is included in the β-CD cavity. In the former case (a), benzenesulfonyl radical, which is produced by EB-induced scission of the S–N bond, cannot attack the anilino radical residue because both *para*- and *ortho*-positions are sterically blocked by β-CD. On the other hand, the anilino radical in (c) can be attacked by the sulfonyl radical in β-CD at the wider open end of the β-CD to give a preferentially *para*-substituted one due to the steric hindrance with β-CD in (b). Since TSA and PTS with a methyl group are included shallowly in the β-CD cavity owing to the methyl group as shown in (d), *para*-selectivity should be smaller than that of BSA/β-CD. The depth of inclusion can also be understood by the magnitude of the high-field shift of the inner H-5 proton of the β-CD moiety upon complexation in the ^{1}H NMR spectra (Fig. S1†).

In conclusion, EB irradiation of an inclusion complex BSA/β-CD induced the Fries rearrangement under a constrained environment which led to changes in reaction rate and selectivity. To the best of our knowledge this is the first example of regioselectivity control in radiation-induced reaction using the β-CD restricted nanospace. These results should provide a breakthrough in finding useful *high sensitive and selective* radiation-induced reactions for nanolithography and nanofabrication by reaction-field control. Further studies on the EB-induced reactions in a restricted matrix are underway.

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