Molecularly-imprinted polymeric logic gates selective for predetermined chemical input species†

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Selective AND and OR logic gates were fabricated by molecular imprinting with simultaneous use of two kinds of template species, with the resultant binding behaviour (AND or OR) of the imprinted polymers governed by intermolecular interactions between the two template species.

The design and synthesis of molecular logic gates are intriguing themes in the field of intelligent materials. Various molecular logic gates utilizing nucleic acids,[1] peptides,[2] synthetic molecules[3] and polymers[4] as design platforms have been devised. A feature of molecular logic gates is that inputs can be selected from an abundant variety of molecules and ions, while conventional logic gates chiefly utilize voltage; to take advantage of this feature in developing molecular logic gates, it is desirable that multiple binding sites can be customized for input species of interest. To date, however, the major strategy has been a combination of preexisting receptor moieties. The establishment of a methodology to design and compose multiple receptor sites that are customized for input of certain chemical species is therefore desirable. Here, we demonstrate the validity of a molecular imprinting technique for developing customized polymeric logic gates (AND, OR) which are usable with predetermined chemical input species.

Molecular imprinting is a known synthetic technique for developing polymeric artificial receptors to given target molecules.[5] In this technique, the selectivity of the resultant polymeric receptor can be predetermined by a template molecule which is added to the polymerization mixture of monomers and cross-linkers. To develop polymeric logic gates, we planned to conduct molecular imprinting using two kinds of template molecules to synthesize artificial receptors which would recognize these two chemical species as inputs (Fig. 1). When the two chosen molecules interact with each other, a binding site is formed which can recognize the resultant complex (Fig. 1a). Such a binding site would be expected to show strong affinity for the complex when both input species are present, while binding each template molecule separately to a limited degree. With the second input species (INPUT-B) chosen to serve as a reporter, the polymer functions as an AND logic gate that shows an output upon sequential binding of both input species. An OR logic gate can be realized by imprinting two kinds of template molecules without interaction with each other (Fig. 1b). Such "parallel" two-molecule imprinting results in two independent binding sites, each showing significant affinity for the corresponding chemical input. If both input molecules possess a reporter function, the polymer should exhibit an output upon binding of either input molecule.

Synthesis of a polymeric AND logic gate (P-AND) was conducted by metal-ion mediated molecular imprinting, in which

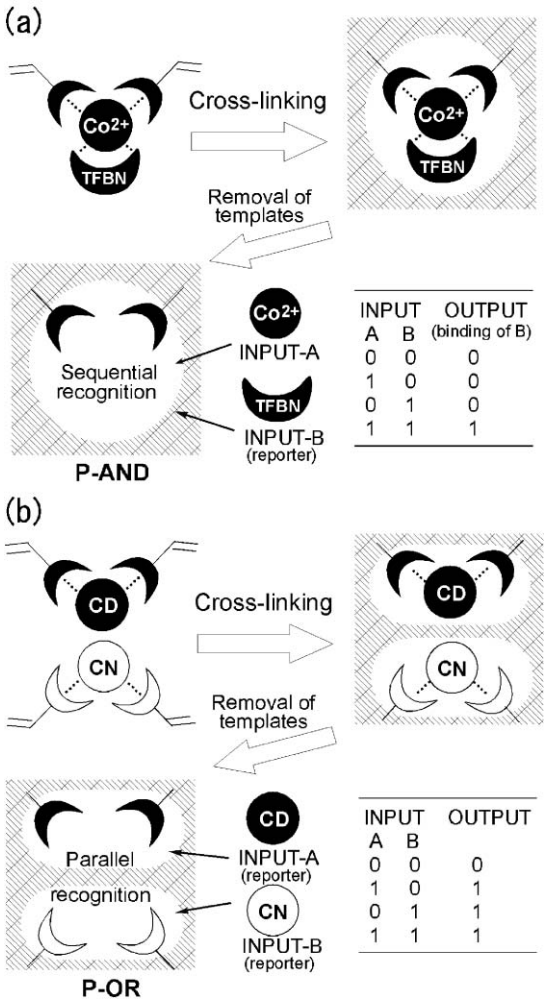

Fig. 1 Schematic representation of molecular imprinting for construction of polymeric logic gates: (a) P-AND and (b) P-OR. 4,4,4-Trifluoro-1-(2-naphthyl)-1,3-butanedione (TFNB), cobalt(II) acetate (Co^{2+}), cinchonidine (CD) and cinchonine (CN) are the template (input) species used.

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a metal ion and a ligand molecule are used as templates in the synthesis of a metal chelating polymer (for details, see ESI†).[6] P-AND was obtained by co-polymerization of 4-vinylpyridine, styrene and divinylbenzene in the presence of cobalt(II) acetate and 4,4,4-trifluoro-1-(2-naphthyl)-1,3-butanedione (TFNB) as templates (Fig. 1a). TFNB, a fluorescent β-diketone, was expected to form a complex with cobalt(II) acetate and 4-vinylpyridine during the polymerization process; thus, the resultant polymer would bind TFNB *via* Co^{2+} adsorbed at the pyridinyl moieties of P-AND.[6] The resulting polymeric logic gate P-AND was assessed as a stationary phase in liquid chromatography using cobalt(II) acetate (added in the eluent) and TFNB (injected) as chemical inputs. The chromatograms obtained show Co^{2+} dependent retention behaviour (Fig. 2a); P-AND exhibited about 6-min retention of TFNB in the presence of the Co^{2+} ion (**2** + **3**), while no significant retention was observed without addition of Co^{2+} ion in the eluent (**3**). The absence of TFNB was simulated by injecting a dummy acetone sample (**1**, **2**), resulting in rapid elution. Setting the output of this system as 6 min absorbance and the threshold as 0.004, outputs corresponding to the truth table of AND logic were successfully obtained, as shown in the inset of Fig. 2a.

Synthesis of a polymeric OR logic gate (P-OR) was conducted using two structurally similar template species and a conventional molecular imprinting protocol (for details, see ESI†).[7] Cinchonidine and cinchonine, which are diastereomers of each other, were added to a chloroform solution of methacrylic acid, 2-trifluoromethylacrylic acid and ethylene glycol dimethacrylate. Co-polymerization resulted in a cross-linked polymer containing binding sites for both cinchonidine and cinchonine. It was demonstrated by chromatography that each input molecule (**4**, **5**) could be solely bound to P-OR (Fig. 2b). Setting the output of this system as the absorbance at 6 min and the threshold as 0.004, a truth table of OR logic was obtained, as shown in the inset of Fig 2b.

The selectivity of the polymeric logic gates was assessed using structurally related compounds as fake inputs. For P-AND, 2-acetylnaphthalene (**3′**) was tested in place of TFNB. For P-OR, quinine (**4′**) and quinidine (**5′**), in which a hydrogen atom in the quinoline ring of cinchonidine/cinchonine is substituted with a methoxy group, were used as fake input species. As shown in Fig. 2a and 2b, the tested fake inputs eluted quickly, exhibiting output "0", which showed that the polymeric logic gates recognized only the predetermined input species. It should be noted that control polymers prepared without the template species showed no significant selectivity and were not able to produce proper truth tables as shown in Fig. 3a–3d. For P-AND, three kinds of control polymers were prepared and assessed: P–Co, with addition of Co(II) acetate only; P-TFNB, with addition of TFNB only; P-None, without addition of any template species. The retention behaviour of the imperfectly imprinted polymers P–Co and P-TFNB and the non-imprint polymer P-None is shown in Fig. 3a, 3b and 3c, respectively. All the control polymers retained the input species for significantly shorter times than P-AND. Furthermore, the retention of TFNB was not significantly enhanced by the addition of Co^{2+} ions, which suggests that the control polymers did not recognize TFNB *via* the Co^{2+} ion. These results showed that the addition of both templates was essential for the logic gate function of P-AND.

A control polymer for P-OR, P-None2, was prepared without addition of any template species. In P-None2, no significant retention of the input species was observed, as shown in Fig. 3d, and the fake input species, quinine and quinidine, were not clearly separated from the true input species, cinchonidine and cinchonine, which suggested that it was difficult for the polymer to

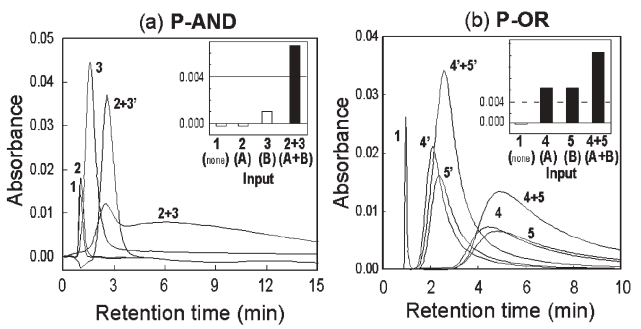

Fig. 2 Retention of input species and fake input species in (a) P-AND and (b) P-OR which were packed in columns (50 × 4.6 mm, i.d.) as stationary phase. Chromatograms were obtained by injection of acetone to represent no input (**1**), acetone in the presence of cobalt(II) acetate in the eluent (**2**), TFNB without cobalt (II) acetate (**3**), and TFNB in the presence of cobalt(II) acetate (**2** + **3**) for P-AND, and by injection of cinchonidine (**4**), cinchonine (**5**), cinchonidine and cinchonine (**4** + **5**), 2-acetylnaphthalene (**3′**), quinine (**4′**), and quinidine (**5′**) for P-OR. Insets indicate absorbance at 6 min in the corresponding chromatograms.

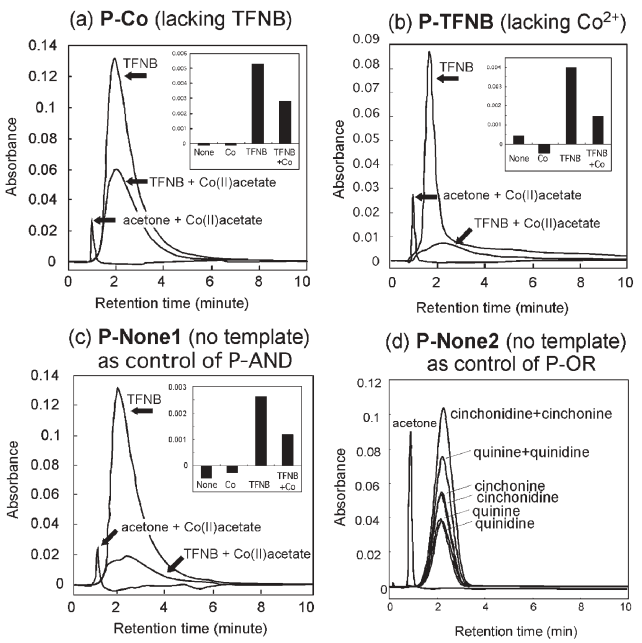

Fig. 3 Retention behaviour of control polymers prepared with one template species or without any template speices; (a) Co(II)–imprint polymer P–Co, (b) TFNB-imprinted polymer P-TFNB, (c) non-imprinted polymer P-None1 as control for P-AND, (d) non-imprinted polymer P-None2 as control for P-OR. The eluent was methanol with or without cobalt(II) acetate (0.5 mM) for P–Co, P-TFNB, and P-None1, and acetonitrile–water–acetic acid (90 : 5 : 5, v/v/v) for P-None2. The flow rate was 1.0 mL min^{-1} and detection was conducted at 255 nm (a), (b), and (c) and at 280 nm (d). The insets in (a), (b), and (c) indicate absorbance at 6 min. No chromatograms of acetone without Co(II) acetate are shown in (a), (b), or (c) because they were not significantly different from that of acetone with Co(II) acetate.

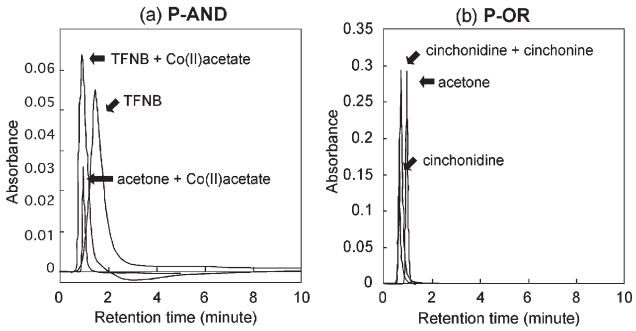

Fig. 4 Retention behaviour of polymeric logic gates in the presence of binding inhibitors (a) acetonitrile (P-AND) and (b) acetic acid (P-OR). The eluent was methanol–acetonitrile (1 : 1, v/v) with/without 1.0 mM of Co(II) acetate for P-AND, and acetonitrile with acetic acid (25%) and water (5%) for P-OR. The flow rate was 1.0 mL min^{-1}, and detection was conducted at (a) 255 nm and (b) 280 nm. No chromatograms of acetone alone (a) and cinchonine (b) are shown because they were not significantly different from those of acetone with Co(II) acetate and cinchonidine, respectively.

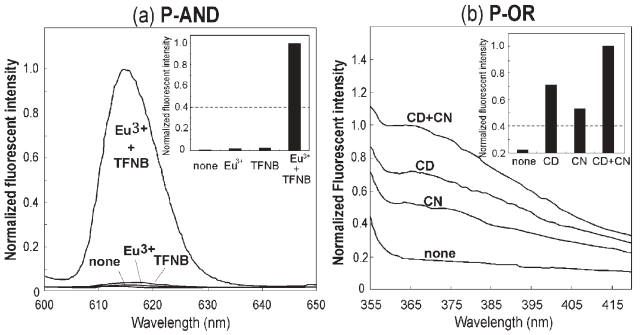

Fig. 5 Fluorescence spectra of P-AND (ex: 345 nm) and P-OR (ex: 340 nm) suspended with paraffin oil in a quartz cell (10 × 10 mm) after incubation with the corresponding input species (100 μM each). Insets indicate the fluorescence intensity at 615 nm and 360 nm for P-AND and P-OR, respectively.

operate as a selective OR logic gate. Because polymers imprinted with either cinchonidine or cinchonine were reported to exhibit selective retention of the template compound,[7] obviously polymers which accept cinchonidine and cinchonine evenly cannot be produced using a single kind of template molecule. Therefore, to develop selective OR logic gate polymers, it is necessary to use both template species simultaneously.

In molecularly imprinted polymeric logic gates, the binding behaviour of the logic gates can easily be tuned, because both the selectivity and the engaging interactions are predetermined by the choice of template and monomers. For instance, selective binding was cancelled by addition of binding inhibitors imitating INHIBIT signals; acetonitrile and acetic acid were chosen as inhibitors for P-AND and P-OR, respectively, because they interfere with coordination and hydrogen bonding between the input species and the polymers. As expected, addition of the inhibitors to the eluent caused the prompt elution of the input species in whatever combination they are present (Fig. 4a and 4b).

The truth tables of AND and OR logic were also obtained by measuring the fluorescence of the input species bound to the polymer. Fluorescence spectra of suspensions of P-AND and P-OR after treatment with their input species are shown in Fig. 5. In measurements of P-AND, Eu^{3+} was used in place of Co^{2+} because it forms a complex with TFNB that shows a strong fluorescence at a longer wavelength than TFNB alone, which is favorable for specific detection of TFNB bound to the polymer *via* metal coordination.[8] As shown in Fig. 5a, P-AND exhibited a strong fluorescence at 615 nm, due to a TFNB–Eu complex, only when both TFNB and Eu^{3+} were present. P-OR showed fluorescence at 360 nm upon treatment with either cinchonidine or cinchonine (Fig. 5b), thus resulting in AND and OR outputs, as shown in the insets of Fig. 5a and 5b.

In conclusion, we have demonstrated that molecular imprinting may be used to synthesize polymers that exhibit AND and OR logic-based binding properties for predetermined input species. The selectivity of these polymeric logic gates can be customized simply by the choice of template. Also, the logic demonstrated by a polymer can be intuitively designed by considering the intermolecular interaction between the input (template) species and the monomers, which means that it may be possible to apply this strategy to the fabrication of other types of polymeric logic gates.‡

Notes and references

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8 Synthesis of P-AND with Eu^{3+} was unsuccessful because of rapid generation of precipitates in the pre-polymerization mixture. The polymerization mixture with Co^{2+} gave no precipitates; therefore, P-AND prepared with Co^{2+} was used throughout this study.