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Molecularly imprinted polymers with halogen bonding-based molecular recognition sites

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Abstract—Molecular recognition materials bearing halogen bonding-based binding sites were synthesized by a non-covalent imprinting technique using a 2,3,5,6-tetrafluoro-4-iodostyrene (**TFIS**) as the functional monomer. The binding sites were generated by co-polymerizing **TFIS**, styrene and divinylbenzene in the presence of the template molecule (4-dimethylaminopyridine—DMAP). The imprinted polymer preferentially adsorbed aminopyridine derivatives, suggesting that halogen bonding may play a role in the selective recognition of analytes by the synthesized synthetic receptor.

Halogen atoms can act as electron acceptors and interact with chemical species that have an ability to act as electron donors.[1] This non-covalent interaction can be strong enough to modulate the aggregation of organic molecules in solid,[2] liquid,[3] liquid crystal[4] and gas phases,[5] and the term 'halogen bonding' has been suggested in order to emphasize the similarity with hydrogen bonding, which is frequently the key non-covalent interaction in chemistry, biology, and materials science.[6] It is well known that halogen molecules or alkyl and aryl halides tend to form complexes with atoms containing lone pairs.[1,6] Interactions occurring between various amino (or pyridine) derivatives and iodoperfluoro compounds give rise to crystalline complexes, which have been confirmed by X-ray analyses.[7] So far halogen bonding has not well-tried for use in solution, but it seems to attract wide interest as a non-covalent interaction. Recent articles[6,7] have shown that halogen bonding is a strong, specific and directional interaction which gives well-defined supramolecular systems.

Molecular imprinting has been known as a preparation technique to yield selective molecular recognition materials.[8] Molecularly imprinted polymers are synthesized by copolymerization of a functional monomer(s) and a cross-linker(s) in the presence of a template molecule to be recognized. The resulting polymers have selective binding sites complementary to the template. In non-covalent imprinting,[9] functional monomers are chosen to complement to template molecule's functional groups. After the polymerization with cross-linker(s), templates are removed by washing with solvents that should weaken the interaction. The advantage of using non-covalent interaction is the ease of pre-organization of complexes between a functional monomer(s) and a template. Previously, we have reported the selective synthetic polymer receptors prepared by molecular imprinting, in which the hydrogen bonds were mainly utilized in the binding sites.[10] On the other hand, Whitcombe et al.[11] have demonstrated that the covalently imprinted polymers showed significantly uptake of 2,3,7,8-tetrachlorodibenzodioxin (TCDD). TCDD bound to the polymer possibly by halogen bonding with aromatic chlorine atoms and π–π interactions in the binding sites, however, they did not clearly show the contribution of halogen bonding.

In this letter, we attempt to construct a molecular recognition material by molecular imprinting using halogen bonding for DMAP (template molecule) and its relative compounds, in which halogen bonding could be a main interaction in the binding sites. Figure 1 shows an illustration of halogen-bonded molecular recognition site generation in this work. The used functional monomer, 2,3,5,6-tetrafluoro-4-iodostyrene (**TFIS**), was synthesized

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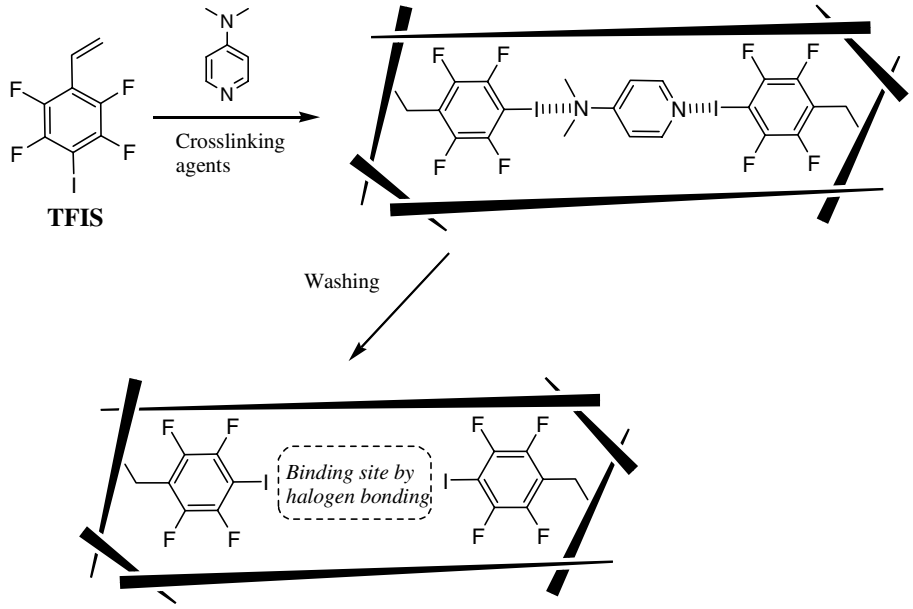
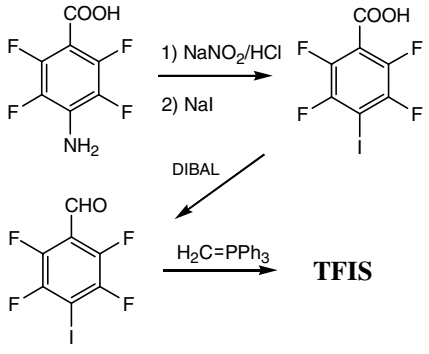


Figure 1. Possible structure of molecularly imprinted polymer using DMAP as template.

from 4-amino-2,3,5,6-tetrafluorobenzoic acid according to Scheme 1. The functional monomer is substituted by four fluorine atoms at 2, 3, 5 and 6 positions, in order to enhance the electron acceptability on the iodine atom, and is expected to interact with two nitrogen atoms of *N*,*N*-dimethylamino and pyridyl in a DMAP. The route relies on the stepwise Sandmeyer reaction for the iodination followed by the reduction of carboxyl group using diisobutylaluminiumhydride (DIBAL) and Wittig reaction of 2,3,5,6-tetrafluoro-4-iodobenzaldehyde. **TFIS** was purified by silica gel column chromatography (eluent: *n*-hexane) in total 14% yield. DMAP-imprinted polymer was prepared as follows:[6–8] **TFIS** (0.3 mmol) and DMAP (0.1 mmol) was dissolved in $CHCl_3$ (2.0 ml), and styrene (0.4 mmol) and divinylbenzene (4.5 mmol) were added as crosslinking agents, then 2,2'-azobis(2,4-dimethyl valeronitrile) (0.08 mmol) was added as an initiator of the radical polymerization. The polymerization mixture was purged with nitrogen gas, sealed, then heated at 60 °C for 12 h. The resulting polymer was ground and sieved to yield the polymer particles (size: less than 32 μm). The particles were washed with methanol, and 87% of the template was removed from the polymer by the treatment.



Scheme 1. Synthesis of functional monomer **TFIS**.

The binding characteristics and imprint effect of the polymers were evaluated after the incubation in acetonitrile solutions of DMAP and structurally related compounds (250 μM) shown in Figure 2. The polymer (10 mg) was added to acetonitrile (1.0 ml) containing DMAP or related compounds. After the suspensions were rotated for 24 h at 20 °C, the polymer particles were removed by filtration with a syringe fitted with a disposable 5 μm filter cartridge. The filtrate solutions were analyzed by an Agilent GC–MS system (model 6890N GC/5973MSD, column: HP-5ms).

In order to evaluate the selectivity of the DMAP-imprinted polymer, the binding of various analytes were examined (Fig. 2). The imprinted polymer weakly adsorbed *N*,*N*-dimethylaniline **2**, 4-picoline **3**, aniline **5**, and pyridine **6**, which possess an amino (*N*,*N*-dimethylamino) or a pyridyl group, compared with the binding of DMAP **1** that has two bondable sites in its structure. The selectivity developed is most likely due to two-point molecular recognition. Thus, the two halogen bonding between the lone pair on the nitrogen atom and the iodine atom is formed in the binding site. The interaction is halogen bonding, rather than hydrogen bonding, because neither hydrogen donor nor acceptor exists in the polymer matrix. Better binding ability for 2-substituted pyridine and quinoline derivatives, such as 2-aminopyridine **7** and 8-aminoquinoline **11**, were shown on the binding of the imprinted polymer, as contrast with 2-picoline **8**, 1-naphthylamine **9** and quinoline **10**. However, the binding abilities of **7** and **11** were inferior to that of DMAP. This means that the molecular recognition is affected by the steric hindrance for the imprinted cavity.

Among the analytes used in this work, 4-aminopyridine **4** showed the strongest binding to the imprinted polymer. This value was ca. 1.7 times as large as that of DMAP. It could be explained that 4-aminopyridine

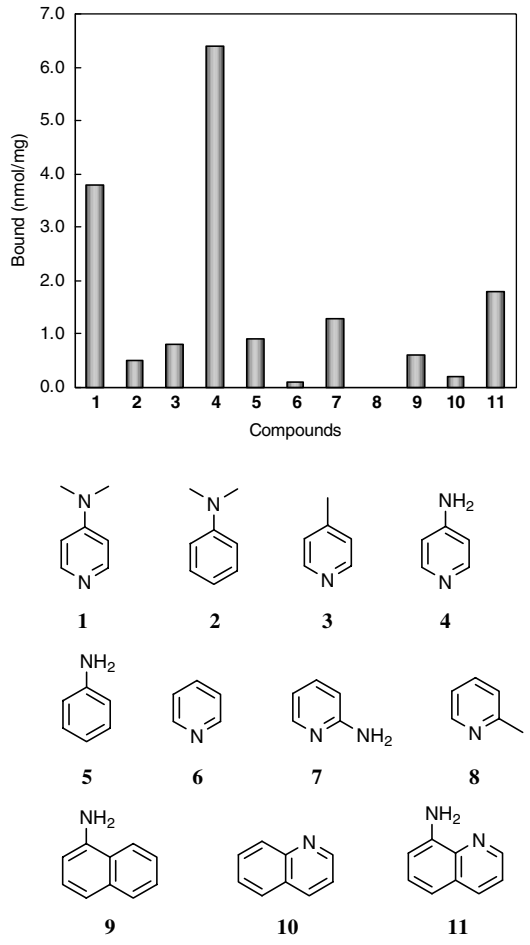


Figure 2. Binding abilities of the imprinted polymer for DMAP and related compounds: **1**, DMAP; **2**, *N*,*N*-dimethylaniline; **3**, 4-picoline; **4**, 4-aminopyridine; **5**, aniline; **6**, pyridine; **7**, 2-aminopyridine; **8**, 2-picoline; **9**, 1-naphthylamine; **10**, quinoline; **11**, 8-aminoquinoline.

was better fitted in the imprinted cavity for the two point halogen bonding between nitrogen and iodine atom because of a less bulkiness basic group at 4-position. Consequently, the selectivity for the imprinted polymer was affected by the orientation of the functional groups as well as the size of analytes.

In conclusion, we have newly developed the halogen bonding-based bidentate imprinted polymer, which can selectively bind pyridine derivatives attached with a 4-basic group. This is the first example for use of halogen bonding in the field of molecularly imprinted polymers as the main interaction driving the intermolecular recognition process with suitable analytes in solution. Further details of characterization on binding sites of imprinted polymer should be addressed to improve the effectiveness of molecular recognition and it will be reported elsewhere.

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