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Molecularly Imprinted Polymer Synthesis Using RAFT Polymerisation

(Sintesis Polimer Molekul Tercetak Menggunakan Pempolimeran RAFT)

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ABSTRACT

In this paper, the synthesis and characterisation of caffeine-imprinted polymers are described. The polymers were prepared in monolithic form via both reversible addition-fragmentation chain-transfer (RAFT) polymerisation and conventional free radical polymerisation, using methacrylic acid and ethylene glycol dimethacrylate as the functional monomer and crosslinking agent, respectively. The potential benefits in applying RAFT polymerisation techniques towards the synthesis of molecularly imprinted polymers (MIPs) are explored and elucidated. The pore structures of the polymers produced were characterised by nitrogen sorption porosimetry and the molecular recognition properties of representative products were evaluated in high-performance liquid chromatography (HPLC) mode. Molecular imprinting effects were confirmed by analysing the relative retentions of analytes on imprinted and non-imprinted HPLC stationary phases. It was found that a caffeine-imprinted polymer synthesised by RAFT polymerisation was superior to a polymer prepared using a conventional synthetic approach; the imprinting factor and column efficiency were found to be higher for the former material.

Keywords: Caffeine; molecular recognition; molecularly imprinted polymers; novel stationary phases; RAFT polymerisation

ABSTRAK

Dalam penyelidikan ini, sintesis dan pencirian terhadap polimer tercetak-kafein telah diterangkan. Polimer tersebut telah disediakan dalam bentuk monolitik melalui pempolimeran tambahan-fragmentasi rantai pindah boleh balik (RAFT) dan pempolimeran konvensional radikal bebas, menggunakan asid metaakrilik sebagai monomer berfungsi dan etilena glikol sebagai ejen taut silang. Potensi yang dapat dimanfaatkan dengan menggunakan teknik pempolimeran RAFT dalam sintesis polimer molekul tercetak (MIPs) telah diterokai dan difahami. Struktur liang polimer yang terhasil telah dicirikan dengan menggunakan porosimeter penyerapan nitrogen manakala pengecaman sifat molekul produk tersebut telah dinilai dalam mod kromatografi cecair berprestasi tinggi (HPLC). Hasil pencetakan molekul dikenal pasti dengan menganalisis perbezaan relatif antara puncak analit-tercetak dan analit-tidak tercetak dalam fasa gerak HPLC. Didapati polimer tercetak-kafein melalui pempolimeran RAFT adalah lebih baik daripada polimer yang disintesis melalui kaedah konvensional; kesan pencetakan dan kecekapan kolum didapati lebih tinggi bagi bahan yang pertama tadi.

Kata kunci: Fasa gerak terbaharu; kafein; pempolimeran RAFT; pengecaman molekul; polimer molekul tercetak

INTRODUCTION

The molecular imprinting of organic polymers is a synthetic process whereby functional and crosslinking monomers are copolymerised in the presence of a target analyte; the analyte acts as a template in a template-directed synthesis process (Cormack & Zurutuza-Elorza 2004). For non-covalent molecular imprinting methods, the functional monomers form a complex with the template molecule in solution; upon polymerisation, the functional groups in the functional monomers are fixed in position by the highly crosslinked, porous polymeric structure. Once polymerisation is complete, removal of the template molecule from the polymer network reveals binding sites which are complementary in size, shape and chemical functionality to the analyte. In this way, a 'molecular memory' is introduced into the polymer, which is now capable of rebinding the analyte with a very high selectivity (Haupt & Mosbach 2000).

MIPs have a broad range of potential applications in separation science (Kempe & Mosbach 1995; Ramström & Ansell 1998) catalysis (O'Connor et al. 2007), biomimetic sensors (Piletsky et al. 1994; Thoelen et al. 2008) and drug delivery (Theodoridis & Manesiotis 2002), *inter alia*. They are normally synthesised by free radical polymerisation (FRP) due to the tolerance of FRP for a wide range of functional groups in the monomers and templates, but also because conventional FRP can normally be carried out in a facile manner under non-stringent reaction conditions. However, even when applied to the synthesis of structurally non-complex polymer architectures, such as linear macromolecules, FRP allows for only limited control over the polymer

growth processes and molecular architectures of the polymeric products (Goto & Fukuda 2004; Hawker 1997). In this light, methods of controlled (living) radical polymerisation (CRP; now also known as reversible-deactivation radical polymerization, or RDRP) have been evolved, and it has been demonstrated repeatedly that CRP processes offer some benefits over FRP. Benefits include the ability to exert tighter control over the molar mass and molar mass distribution of products and to prepare block copolymers and other polymers, both linear and non-linear, of complex architecture (Mayadunne et al. 1999).

As an alternative to conventional FRP for the production of MIPs, our hypothesis was that the controlled nature of CRP would translate into MIPs with properties superior to those displayed by MIPs prepared by FRP, for example improved homogeneity of binding sites, higher binding constants and enhanced chromatographic performance could be anticipated.

The recent emergence of techniques for implementing CRP has enabled polymer chemists to exert very precise control over the polymerisation processes while retaining much of the practical versatility of FRP (Matyjaszewski & Xia 2001; Moad et al. 2000; Perrier & Takolpuckdee 2005). The CRP techniques that have received most attention are nitroxide-mediated radical polymerisation (NMRP), atom-transfer radical polymerisation (ATRP) and reversible addition-fragmentation chain-transfer (RAFT) polymerisation.

In recent years, the NMRP technique has been exploited extensively for the synthesis of narrow molar mass distribution homopolymers and block copolymers of styrene and acrylates (Georges et al. 1993; Hawker 2001). Svec and co-workers were the first to emphasize the potential advantages of using NMRP for the preparation of macroporous polymers by the direct copolymerisation of monovinyl and divinyl monomers in the presence of a porogenic solvent (Peters et al. 1999; Viklund et al. 2001). ATRP is more versatile than NMRP, but it requires unconventional initiating systems that often have poor compatibility with polymerisation media (Malic & Evans 2006; Monteiro & de Brouwer 2000; Vana et al. 2002). Furthermore, metal contamination of the polymeric products can be problematic. More recently, RAFT polymerisation has become established as a valuable method of CRP and is one of the most versatile ways to confer 'living' characteristics onto radical polymerisations. The method relies on efficient chain-transfer processes, mediated by RAFT agents such as thiocarbonyl-containing dithioesters (Moad et al. 2005).

RAFT polymerisation is applicable to a wide range of monomers (indeed, many of the monomers polymerisable by FRP) and reaction conditions and, unlike ATRP, there are no metal contaminants present in the final products. RAFT polymerisation has been used for the grafting of crosslinked molecularly imprinted polymers from mesoporous silica beads modified with an azo initiator (Farnoosh & Titirici 2008; Titirici & Sellergren 2006). An alternative approach to tether MIPs to silica surfaces using RAFT polymerisation was reported by Bindushree et al. (2006). RAFT polymerisation has also been used to prepare MIPs with fast binding kinetics (Lu et al. 2007) and tailor-made structures (McLeary & Klumperman 2006; Southard et al. 2007) and very recently for the preparation of polymer microspheres (Pan et al. 2009). However, its application to molecular imprinting is still very much under-developed and its true potential remains largely unexplored. The main objective of the present work was therefore to explore the potential benefits in applying RAFT polymerisation techniques towards the synthesis of MIPs. In this study, caffeine was selected as a template because it has been used previously as a template in the production of MIPs through conventional synthesis approaches by our research group and others. Caffeine has also served as the template for the production of imprinted sensors (Lai et al. 1998; Yoshimi et al. 2001) and imprinted polymer microspheres used in radioligand binding assays (Ye et al. 2000).

Materials and Methods

Chemicals and materials

Potassium ferricyanide (99.99%), carbon disulfide (anhydrous, ≥99.0%), diethyl ether (CHROMASOLV®Plus for HPLC, ≥99.9%), ethyl acetate (anhydrous, 99.8%), phenylmagnesium bromide (1.0 M in THF) and caffeine (99%) were purchased from Sigma Aldrich. Petroleum ether 40-60°C (anhydrous, ≥99.0%) was purchased from Riedel-de-Haën. Silica gel (for flash chromatography) was purchased from BDH. Ethylene glycol dimethacrylate (EGDMA; 98.0%), 2,2'-azo*bis*isobutyronitrile (AIBN; 98%), chloroform (anhydrous, ≥99.0% contains 0.5-1.0% ethanol as stabilizer), methacrylic acid (MAA; 99.0%), acetonitrile (ReagentPlus®, 99.0%), THF and acetone (anhydrous, 99.8%) were purchased from Aldrich.

EGDMA and MAA were dried over anhydrous sodium sulfate and distilled *in vacuo*, respectively, prior to use. AIBN was recrystallised from methanol at low temperature. All other chemicals were used as received.

Synthesis of the RAFT agent, cyanoisopropyl dithiobenzoate (CPDB)

CPDB was synthesised by the thermolysis of 2,2'-azo*bis*isobutyronitrile in the presence of *bis*(thiobenzoyl)disulfide, according to a literature procedure; the ^{1}H NMR and ^{13}C NMR spectra of the CPDB obtained were in agreement with the published literature data (Liu et al. 2005; Moad et al. 2005).

Preparation of caffeine-imprinted polymer via RAFT polymerisation

The synthesis of the MIP for caffeine (**P1**) was based upon a procedure reported by Philip and Mathew (2008). Caffeine (0.113 g, 0.5 mmol), MAA (0.199 g, 2.3 mmol), EGDMA

(2.300 g, 11.6 mmol) and AIBN (0.042 g, 0.25 mmol) were dissolved in chloroform (4 mL) in a thick-walled glass Kimax culture tube together with CPDB (0.111 g, 0.5 mmol). The solution was deoxygenated with oxygen-free nitrogen for 10 min while cooling on an ice-bath. The tube was sealed with a screw cap under nitrogen and placed in an oil-bath for 48 h with the temperature maintained at 60ºC.

P1 was obtained as a polymer monolith. The monolith was subsequently crushed, mechanically ground using a Fritsch Pulverisette ball mill and wet-sieved using acetone. Particles of size < 25 μm were collected after sedimentation (3×) from acetone. In order to remove traces of unreacted monomers and the template from the polymer, the polymer was extracted overnight in a Soxhlet apparatus using methanol and then dried at 40ºC under vacuum (**P1**; 1.611 g, 64%).

PREPARATION OF CAFFEINE-IMPRINTED POLYMER AND NON-IMPRINTED POLYMER VIA FRP

The caffeine-imprinted polymer synthesised *via* FRP (**P2**) was prepared in the same manner as **P1** but in the absence of CPDB (**P2**: 1.929 g, 77%). A non-imprinted control polymer (**P3**) was prepared in the absence of both CPDB and caffeine (**P3**: 1.819 g, 73%).

CHARACTERISATION TECHNIQUES

^{1}H NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer at 500 MHz using $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer at 100 MHz with $CDCl_3$ as solvent.

Fourier transform infrared (FTIR) spectra of the polymers were acquired using a Spectrum One FTIR Spectrometer from Perkin Elmer with Spectrum V3.02 as the software. The polymers were prepared as dispersions in KBr.

Nitrogen sorption porosimetry measurements were performed on an ASAP 2010 accelerated surface area and porosimetry analyzer (Micromeritics Instrument Corporation, Norcross, GA). Prior to measurements, 300 – 400 mg portions of the samples were degassed overnight at 100ºC under high vacuum. The specific surface areas (*S)* were calculated using the standard BET method, and specific pore volumes (V_p) and average pore diameters (d_p) using BJH theory.

CHROMATOGRAPHIC EVALUATION OF POLYMERS

COLUMN PACKING

An Alltech model 1666 slurry packer was used to pack the polymers into empty stainless steel HPLC columns using procedures recommended by the manufacturer. The HPLC columns were 0.46 i.d. × 15 cm in dimension and were fitted with 0.2 μm frits. Approximately 1.5 g of polymer was sufficient to pack each column. Acetone was used as the slurrying and packing solvent. The columns were packed at an air pressure of 15 psi and a solvent pressure of 500 psi (packing time per column ~ 30 min).

COLUMN WASHING

The columns were washed off-line using a Gilson model 303 HPLC pump using a mixture of acetonitrile and acetic acid (95/5, v/v) at a flow-rate of 0.3 mL/min and a pressure of 120 psi. Column **P3** was washed first, followed by the **P2** column and then the **P1** column, to avoid the possibility of any cross-contamination of polymers with template and RAFT agent.

The analysis of the packed columns was carried out on a Waters HPLC system. The system comprised of a Waters 1535 binary pump, a waters 717 autosampler and a Waters 2487 dual wavelength absorbance detector. The software used for operation of the system and data handling was Waters breeze.

The analyses were performed under isocratic conditions. All the procedures were carried out at an ambient temperature. The UV detector wavelength was set at 274 nm. Acetone was used as the void marker and the flow-rate was set at 0.5 mL/min with acetonitrile as mobile phase. 10 μL of a 10 mM standard solution of analyte in chloroform was injected onto each column and retention factors (*k'*) calculated according to standard chromatographic theory (1),

$$k' = \frac{(t_r - t_o)}{t_o}, \tag{1}$$

where t_r and t_0 are the retention times of the analyte and the void marker, respectively, on the same column. The imprinting factors (IF) were calculated from the retention factors obtained for the analyte on the MIP and NIP columns (2),

$$IF = \frac{k'_{MIP}}{k'_{NIP}}. \tag{2}$$

The theoretical plate number, N, which is normally expressed in terms of the number of theoretical plates per metre, is a concept giving a quantitative measure of the efficiency of a column. The N value calculated for theoretical plates is an indirect measure of peak width for a peak at a specific retention time, as expressed by (3).

$$N = 5.54.\left(\frac{t_r}{W_{0.5}}\right)^2, \tag{3}$$

where N is the number of theoretical plates, t_r is the retention time of the analyte and $W_{0.5}$ is the peak width at half height, calculated for each analyte using classical chromatography theory assuming ideal peaks. Columns with high plate numbers are considered to be more efficient (i.e. have higher column efficiency) than columns with lower plate numbers. A column with a high number of plates will have a narrower peak at a given retention time than a column with a lower number of plates.

Results and Discussion

As outlined in the introduction, the main objective of the present work was to explore the potential benefits in applying the CRP techniques towards the synthesis of MIPs. The polymerisation method of choice in the present work was RAFT polymerisation and caffeine was selected as a model template for the purposes of the study.

Synthesis of RAFT agent

The RAFT agent cyanoisopropyl dithiobenzoate (CPDB) was synthesised according to the method of Liu et al. (2005). CPDB was selected as the RAFT agent because it has been used previously for the successful polymerisation of methacrylates and styrenes (Moad et al. 2008; Perrier et al. 2003).

Synthesis and characterisation of MIPs and NIP

The MIPs (**P1** and **P2**) and NIP (**P3**) were synthesised successfully in the form of polymer monoliths and in good yields, using two different polymerisation approaches: RAFT polymerisation (**P1**) and conventional FRP (**P2** and **P3**). The monomers used were MAA (functional monomer) and EGDMA (crosslinking agent) and caffeine was used as template in the production of **P1** and **P2**. Figure 1 shows the chemical structures of CPDB, caffeine, MAA and EGDMA. The polymers were synthesised on a 2.5 g monomer scale. Polymer **P1** was obtained as a pink/purple coloured optically-transparent polymer monolith whereas **P2** and **P3** were obtained as white, opaque polymer monoliths.

P1 has the typical appearance of a gel-type polymer when in the dry state it was optically transparent. In contrast, **P2** and **P3** scattered white light, suggestive of well-developed pore structures even when dry. These observations were confirmed by nitrogen sorption porosimetry experiments (Table 1); the specific surface area of **P1** in dry state in that it was <5 $m^2 g^{-1}$, so it was effectively non-porous when dry. For **P2** and **P3**, the specific surface areas were 270 and 320 $m^2 g^{-1}$, respectively. Furthermore, the average pore diameters for **P1**, **P2** and **P3** (9.09, 7.46 and 7.56 nm, respectively) and specific pore volumes (0.01, 0.50 and 0.61 $cm^3 g^{-1}$, respectively) confirmed the fact that the presence of RAFT agent in the **P1** polymerisation had a profound impact upon the morphology of the product (N.B. since **P1** is essentially non-porous in the dry state, the average pore diameter quoted for this material should be treated with caution). Very interestingly, in earlier work carried out in our laboratories concerning the use of ATRP to synthesise MIPs, we discovered that the imprinted products also had low specific surface areas in the dry state (Skinner 2002).

Structural characterisation

The polymers were characterised by FTIR spectroscopy. Unsurprisingly, given the fact that the same monomers were used for each polymerisation, the results showed that the MIPs prepared *via* RAFT polymerisation and conventional FRP had rather similar FTIR spectra. The bands at 1729 cm^{-1} (C=O ester stretch) and 1155 cm^{-1} (C-O ester stretch) supported the presence of EGDMA residues in the MIPs. The presence of a band at 1635 cm^{-1} (assigned to the C=C stretch of pendent, unreacted vinyl groups), which was more intense for polymers synthesised in the presence of the RAFT agent, suggested that **P1** was of lower crosslink density than **P2** and **P3** and this observation ties in nicely with the nitrogen sorption porosimetry data and visual observations. The broad band at around 3430–3600 cm^{-1} could be ascribed to the O-H stretching vibration of MAA residues. Unsurprisingly, the signal ascribed to the thiocarbonyl group could only be observed in the FTIR spectrum of **P1** (2100-2277 cm^{-1}); as expected, given the low levels of CPDB used in the synthesis of **P1**, this was a very weak signal.

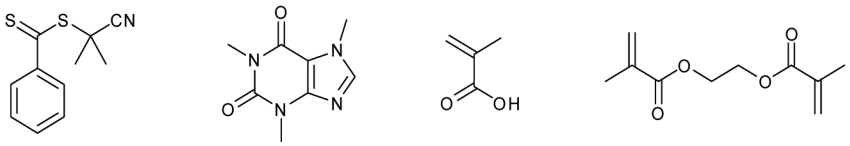

FIGURE 1. Chemical structures of, from left to right, the RAFT agent (CPDB), template (caffeine), functional monomer (methacrylic acid; MAA) and crosslinking agent (ethylene glycol dimethacrylate; EGDMA) exploited in this study

TABLE 1. Nitrogen sorption porosimetry data for polymers **P1**, **P2** and **P3**. [a] MIP synthesised in the presence of CPDB. [b] MIP synthesised in the absence of CPDB

Polymer code	Specific surface area / $m^2 g^{-1}$	Specific pore volume / $cm^3 g^{-1}$	Mean pore diameter / nm
P1[a]	< 5	0.01	9.09
P2[b]	270	0.50	7.46
P3	320	0.61	7.56

RETENTION FACTORS (k') AND IMPRINTING FACTORS (IF) FROM HPLC STUDIES

The molecular recognition properties of the polymers were evaluated in HPLC mode as described in the experimental section. Initially, after equilibrating the polymer-filled HPLC columns with acetonitrile, the elution of a 10 mM standard solution of caffeine was investigated on each of the columns in turn, with acetonitrile as the mobile phase under isocratic conditions (injection volume = 10 μL). The retention factors on the imprinted (k'_{MIP}) and non-imprinted (k'_{NIP}) stationary phases and the imprinting factors were calculated. Acetone was used as a void marker.

The elution profiles of caffeine, under identical chromatographic conditions, on **P1**, **P2** and **P3** as the stationary phase, are shown in Figure 2. On the **P1** and **P2** columns, caffeine was eluted with a retention factor of 0.53 and 0.45, respectively (Table 2). Furthermore, the chromatograms showed the pronounced peak-tailing which is characteristic of imprinted HPLC stationary phases. In contrast and as expected, caffeine was retained significantly less strongly on the non-imprinted **P3** column (retention factor 0.30); the elution peak on **P3** was broad and there was minimal tailing.

The imprinting factors (IF), calculated according to the standard chromatographic theory, are a measure of the effectiveness of the molecular imprinting. The higher the IF value, the better the molecular recognition. The IF was found to be higher for **P1** (1.8) than for **P2** (1.5) (Table 2). Thus, although the polymer prepared in the presence of the RAFT agent (**P1**) had a very low dry-state specific surface area, it performed surprisingly well as a chromatographic stationary phase and even outperformed a stationary phase produced by a conventional synthesis method.

The **P1** and **P2** stationary phases gave elution peaks which were significantly narrower than **P3**, indicating higher column efficiency. The injection on each column was repeated three times to give the average plate numbers, and the number of theoretical plates for **P1** and **P2** were calculated to be 4070 m^{-1} and 2800 m^{-1}, respectively, whereas the value for **P3** was only 530 m^{-1}. Rather significantly and indeed in keeping with our original hypothesis, the column packed with the polymer synthesised in the presence of the RAFT agent (**P1**) had the highest chromatographic efficiency of all.

Finally, although not exemplified here in detail due to restrictions of space, as an extension to the current study we have demonstrated yet another advantage of using CRP to synthesise MIPs; the dormant RAFT agent present in **P1** can be exploited in subsequent polymerisations to graft a second polymer from the pre-existing polymer. These findings will be reported elsewhere, however, grafting of poly(hydroxyethyl methacrylate), for example, increases the hydrophilicity of the MIPs and makes them more attractive for use in fully-aqueous or partially-aqueous media, since non-specific binding in water is normally suppressed when the polymers are less apolar.

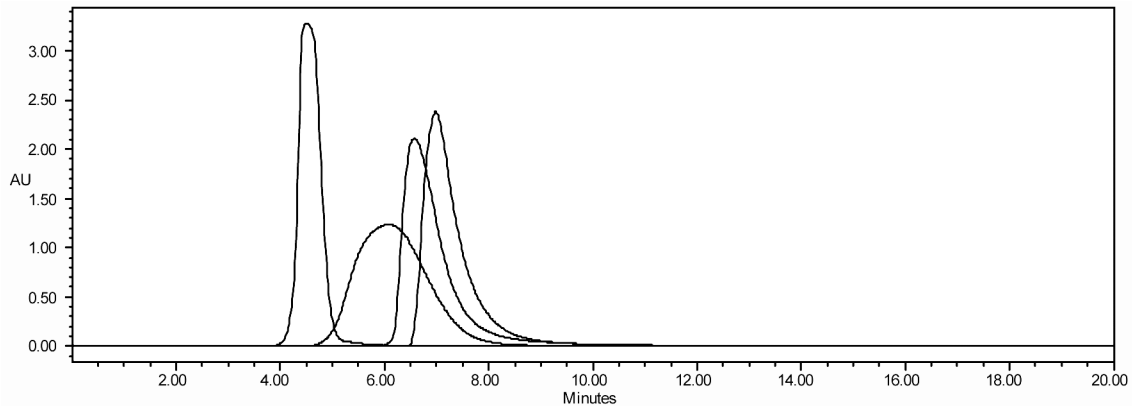

FIGURE 2. Overlay of elution profiles of, from left to right: acetone on **P3** (NIP); caffeine on **P3**; caffeine on **P2**; caffeine on **P1**. 10 μL of a 10 mM standard solution of caffeine was injected

TABLE 2. Chromatographic data obtained for polymers **P1**, **P2** and **P3**. [a] MIP synthesised in the presence of CPDB. [b] MIP synthesised in the absence of CPDB

Polymer code	Retention factor (k')	Imprinting factor (IF)	Number of theoretical plates / m^{-1}
P1[a]	0.53	1.8	4070
P2[b]	0.45	1.5	2800
P3	0.30	-	530

CONCLUSIONS

In summary, monolithic caffeine-imprinted polymers have been synthesised in good yield, *via* both RAFT polymerisation and conventional FRP. The monoliths were ground to deliver imprinted particles which were then applied as stationary phases in HPLC. In spite of its low dry-state specific surface area, it was found that a polymer synthesised in the presence of the RAFT agent CPDB performed very effectively indeed as a novel stationary phase. Indeed, the polymer out-performed an imprinted stationary phase produced by conventional FRP; the molecular recognition was more pronounced and the column efficiency was significantly higher. The novel imprinted material synthesised by RAFT polymerisation was amenable to facile post-polymerisation chemical modification using *grafting from* strategies since the RAFT agent remains chemically bound to the imprinted polymer in an active form after the molecular imprinting stage.

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