Controlled Separation and Release of Organoiodine Compounds Using Poly(2-methoxyethyl acrylate)-Analogue Microspheres

Takuma Kureha,† Yuichiro Nishizawa,† and Daisuke Suzuki‡†‡

†Graduate School of Textile Science & Technology and ‡Division of Smart Textiles, Institute for Fiber Engineering, Interdisciplinary Cluster for Cutting Edge Research, Shinshu University, 3-15-1 Tokida, Ueda 386-8567, Japan

ABSTRACT: A selective adsorption/desorption of organoiodine compounds was achieved on poly(2-methoxyethyl acrylate)-analogue microspheres, wherein the side chains in the polymers act as halogen-bonding sites. These results demonstrate that the halogen-bonding sites in the side chains exhibit adequate specific affinity for organoiodine compounds. In addition, the water-swollen pMEA-analogue microspheres (microgels) showed a thermoresponsive swelling/deswelling behavior that permitted a controlled release of the organoiodine compounds upon changing the temperature. Thus, it seems plausible that a variety of problems associated with, e.g., the recovery of rare iodine-containing compounds, the delivery of iodine-containing drugs, or the removal of halogen compounds from wastewater, could be resolved by polymer microspheres that exhibit controlled halogen bonding.

INTRODUCTION

Organoiodine compounds play an important role in everyday life. For example, functional iodine compounds have found applications as antibacterial and antiviral drugs, X-ray absorbers, and as components for food and cosmetics.1−7 Especially, marine-derived organoiodine compounds are highly valuable, and they have received much attention due to their biological activity, which includes inhibitory activity against cancer and diabetes.8−10 However, the variety and abundance of marine iodine compounds are much lower than those of the corresponding chlorine and bromine analogues.9 Moreover, organic syntheses of new iodine-containing drugs produce in many instances the corresponding iodine-free compounds in addition to the targeted organoiodines.1 Thus, the selective recovery and reuse of the target iodine compounds as starting materials, catalysts, and synthesized products in aqueous solution should be highly desirable, irrespective of the concentration of these compounds in solution. On the other hand, the presence of mass-produced organoiodine compounds in industrial wastewater or natural water resources are of particular concern for safe drinking water, as organoiodine compounds can be toxic, mutagenic, or carcinogenic, and their removal from drinking water is highly important.11

However, to the best of our knowledge, suitable materials for a selective separation of such iodine compounds have not yet been designed. Thus far, the removal of halogen-containing compounds from aqueous solution has been achieved predominantly using metallic materials, such as layered double hydroxides (LDHs).12−14 However, these LDHs usually require a reduction upon releasing the adsorbed halide anions,14 which increases the number of reaction steps.

Against this background, we focused on the use of polymer microspheres, as these have large specific surface areas and high mobility and exhibit a particular ease of recovery and handling.15−19 We found that polymer microspheres selectively adsorb and release halogen compounds.20,21 These microspheres consist of hydrophobic poly(2-methoxyethyl acrylate) (pMEA) and a poly(oligo(ethylene glycol) methacrylate) hydrogel matrix, i.e., they represent polymer/polymer composite hydrogel microspheres (microgels). These microgels benefit from not only the aforementioned microsphere features but also the intrinsic features of the hydrogel network, which allows halogen compounds to enter the inside of the microgels via diffusion and to exit the microgels upon applying external stimuli.22−34 In such microgels, the methoxy groups of the pMEA side chains are crucial for the halogen bonding, which occurs via noncovalent interactions and results in anomalously short intermolecular distances.35−39 Consequently, halogen bonding in composite microgels leads to a strong adsorption of halogen compounds in the presence of other compounds under concomitant formation of strong atomic interactions and high selectivity.21

However, for low concentrations of several compound mixture, where iodine-, bromine- chloride-, and halogen-free...
compounds coexist in water, the iodine-free compounds are usually also absorbed by the composite microgels, indicating that the selectivity of the adsorption of iodine-containing compounds is still low. The very strong interactions between pMEA and halogen-containing compounds thus occur irrespective of the nature of the halogen atom, which stands in contrast to the behavior of halogen atoms with Lewis acids, wherein the strength of the donor–acceptor interaction depends on the polarizability of the halogen atom, which decreases in the order I > Br > Cl.\(^\text{35–39}\)

A strategy that allows the highly selective adsorption of iodine-containing compounds at low cost and independent of time and place would be highly attractive for industrial (e.g., water treatment and iodine-recycling systems) and medical applications (drug development). With this objective in mind, we changed the number and position of oxygen atoms, which are the Lewis-basic acceptors for the halogen bonds, in the polymer chain to control the strength of halogen bonding between the microspheres and the iodine-containing compounds. The induced dipole moment of oligo(ethylene glycol) depends on its molecular weight, and the polarizability of the polymer chain can thus be changed by the number of carbon–oxygen bonds.\(^\text{40–42}\) The strength of halogen bonding relating to the polarizability should accordingly decrease with increasing number of carbon–oxygen bonds in the polymer side chain. Therefore, we hypothesized that pMEA analogues, which have more than two methoxy or ethoxy groups in their side chains, should be able to interact specifically with the iodine compounds due to the decreased polarity. In this study, we synthesized the first pMEA-analogue microspheres by free-radical polymerization in water and subsequently examined their separation potential with respect to iodine-containing compounds.

## RESULTS AND DISCUSSION

### Synthesis and Characterization of the Tested Microspheres

The tested microspheres and the conditions for their synthesis are listed in Table 1. Atomic force microscopy (AFM) images and the chemical structures of the tested microspheres are shown in Figure 1. The average size distributions of these microspheres are also shown in Figure S1. In this study, the initiator potassium persulfate (KPS), which leads to negatively charged surfaces, was used to start the polymerizations, as the effects of electrostatic attractions between the microspheres and the anionic halogen compounds can be neglected. The electrophoretic mobility (EPM) of the tested microspheres was negative (Table 1). Nonfunctionalyzed pMEA and pMEA-analogue microspheres were prepared by soap-free precipitation polymerization, whereby the monomers were dissolved in water during the polymerization, and the resulting polymers precipitated in water to form the microspheres. To compare the adsorption behavior of the halogen-containing compounds, polystyrene (pSt), poly(butyl acrylate) (pBA), and poly(4-methoxystyrene) (pMSt) were selected as solid control microspheres. As the methoxy groups in the pMSt microspheres act as electron-donating groups due to the resonance effect,\(^\text{43}\) the difference of the dielectric polarization between the pMEA (analogues) and pMSt microspheres can be discussed.

As poly(2-(2-ethoxyethoxy) ethyl acrylate) (pET2A) chains have a relatively low critical solution temperature (LCST; \(\sim 15^\circ\text{C}\)),\(^\text{44–46}\) the solid pET2A microspheres did not disintegrate at room temperature in the absence of a cross-linker. We note that at temperatures below 15 °C, hydrodynamic diameter (\(D_h\)) of pET2A microspheres decreased (Figure S2a), suggesting that the disintegration of pET2A microspheres occurred due to the hydration of pET2A chains. Conversely, poly(2-(2-methoxyethoxy) ethyl acrylate) (pMEA) and poly(2-(2-(2-methoxyethoxy) ethyl) acrylate) (pME3A) microspheres were not obtained in the absence of a cross-linker during the polymerizations, due to their relatively high LCST values (pMEA2: \(\sim 43^\circ\text{C}\); pME3A: \(\sim 63^\circ\text{C}\)).\(^\text{44–46}\) Thus, the cross-linker ethylene glycol dimethacrylate (EGDMA) was added to the polymerizations (5 mol %), which afforded stable pME2A and pME3A microgels (Table 1 and Figure 1). These microgels are thermoresponsive, as their \(D_h\) decreased with increasing temperature (Figure S2b,c). The difference between the solid and hydrogel states of these microspheres also influenced the adsorption behavior of low-molecular-weight compounds (vide infra).

### Adsorption Behavior of Halogen Dyes in pMEA-Analogue Microspheres

To examine the origin of the halogen-bonding, anionic halogen-containing xanthene dyes, such as eosin Y (EoY), erythrosine (Ery), phloxine B (PhB), and rose bengal (RB), were selected as organohalogen model compounds (Figure S3). Especially, iodine-containing Ery and RB are often used in food and cosmetics.\(^\text{1}\) To compare the halogen bonding with other, e.g., hydrophobic interactions, other anionic dyes that do not contain halogen atoms, such as orange II (OrII) and tartrazine (Ttz), were also examined. Figure 2 shows the adsorption isotherm for each dye for the tested microspheres at 25 °C. Langmuir (eq 1) and Freundlich (eq 3) models were applied to analyze the adsorption equilibrium data. These isotherms are shown in Figure S4. In all cases, the correlation coefficient (\(R^2\)) of the Langmuir model was close to 1 and much larger than that of the Freundlich model, indicating a good fit of the Langmuir model. Table 2 shows the values of the Langmuir isotherm parameters, and all values are summarized in Table S1. Here, the adsorption capacity (\(Q_m\)) values determined by the Langmuir model were normalized as moles of dye per total surface area (\(N_m/\text{m}^2\) or \(N_m/\text{m}^3\)) of tested microsphere to compare the adsorption behavior under consideration of the different size and state (e.g., solid or gel) of these microspheres and the different molecular weight of each dye. Furthermore, the essential characteristics of the Langmuir isotherm can be described by a separation factor (\(R_s\)) relating to the Langmuir constant (\(b\)), which is defined by eq 2 (Tables 2 and S1). The value of \(R_s\) indicates the shape of the Langmuir isotherm and...
Figure 1. Representative AFM images and chemical structures of the microspheres tested in this study. The coefficients of variation for the microspheres ($N = 50$) are shown for comparison.

Figure 2. Adsorption isotherms for the tested dyes on each microsphere at 25 $^\circ$C. Each point represents an average of three replicate adsorption experiments; the error bars denote standard deviations.
the nature of the adsorption process: irreversible ($R_L = 0$), favorable ($0 < R_L < 1$), linear ($R_L = 1$), or unfavorable ($R_L > 1$).47

Initially, we would like to discuss the significance of the polarization of the polymer side chains, which contribute to the halogen bonding. In contrast to pMEA, the methoxy group in pMSt acts as an electron-donating group, i.e., Lewis acid, due to resonance effect.43 The adsorbed amounts of halogen-containing dyes on the pMSt microspheres were much lower than those on the pMEA microspheres, and close to those on the pSt and pBA microspheres (Figure 2 and Table 2). In addition, the pMSt paste was not stained with, e.g., the red appearance of Ery or EoY after centrifugation, although facile staining of the pMEA paste was observed (Figure 3), which

| dye          | adsorbent$^a$ | $Q_m$ (mg/g) | $N_{m/s}$ (μmol/m$^2$) | $N_{m/v}$ (μmol/m$^3$) | $b$ (L/mg) | $R_L$ at 0.1 mM |
|--------------|---------------|--------------|-------------------------|-------------------------|------------|-----------------|
| erythrosine  | pMEA          | 164          | 6.61                    | 20.6                    | 0.031      | 0.21            |
|              | pET2A         | 119          | 10.3                    | 15.1                    | 0.028      | 0.25            |
|              | pME2A         | 129          | N.A.$^d$                | 31.8                    | 0.014      | 0.64            |
|              | pME3A         | 127          | N.A.$^d$                | 31.3                    | 0.004      | 0.87            |
|              | pMSt          | 35.3         | 1.12                    | 4.46                    | 0.003      | 0.96            |
| rose bengal  | pMEA          | 311          | 10.9                    | 33.9                    | 0.050      | 0.08            |
|              | pET2A         | 237          | 17.6                    | 25.8                    | 0.045      | 0.11            |
|              | pME2A         | 215          | N.A.$^d$                | 45.8                    | 0.027      | 0.30            |
| eosin Y      | pMEA          | 131          | 6.06                    | 21.0                    | 0.025      | 0.28            |
|              | pET2A         | 47.2         | 5.01                    | 7.58                    | 0.010      | 0.69            |
|              | pME2A         | 93.9         | N.A.$^d$                | 29.5                    | 0.006      | 0.80            |
|              | pME3A         | 91.7         | N.A.$^d$                | 28.7                    | 0.003      | 0.94            |
|              | pMSt          | 23.6         | 0.95                    | 3.79                    | 0.004      | 0.88            |
| phloxine B   | pMEA          | 157          | 6.76                    | 21.1                    | 0.041      | 0.13            |
|              | pET2A         | 70.6         | 4.73                    | 9.45                    | 0.008      | 0.75            |
|              | pME2A         | 101          | N.A.$^d$                | 26.4                    | 0.005      | 0.85            |
|              | pME3A         | 90.8         | N.A.$^d$                | 28.5                    | 0.007      | 0.81            |
|              | pMSt          | 17.8         | 0.83                    | 2.86                    | 0.001      | 0.98            |
| tartrazine   | pMEA          | 15.9         | 1.03                    | 3.30                    | 0.002      | 0.97            |
|              | pET2A         | 23.8         | 3.36                    | 3.82                    | 0.001      | 0.99            |
|              | pME2A         | 61.0         | N.A.$^d$                | 19.1                    | 0.009      | 0.72            |
|              | pME3A         | 90.8         | N.A.$^d$                | 28.5                    | 0.007      | 0.81            |
|              | pMSt          | 17.8         | 0.83                    | 2.86                    | 0.001      | 0.98            |

$^a$[Microsphere] = 0.1 wt %, $^b$ $N_{m/s}$ represents the adsorbed moles of dye per total surface area of the tested microspheres. $^c$ $N_{m/v}$ represents the adsorbed moles of dye per total volume of tested microspheres. The specific volume of the pME2A and pME3A microgels was calculated based on the assumption that the fully swollen microgels contain ∼80% water. $^d$ $N_{m/s}$ could not be determined, as it is difficult to determine the surface area of the microgels.

![Erythrosine-adsorbed (0.5 mM) microspheres (0.5 wt%) after centrifugation](image)

![Eosin Y-adsorbed (0.5 mM) microspheres (0.5 wt%) after centrifugation](image)

Figure 3. Photographs of solid pMSt, pMEA, and pET2A microspheres (0.5 wt %) after centrifugation in the presence of erythrosine (top) and eosin Y (bottom) at 0.5 mM and 25 °C. The displayed values of the adsorption capacity, $Q_m$ (mg/g), for each microsphere were obtained from the isotherm analysis (Table 2).
indicating that the inductive effect due to the permanent dipole of the methoxyl groups in pMEA should be an important factor for halogen bonding. As reported, the hydrophobic interactions between the tested solid microspheres and the dyes should lead to an adsorption of the tested dyes on the pMS, pSt, and pBA control microspheres, which results in $R_L < 1$ (Tables 2 and S1). Indeed, the quantity of the hydrophilic dye Ttz, which exhibits the lowest octanol–water partition coefficient ($\log K_{ow}$; Figure 3), adsorbed on the solid microspheres was smaller than those of the other dyes (Figure 2). A similar behavior was also observed for the adsorption of OrII (Table S1).

In the case of solid pET2A microspheres, wherein the number of oxygen atoms in the side chains is twice that of the pMEA microspheres (Figure 1), the adsorbed amounts of iodine-containing dyes Ery and RB per unit gram of pET2A were close to those of the pMEA microspheres (Figure 2), although the hydrodynamic diameter ($D_h$) of the pMEA microspheres ($D_h = 214$ nm) is smaller than that of the pET2A microspheres ($D_h = 453$ nm; Table 1). As a result, the $N_{ads}$ values of Ery and RB for pET2A were higher than those for pMEA, whereas the $R_L$ values of Ery and RB were close to those for pME2A (Table 2), which suggests that halogen bonding occurred in the pET2A microsphere system. Assuming that the numbers of side chains per surface area are identical for the pMEA and pET2A microspheres, the number of halogen-bonding sites (oxygen atoms) in pET2A is higher than that in pMEA microspheres, which should result in an increased amount of adsorbed iodine compounds.

On the other hand, in the case of the pME2A microgels, where the number of oxygen atoms is identical to that in the pET2A side chains (Figure 1), the Langmuir constant values of Ery and RB were lower than those of the pMEA and pET2A microspheres (Table 2), which indicates that the strength of the halogen bonding between pME2A and the iodine dyes is lower than that between pMEA and pET2A. Notably, the saturated adsorption amounts of Ery and RB per unit gram of pME2A microgels were close to those of the solid pMEA and pET2A microspheres [e.g., for the adsorption of Ery: $Q_m = 119$ mg/g (pET2A) and $Q_m = 129$ mg/g (pME2A); Table 2], suggesting that the swollen microgels can absorb low-molecular-weight compounds by osmotic pressure. This result is supported by the fact that the halogen-free dyes Ttz and OrII were also absorbed by the pME2A and pME3A microgels (Figure 2), i.e., the $N_{ads}$ values of Ttz and OrII for these microgels were higher than those for the solid control microgels (Table S1).

The fact that the Langmuir constants (or $R_L$ values) of iodine-containing compounds are different between pET2A and pME2A cannot be explained easily, as there are several possible factors involved: (i) the terminal ethoxy groups in the pET2A side chains may promote the polarization more than the terminal methoxy groups in the pME2A side chains, which would result in an increased vectorial sum of the dipole moment in pET2A. This notion is proposed as the polarizability of oligo(ethylene glycol) molecules depends on the conformer and the number of ethylene glycol units, suggesting that the polarizability may also depend on the number of carbon atoms and thus differ for methoxy and ethoxy groups; (ii) The hydrophobic interaction between solid pET2A microspheres and the dyes supports the adsorption on the surface, which should be hard to accomplish in water-swollen pME2A microgels. Although the iodine compounds can be diffused into the pME2A microgels, i.e., there are many opportunities for contact with the halogen-binding sites compared to the case of solid pET2A microspheres at $25^\circ$C, the Langmuir constants of iodine compounds for pET2A microspheres were larger than those for pME2A microgels. Furthermore, the Langmuir constants of Ery and RB for pME3A microgels, where the number of oxygen–carbon bonds is higher than that in pME2A side chains (Figure 1), were smaller than those for pMEA, pET2A, and pME2A (Table 2). Therefore, we concluded that the polarizability of the entire polymer side chain contributes to halogen-bonding and hydrophobic interactions and represents therefore an important factor for the strong adsorption of iodine compounds.

Conversely, the adsorbed amounts of iodine-free compounds, including the bromine-containing dyes EoY and PhB, on the pET2A microspheres were smaller than those of iodine-containing dyes (Figure 2), even though the pET2A microspheres exhibit a suitable halogen-bonding capacity for iodine compounds. Consequently, the $R_L$ values of EoY and PhB were close to 1 and higher than those for pMEA [e.g., at 0.1 mM EoY: $R_L \sim 0.69$ (pET2A); $R_L \sim 0.28$ (pMEA); Table 2], which suggests that the strength of the halogen bonding at the adsorption site in pET2A side chain decreased compared to that in pMEA. Consequently, the iodine-containing dye Ery was adsorbed on the pET2A microspheres, resulting in a transparent supernatant, although EoY was also present therein (Figure 3). We therefore concluded that the polarizability of pET2A was smaller than that of pMEA, due to the fact that the dipole moments in the pET2A side chain are arranged in such a fashion that they cancel each other. Accordingly, the pET2A microspheres exhibit a halogen-bonding ability for iodine compounds, and they do not bind significant amounts of bromine compounds. This trend was also observed for pME2A and pME3A microgels (e.g., pME2A: $R_L \sim 0.64$ for Ery and $R_L \sim 0.80$ for EoY; Table 2).

**Selective Adsorption and Release of Iodine Compounds.** To achieve a highly selective adsorption of iodine compounds on such microspheres, we selected the pET2A microspheres, which exhibit a more suitable halogen-bonding ability for the adsorption of iodine compounds than pMEA microspheres. In the present study, anionic RB was targeted as an iodine-containing dye, and iodine-free EoY, OrII, and Ttz were selected as competitive inhibitors for the adsorption of RB. The visible absorption spectrum of a mixture of these four dyes is shown in Figure S5. It should be noted that the exact uptake of each dye cannot be quantified using a calibration curve derived from the absorption spectrum of the dye mixture, as the absorption peaks of Ery and PhB overlap. Figure 4 shows the adsorption rate of each tested dye on the pMEA and pET2A microspheres (0.1 wt %), indicating that the adsorbed amounts of RB on both microspheres were highest when the concentrations of all dyes were comparable. However, at low dye concentrations (e.g., 0.1 mM), the pMEA microspheres adsorbed preferentially bromine-containing EoY rather than OrII and Ttz (e.g., EoY: $\sim 35\%$ at 0.1 mM and $\sim 28\%$ at 0.5 mM; Figure 4a), suggesting that halogen bonding also occurs between EoY and the pMEA microspheres via the methoxy groups that are not involved in the adsorption of RB. This phenomenon decreases the RB adsorption rate regardless of the dye concentrations.

On the other hand, for the pET2A microspheres, the adsorption of RB accounts for $\sim 70\%$ of all dyes even at dye concentrations as low as 0.1 mM (Figure 4b). However, the maximum adsorption rate of RB reached $\sim 91\%$ at 1 mM,
selected the thermoresponsive pME2A microgels to release RB, as the $D_h$ of the pME2A microgels decreases with increasing temperature up to 50 °C (Figure S2b). Indeed, the released quantity of RB increased when the temperature was raised to 50 °C, although the release behavior did not significantly change between 50 and 70 °C (Figure S, center). In our previous studies on pMEA composite microgels, the chain length of the ethylene oxides in the thermoresponsive pOEG gel matrix (five or six carbon atoms) played an important role for the temperature-dependent release of RB.21 

However, this case should be different from that of the thermoresponsive poly(N-isopropylacrylamide) (pNIPAm) microgels,48,49 where the isopropyl groups form the hydrophobic domain, and the uptake of Ery increases with rising temperature. Indeed, the anionic pNIPAm microgels did not release significant amounts of RB upon deswelling the pNIPAm microgels at high temperature (Figures S, right and S6). It should also be noted that the amount of RB adsorbed in the pNIPAm microgels, which do not contain any halogen-bonding sites, was smaller than that of the pME2A microgels at 25 °C (e.g., $Q_4$ for RB at 1 mM: ∼140 mg/g for pME2A; $Q_2$ for RB at 1 mM: ∼70 mg/g for pNIPAm; Figure S). 

The unique release behavior of the pME2A microgels may be due to the fact that the thermoresponsive behavior between the pNIPAm and the polymers that contain oligo(ethylene glycol) side chains is different. Lutz et al. proposed a mechanism that could explain the thermoresponsive behavior of pOEG-based polymers and gels:50 above their LCSTs, the cleavage of hydrogen bonds between the ethylene glycol units and water should be the driving force for the phase transition. The dehydrated oligo(ethylene glycol) chains should fold along the apolar backbone due to hydrophobic interactions, as there are no strong hydrogen-bond donors in pOEG-based polymers, i.e., interactions between the oligo(ethylene glycol) side chains were be observed by $^1$H NMR spectroscopy or dynamic light scattering. On the other hand, above the LCST of pNIPAm, the local packing of isopropyl groups of two neighboring chains and/or hydrogen bonds between amide groups should promote the formation of small hydrophobic nanopockets, where the association of isopropyl groups minimizes the exposed surface area.23 Thus, the formation of hydrophobic isopropyl domains in the pNIPAm microgels inhibits the release of organic dyes, whereas the deswollen pME2A microgels do not hamper the release of RB at high temperature (Figure S). We intend to further investigate the microscopic structural changes in these pMEA-analogue microgels in detail using a multifaceted approach that includes small-angle X-ray scattering4,45,49 and high-speed atomic force microscopy.52 

**CONCLUSIONS**

Highly selective adsorption and controlled release of iodine-containing compounds were accomplished on pMEA-analogue microgels that contain side chains with the ability to engage in halogen bonding with iodine-containing compounds in water. The two ethoxy groups in the pET2A side chains exhibit a moderate halogen-bonding strength on account of their polarizability, i.e., iodine-containing compounds were adsorbed, whereas bromine-containing compounds were not adsorbed in significant amounts, which was characterized by adsorption isothersms of several anionic dyes. The results showed that these microgels exhibit a high selectivity for the adsorption of iodine-containing compounds in the presence of iodine-free compounds. For example, the iodine-containing dye RB
accounts for >90% of all adsorbed dyes. Moreover, pME2A microgels allow a controlled release of iodine-containing dyes due to their thermoresponsive swelling/deswelling behavior. These findings should thus represent an important first step toward the development of highly selective separation methods for iodine-containing compounds, which is highly important for, e.g., the recovery of valuable drugs, the reuse of iodine-containing catalysts, and the removal of harmful iodine-containing compounds from wastewater.

**EXPERIMENTAL SECTION**

**Materials.** 2-Methoxylethyl acrylate (MEA, purity 98%), styrene (St, 99%), butyl acrylate (BA, 99%), potassium peroxodisulfate (KPS, 95%), sodium dodecyl sulfate (SDS, 95%), disodium hydrogenphosphate (99%), eosin Y (EoY, 95%), phloetine B (PhB, 98%), erythrosine (Ery, 95%), rose bengal (RB, 95%), orange II (OrII, 98%), tartrazine (Ttz, 98%), and ethanol (EtOH, 99.5%) were purchased from Wako Pure Chemical Industries and used as received. 2-(2-Ethoxyethoxy)ethyl acrylate (ET2A, 98%), 4-methoxystyrene (MSt, 98%), N-isopropylacrylamide (NIPAm, 98%), and N,N’-methylenebis(acrylamide) (BIS, 97%) were purchased from Tokyo Chemical Industry and used as received. 2-(2-Methoxyethoxy)ethyl acrylate (ME2A, 95%) was purchased from Monomer-Polymer and Dajac Labs, Inc. 2-[2-(2-Methoxyethoxy)ethoxy]ethyl acrylate (Me3A, 98%) was kindly donated by Kyoeisha Chemical Co., Ltd. The cross-linker, ethylene glycol dimethacrylate (EGDMA, 98%), was purchased from Sigma-Aldrich and used as received. Water used for microsphere preparations was distilled and then ion-exchanged (EYELA, SA-2100E1).

**Synthesis of pMEA Analogue and Control Microspheres.** All microspheres were prepared via aqueous precipitation or emulsion polymerization using potassium peroxodisulfate (KPS). Polymerizations were performed in a three-necked round-bottom flask (300 mL) equipped with a mechanical stirrer, condenser, and nitrogen gas inlet. The initial total concentrations of each monomer for solid and hydrogel microspheres are listed in Table 1. For pMEA-analogue microspheres, the initial monomer concentration was held constant at 50 mM. The monomer solutions of ET2A (1.88 g, 100 mol %), ME2A (1.65 g, 95 mol %), and ME3A (2.07 g, 95 mol %) were prepared. The details of synthetic conditions are shown in Table 1. These monomers were dissolved in water (95 mL) completely in the round-bottom flask. For NIPAm microgels, the initial total monomer concentration was held constant at 100 mM. The monomer solutions of ET2A (1.88 g, 100 mol %), ME2A (1.65 g, 95 mol %), and ME3A (2.07 g, 95 mol %) were prepared. The details of synthetic conditions are shown in Table 1. These monomers were dissolved in water (95 mL) completely in the round-bottom flask. For NIPAm microgels, the initial total monomer concentration was held constant at 150 mM. A mixture of NIPAm (1.613 g, 95 mol %), BIS (0.116 g, 5 mol %), and SDS (2.8 mg, 0.1 mM) was prepared as the monomer solution. All monomer solutions were dissolved in water (95 mL) in the round-bottom flask and heated to 70 °C under constant stirring (250 rpm) and a stream of nitrogen. The solutions were allowed to stabilize for at least 30 min prior to initiation. Free-radical polymerizations were subsequently initiated using KPS (0.054 g) in water (5 mL). The solutions were stirred for 24 h (4 h for NIPAm), and after the completion of the polymerizations, the obtained dispersions were cooled to room temperature. Each batch of microspheres was purified via two cycles of centrifugation/redispersion in water using a relative centrifugal force (RCF) of 20 000g, followed by dialysis for a week with daily water changes.

**Characterization of the Microspheres.** The hydrodynamic diameter ($D_h$) of the microspheres was determined by DLS (Malvern Instruments Ltd., Zetasizer Nano S). The time-dependent scattering intensity was detected at a total scattering angle of 173°. $D_h$ values of the microspheres were calculated from the measured diffusion coefficient using the Stokes–Einstein equation (Zetasizer software v6.12). The DLS experiments were conducted at a microsphere concentration of 0.001 wt %, Samples were allowed to thermally equilibrate at the desired temperature for 10 min prior to each measurement. The autocorrelation functions used an average of 15 intensity measurements (acquisition time: 30 s). The electrophoretic mobility (EPM) of the microspheres was measured using a Zetasizer Nano ZS (Malvern) at a microsphere concentration of 0.001 wt %. Samples were allowed to thermally equilibrate at 25 °C for 10 min prior to each measurement. The zeta potential of the solid microspheres was calculated from the measured mobility using the Smoluchowski equation (Zetasizer software v1.0). Atomic force microscopy (AFM) images were recorded under ambient conditions using an SPM-9500J3 microscope (Shimadzu, Kyoto, Japan) operating in contact mode, to visualize the microspheres deposited on circular mica substrates. For the sample preparation, microsphere dispersions (0.5 μL) at the required concentration were applied on freshly prepared mica substrates and dried for 60 min. AFM images were recorded using a Si$_2$N$_4$ probe (Olympus, OMCL-AC240FS; scanning speed = 0.2 Hz; operating voltage = 0.3 V).

**Dye Adsorption Experiments.** Stock solutions of anionic dyes (20 mM) in a sodium phosphate buffer (80 mM, pH = 7.0) were prepared. The tested microsphere dispersions were poured into a vial. The final concentration of the microspheres was 0.1 wt % for all experiments. The microgel dispersions were allowed to thermally equilibrate at the desired temperature for 1 h under constant stirring (300 rpm) in an incubator (CN-25C, Mitsubishi Electric Engineering Co., Ltd.). After the dispersions had stabilized in the incubator, the appropriate dye stock solutions were injected into the vials. The final dye concentrations were adjusted appropriately for the required conditions (0.1–2 mM). After 1 h of exposure, the mixtures were divided into three centrifuge tubes (SC-0200, Ina-Optika Co., Ltd.). The mixtures were centrifuged (RCF: 20 000g) to pack the microspheres at the bottom of each tube. The supernatant liquids were carefully removed from the centrifuge tubes without disturbing the microsphere pellets at the bottom, and the absorbance of each supernatant was measured using a UV–vis spectrophotometer (JASCO, V-630iRM).

**Analysis of the Adsorption Isotherms.** The Langmuir model is based on the assumption that maximum adsorption corresponds to the formation of a monolayer of the adsorbate on the adsorbent surface. The energy of adsorption is constant and no transmigration of adsorbate occurs on the surface. The mathematical form of Langmuir equation is

$$\frac{C_s}{Q_e} = \frac{C_s}{Q_m} + \frac{1}{Q_m b}$$

where $C_s$ (mg/L) represents the equilibrium dye concentration in solution, $Q_e$ (mg/g) is the amount of adsorbed dyes by the microspheres, $Q_m$ (mg/g) is the adsorption capacity, i.e., the amount of dye that can be absorbed by a unit mass of the adsorbent for the formation of monolayer on the surface, and $b$ (L/mg) is the Langmuir constant, which is related to the affinity between the dyes and microspheres. A dimensionless...
equilibrium parameter \((R_L)\), known as the separation factor, can be calculated using the following equation

\[
R_L = \frac{1}{1 + bC_0}
\]  

(2)

where \(C_0\) (mg/L) is the initial dye concentration in solution. The Freundlich isotherm can be used to describe the adsorption on both homogeneous and heterogeneous surfaces. The linearized form of Freundlich isotherm is

\[
\log Q_e = \log K_f + \frac{1}{n} \log C_e
\]  

(3)

where \(K_f\) and \(n\) represent the Freundlich constants that describe the adsorption capacity at unit concentration and the intensity of adsorption, respectively.

**Dye-Release Experiments.** The optimal conditions for RB adsorption were used to prepare a mixture of the microspheres and RB in a manner described above. After the supernatant was removed from each centrifuge tube, each microgel pellet was redispersed in a different buffer solution at 25, 50, or 70 °C and placed in the centrifuge tubes at concentrations identical to those used in the adsorption experiments. Each dispersion was subsequently mixed for 1 h at 25, 50, or 70 °C using a thermomixer (Thermomixer R, Eppendorf). Each mixture was then centrifuged (RCF: 20 000 g), and the supernatant liquids were removed from the centrifuge tubes. The absorbance of each supernatant was subsequently measured using a UV–vis spectrophotometer.

**ASSOCIATED CONTENT**

* Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01556.

Information on the thermoresponsive behavior of the microgels; UV–vis spectra of the tested dyes; isotherms; other related parameters (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail: d_suzuki@shinshu-u.ac.jp.

**ORCID**

Daisuke Suzuki: 0000-0003-0444-156X

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

T.K. acknowledges a grant-in-aid for JSPS Research Fellows (15J11133). D.S. acknowledges a grant-in-aid for Scientific Research on Innovative Areas (26102517 and 16H00760) and a Grant-in-Aid for Young Scientists A (17H04892) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology (MEXT).

**REFERENCES**

(1) Kaiho, T. In Iodine Chemistry and Application; Kaiho, T., Ed.; John Wiley & Sons, Inc.: Hoboken, 2014; pp 1–656.

(2) Zhdkanik, V. Y.; Stang, P. J. Recent Developments in the Chemistry of Polyvalent Iodine Compounds. Chem. Rev. 2002, 102, 2523–2584.

(3) Cloete, T. E. Resistance mechanisms of bacteria to antimicrobial compounds. Int. Biodeterior. Biodegrad. 2003, 51, 277–282.

(4) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. Chem. Rev. 2011, 111, 1215–1292.

(5) Biondi, B.; Wartofsky, L. Treatment With Thyroid Hormone. Endocr. Rev. 2014, 35, 433–512.

(6) Miller, K. D.; Siegel, R. L.; Lin, C. C.; Mariotto, A. B.; Kramer, J. L.; Rowland, J. H.; Stein, K. D.; Alteri, R.; Jemal, A. Cancer Treatment and Survival Statistics, 2016. Ca-Cancer J. Clin. 2016, 66, 271–289.

(7) Peng, H.; Chen, C.; Cantin, J.; Saunders, D. M. V.; Sun, J.; Tang, S.; Codling, G.; Hecker, M.; Wiseman, S.; Jones, P. D.; Li, A.; Rockne, K. J.; Sturchio, N. C.; Cai, M.; Giesy, J. P. Untargeted Screening and Distribution of Organo-Iodine Compounds in Sediments from Lake Michigan and the Arctic Ocean. Environ. Sci. Technol. 2016, 50, 10097–10105.

(8) Kopper, F. C.; Carpentere, L. J.; McPiggans, G. B.; Palmer, C. J.; Waite, T. J.; Boneberg, E. M.; Woitsch, S.; Weiller, M.; Abela, R.; Grolimund, D.; Potin, P.; Butter, A.; Luther, G. W.; Kronkeck, P. M. H.; Meyer-Klauckel, W.; Feiters, M. Iodide accumulation provides kelp with an inorganic antioxidant impacting atmospheric chemistry. Proc. Natl. Acad. Sci. U.S.A. 2008, 105, 6954–6958.

(9) Wang, L.; Zhou, X.; Fredimoses, M.; Liao, S.; Liu, Y. Naturally occurring organoiodines. RSC Adv. 2014, 4, 57330–57336.

(10) Fuge, R.; Johnson, C. C. Iodine and human health, the role of environmental geochemistry and diet, a review. Appl. Geochem. 2015, 63, 282–302.

(11) World Health Organization. Guidelines for Drinking-Water Quality, 4th ed.; WHO Press: Geneva, Switzerland, 2011.

(12) Chitrakar, R.; Sonoda, A.; Makita, Y.; Hirotsu, T. Calcined Mg-Al Layered Double Hydroxides for Uptake of Trace Levels of Bromate from Aqueous Solution. Ind. Eng. Chem. Res. 2011, 50, 9280–9285.

(13) Chitrakar, R.; Makita, Y.; Sonoda, A.; Hirotsu, T. Fe-Al layered double hydroxides in bromate reduction: Synthesis and reactivity. J. Colloid Interface Sci. 2011, 354, 798–803.

(14) Theiss, F. L.; Couperthwaite, S. J.; Ayoko, G. A.; Frost, R. L. A review of the removal of anions and oxyanions of the halogen elements from aqueous solution by layered double hydroxides. J. Colloid Interface Sci. 2014, 417, 356–368.

(15) Kawaguchi, H. Functional polymer microspheres. Prog. Polym. Sci. 2000, 25, 1171–1210.

(16) Kohri, M. Development of HRP-mediated enzymatic polymerization under heterogeneous conditions for the preparation of functional particles. Polym. J. 2014, 46, 373–380.

(17) Shibuya, K.; Nagao, D.; Ishii, H.; Konno, M. Advanced soap-free emulsion polymerization for highly pure, micron-sized, monodisperse polymer particles. Polymer 2014, 55, 535–539.

(18) Kitayama, Y.; Yoshikawa, K.; Takeuchi, T. Efficient Pathway for Preparing Hollow Particles: Site-Specific Crosslinking of Spherical Polymer Particles with Photoresponsive Groups That Play a Dual Role in Shell Crosslinking and Core Shielding. Langmuir 2016, 32, 9245–9253.

(19) Kamaly, N.; Yameen, B.; Wu, J.; Farokhzad, O. C. Degradable Controlled-Release Polymers and Polymeric Nanoparticles: Mechanisms of Controlling Drug Release. Chem. Rev. 2016, 116, 2602–2663.

(20) Kureha, T.; Hiroshige, S.; Matsui, S.; Suzuki, D. Water-immiscible bioncoated inks and film formation from aqueous dispersions of poly(2-methoxyethyl acrylate) microspheres. Colloids Surf., B 2017, 155, 166–172.

(21) Kureha, T.; Suzuki, D. Nanocomposite Microgels for the Selective Separation of Halogen Compounds from Aqueous Solution. Langmuir, in press, 2017. 10.1021/acs.langmuir.7b01485.

(22) Saunders, B. R.; Vincent, B. Microgel particles as model colloids: theory, properties and applications. Adv. Colloid Interface Sci. 1999, 80, 1–25.

(23) Pelton, R. Temperature-sensitive aqueous microgels. Adv. Colloid Interface Sci. 2000, 85, 1–33.

(24) Nayak, S.; Lyon, L. A. Soft Nanotechnology with Soft Nanoparticles. Angew. Chem., Int. Ed. 2005, 44, 7768–7780.
(25) Hoare, T.; Pelton, R. Characterizing charge and crosslinker distributions in polyelectrolyte microgels. *Curr. Opin. Colloid Interface Sci.* 2008, 13, 413–428.

(26) Pich, A.; Richtering, W. Microgels by Precipitation Polymerization: Synthesis, Characterization, and Functionalization. In *Chemical Design of Responsive Microgels*; Advances in Polymer Science; Springer, 2010; Vol. 234, pp 1–37.

(27) Lu, Y.; Ballauf, M. Thermosensitive core-shell microgels: From colloidal model systems to nanoreactors. *Prog. Polym. Sci.* 2011, 36, 767–792.

(28) Kawamura, A.; Hata, Y.; Miyata, T.; Uragami, T. Synthesis of glucose-responsive biocogjugated gel particles using surfactant-free emulsion polymerization. *Colloids Surf., B* 2012, 99, 74–81.

(29) Hellweg, T. Responsive core-shell microgels: Synthesis, characterization, and possible applications. *J. Polym. Sci., Part B: Polym. Phys.* 2013, 51, 1073–1083.

(30) Musyanovych, A.; Landfester, K. Polymer Micro- and Nanocapsules as Biological Carriers with Multifunctional Properties. *Macromol. Biosci.* 2014, 14, 458–477.

(31) Habicht, A.; Schmolke, W.; Goerigk, G.; Lange, F.; Saalwachter, K.; Ballauf, M.; Seifert, S. Critical Fluctuations and Static Inhomogeneities in Polymer Gel Volume Phase Transitions. *J. Polym. Sci., Part B: Polym. Phys.* 2015, 53, 1112–1122.

(32) Schroeder, R.; Rudov, A. A.; Lyon, L. A.; Richtering, W.; Pich, A.; Potemkin, I. I. Electrostatic Interactions and Osmotic Pressure of Counterions Control the pH-Dependent Swelling and Collapse of Polyampholyte Microgels with Random Distribution of Ionizable Groups. *Macromolecules* 2015, 48, 5914–5927.

(33) Xing, X.; Hua, L.; Ngai, T. Depletion versus stabilization induced by polymers and nanoparticles: The state of the art. *Curr. Opin. Colloid Interface Sci.* 2015, 20, 54–59.

(34) Suzuki, D.; Horigome, K.; Kureha, T.; Matsu, S.; Watanabe, T. Polymeric hydrogel microspheres: design, synthesis, characterization, assembly and applications. *Polym. J.* 2017, 49, 695–702.

(35) Murray-Rust, P.; Motherwell, W. D. S. Computer retrieval and analysis of molecular geometry: 4. Intermolecular interactions. *J. Am. Chem. Soc.* 1979, 101, 4374–4376.

(36) Politzer, P.; Lane, P.; Concha, M. C.; Ma, Y.; Murray, J. S. An overview of halogen bonding. *J. Mol. Model.* 2007, 13, 305–311.

(37) Erdélyi, M. Halogen bonding in solution. *Chem. Soc. Rev.* 2012, 41, 3547–3557.

(38) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. Halogen bonding in solution: thermodynamics and applications. *Chem. Soc. Rev.* 2013, 42, 1667–1680.

(39) Robertson, C. C.; Wright, J. S.; Carrington, E. J.; Perutz, R. N.; Hunter, C. A.; Brammer, L. Hydrogen bonding vs. halogen bonding: the solvent decides. *Chem. Sci.* 2017, 8, 5392–5398.

(40) Zaslavsky, B. Y.; Miheeva, L. M.; Masimov, E. A.; Djafarov, S. F.; Rechardt, C. Solvent polarity of aqueous polymer solutions as measured by the solvatochromic technique. *J. Chem. Soc., Faraday Trans.* 1990, 86, 519–524.

(41) Wang, R. L. C.; Kreuzer, H. J.; Grunze, M.; Pertsin, A. J. The effect of electrostatic fields on an oligo(ethylene glycol) molecule: dipole moments, polarizabilities and field dissociation. *Phys. Chem. Chem. Phys.* 2000, 2, 1721–1727.

(42) He, X.; Lopes, P. E. M.; MacKerell, A. D., Jr. Polarizable Empirical Force Field for Acyclic Polyalcohols Based on the Classical Drude Oscillator. *Biopolymers* 2013, 99, 724–738.

(43) Domenicano, A.; Murray-Rust, P. Geometrical substituent parameters for benzene derivatives: inductive and resonance effects. *Tetrahedron Lett.* 1979, 20, 2283–2286.

(44) Sato, K.; Kobayashi, S.; Kusakari, M.; Watabiki, S.; Oikawa, M.; Hoshiba, T.; Tanaka, M. The Relationship Between Water Structure and Blood Compatibility in Poly(2-methoxyethyl Acrylate) (PMEA) Analogues. *Macromol. Biosci.* 2015, 15, 1296–1303.

(45) Hoshiba, T.; Nemoto, E.; Sato, K.; Orui, T.; Otaki, T.; Yoshiihori, A.; Tanaka, M. Regulation of the Contribution of Integrin to Cell Attachment on Poly(2-Methoxyethyl Acrylate) (PMEA) Analogous Polymers for Attachment-Based Cell Enrichment. *PLoS One* 2015, 10, e0136066.

(46) Hoshiba, T.; Nemoto, E.; Sato, K.; Maruyama, H.; Endo, C.; Tanaka, M. Promotion of Adipogenesis of 3T3-L1 Cells on Protein Adsorption-Suppressing Poly(2-methoxyethyl acrylate) Analogos. *Biomacromolecules* 2016, 17, 3808–3815.

(47) Weber, T. W.; Chakravarty, R. K. Pore and solid diffusion models for fixed-bed adsorbers. *AIChE J.* 1974, 20, 228–238.

(48) Kureha, T.; Sato, T.; Suzuki, D. Relationship between Temperature-Induced Changes in Internal Microscopic Structures of Poly(N-isopropylacrylamide) Microgels and Organic Dye Uptake Behavior. *Langmuir* 2014, 30, 8717–8725.

(49) Kureha, T.; Shibamoto, T.; Matsu, S.; Sato, T.; Suzuki, D. Investigation of Changes in the Microscopic Structure of Anionic Poly(N-isopropylacrylamide-co-Acrylic acid) Microgels in the Presence of Catonic Organic Dyes toward Precisely Controlled Uptake/Release of Low-Molecular-Weight Chemical Compound. *Langmuir* 2016, 32, 4575–4585.

(50) Lutz, J. F.; Weichenhan, K.; Akdemir, Ö.; Hoth, A. About the Phase Transitions in Aqueous Solutions of Thermoresponsive Copolymers and Hydrogels Based on 2-(2-methoxyethoxy)ethyl Methacrylate and Oligo(ethylene glycol) Methacrylate. *Macromolecules* 2007, 40, 2503–2508.

(51) Ahmed, Z.; Gooding, E. A.; Pimenov, K. V.; Wang, L.; Asher, S. A. UV Resonance Raman Determination of Molecular Structure of Poly(N-isopropylacrylamide) Volume Phase Transition. *J. Phys. Chem. B* 2009, 113, 4248–4256.

(52) Matsu, S.; Kureha, T.; Hiroshige, S.; Shibata, M.; Uchihashi, T.; Suzuki, D. Fast Adsorption of Soft Hydrogel Microspheres on Solid Surfaces in Aqueous Solution. *Angew. Chem., Int. Ed.* 2017, 56, 12146–12149.

(53) Langmuir, I. The Constitution and Fundamental Properties of Solids and Liquids. II. Liquids. *J. Am. Chem. Soc.* 1917, 39, 1848–1906.

(54) Freundlich, H. Über Die Adsorption in Lösungen. *Z. Phys. Chem.* 1906, 57, 385–470.