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# Performance analysis of molecularly imprinted polymers for carboxylate and aminophosphate templates using commercially available basic functional monomers

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**Abstract**

A survey of commercially available amine-based monomers for binding and selectivity of carboxylate and phosphonic acid templates has revealed that the best selectivity is found for the pyridine-based monomers, while the highest affinity was found for 2-(dimethylamino)ethyl methacrylate (2-DEMA, **1**). In fact, a more general finding is that selectivity is higher for aromatic amine-based monomers even though affinity remains higher for aliphatic amine-based monomers. An attempt to combine the optimal properties of these two classes of amine monomers, i.e. 2-vinylpyridine (2-VPY, **2**), and 2-DEMA by using both simultaneously in a single imprinted polymer resulted in an MIP whose properties were dominated by the aliphatic amine-based monomer 2-DEMA. A controversy between the two commercially available vinylpyridine monomers, 2-VPY and 4-vinylpyridine (4-VPY, **3**), was investigated, revealing that neither monomer is generally better for molecular imprinting; rather, the choice of 2-VPY or 4-VPY is template specific (although the preponderance of data tends to frequently favor 4-VPY). Phosphonic acid templates proved to be less successful as templates for molecular imprinting versus carboxylate functionalized templates, although binding was obtained and shown to be controllable via an ion-exchange process.


*Keywords:* Carboxylate; Aminophosphate; Molecularly imprinted polymers

## 1. Introduction

Since the introduction of molecularly imprinted organic polymers by Wulff nearly 30 years ago, the methodology has undergone a number of important developments [1]. One of the most important has come from the labs of Mosbach who developed the non-covalent imprinting strategy [2]. This imprinting strategy is outlined in Fig. 1, where functional monomers are associated with a template via non-covalent interactions, primarily electrostatic interactions between acids and bases. For example, the first functional monomer employed for non-covalent molecularly imprinted polymer (MIP) formation was methacrylic acid (MAA), which forms organic salt complexes with basic templates. The complex is then copolymerized with a crosslinking monomer, followed by removal of the template using extraction procedures. This leaves binding sites in the polymer that provide a complementary array of functional groups lining a shape selective cavity. Although this strategy has been very successful, there are many templates for which MAA is not sufficient. The largest body of templates in this category would be those with acidic functionality, with the greatest interest in binding carboxylic and phosphonic acids of biological importance. A previous study has reported a number of useful amine-based functional monomers for imprinting acidic templates; however, all but one require synthetic effort, which may be inconvenient for the general community who wish to imprint acidic functionalized templates [3]. To make imprinting acids easier and more convenient, the purpose of this study was to survey commercially available amine-based monomers to determine which provides the highest selectivity performance for carboxylate and phosphonate targets.

There are a number of commercially available monomers possessing interactive amine functionality that can be used for molecular imprinting acids (Aldrich), which are shown in Fig. 2. From the commercial pool, five monomers were chosen as viable candidates for study. These monomers have been investigated for molecular imprinting in various studies, but have not yet been directly compared in

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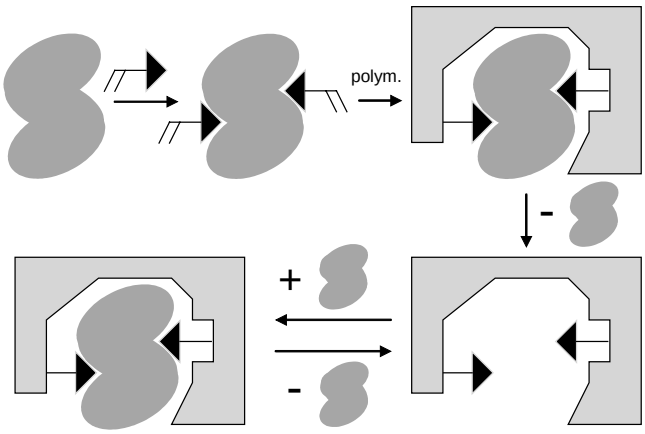



Fig. 1. Outline of the molecular imprinting strategy.

parallel on the same system. A decade ago, 4-vinylpyridine (4-VPY, **3**) and 1-vinylimidazole (1-Vim, **4**) were evaluated as functional monomers for MIPs using amino acid derivatives as templates, whereupon MIPs incorporating 4-VPY were found to provide better racemic resolution than MIPs formulated with 1-Vim [4]. Since this initial study, several other groups have successfully employed 4-VPY to form MIPs with specific binding properties [5–10]. A number of reports have also looked at 1-Vim as a functional monomer, however, these are primarily for formation of catalytic MIPs, and binding was not rigorously evaluated [11,12]. Another pyridinyl monomer, 2-vinylpyridine (2-VPY, **2**), was more recently examined for binding selectivity under aqueous reverse-phase conditions [9], while normal-phase examples used 2-VPY in conjunction with methacrylic acid [13,14]. MIPs incorporating aliphatic amine-functionalized monomers such as 2-(dimethylamino)ethyl methacrylate (2-DEMA, **1**), have been successful for chromatography and

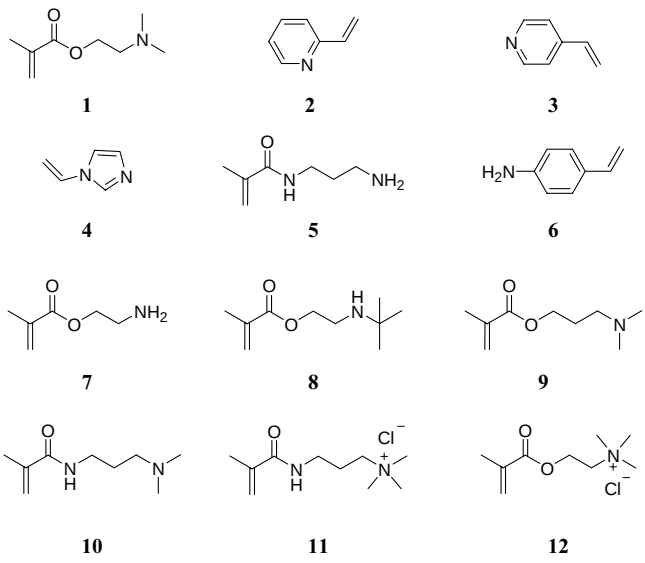



Fig. 2. Structures of commercially available amine-based functional monomers.

sensor applications [15–17]. The monomer, 3-aminopropyl methacrylamide (3-APM, **5**), is potentially useful as a primary amine monomer candidate for binding and catalysis, although selectivity has not yet been achieved [3].

Several potential monomers in Fig. 2 were ruled out as candidates for different reasons; for example, photoinitiated polymerization was inhibited by 4-vinylaniline (**6**). The 2-aminoethyl methacrylate (**7**) undergoes rearrangement to 2-hydroxyethyl methacrylamide which is no longer an amine-based monomer. This problem is avoided when the amine is fully substituted, as in the case of functional monomer **1** (2-DEMA); or when large groups are on or adjacent to the amine which sterically encumbers interactions with the amine such as 2-(*tert*-butylamine)ethyl methacrylate (**8**) which cannot be used because the butyl group blocks the necessary interactions for formation of the pre-polymer complex. Because of similarities to 2-DEMA and 3-APM, 3-(dimethylamino)propyl methacrylate (**9**) and 3-(dimethylamino)propyl methacrylamide (**10**) were not investigated. The monomers 3-(acrylamidopropyl)trimethylammonium chloride (**11**) and 2-(acryloxyl)ethyl trimethylammonium chloride (**12**) are only soluble in aqueous solvents and were not compatible with the organic solvent conditions necessary for imprint polymerization.

## 2. Experimental

### 2.1. General

Unless otherwise noted, chemicals were purchased from Aldrich. All solvents were purchased from commercial sources and used as received. (1*S*)-(+)-(*N*-Carbobenzoxy1-aminoethyl) phosphonic acid (**13**), (1*R*)-(−)-(*N*-carbobenzoxy1-aminoethyl) phosphonic acid, (1*S*)-(+)-(1-benzyloxy-carbonylamino-2-methyl-propyl)-phosphonic acid (**14**), and (1*R*)-(−)-(1-benzyloxy-carbonylamino-2-methyl-propyl)-phosphonic acid were all synthesized by a procedure similar to that described previously for (*N*-carbobenzoxy1-aminoethyl) phosphonic acid [18].

### 2.2. Polymer preparation

The following procedure was used for all imprinted polymers. Ethylene glycol dimethacrylate (2.84 ml, 15.1 mmol), acetonitrile (4 ml), functional monomer (3.1 mmol), 2,2′-azobis(2-methylpropionitrile) (0.031 g, 0.19 mmol), and template (0.77 mmol) were mixed together and placed into two screw top test tubes. The solutions were purged with nitrogen for 5 min, capped, and then sealed with teflon tape and parafilm. The samples were placed into a photochemical turntable reactor (ACE Glass Inc.) which was immersed in a constant temperature bath. A standard laboratory UV light source (a Canrad-Hanovia medium pressure 450 W mercury arc lamp) jacketed in a borosilicate double-walled immersion well was placed at the center of a turntable holding the

samples. The polymerization was initiated photochemically at 20 °C and the temperature maintained by both the cooling jacket surrounding the lamp and the constant temperature bath holding the entire apparatus and the polymerization allowed to proceed for 10 h. The polymers were extracted with methanol using a soxhlet apparatus for 24 h to remove the template, porogen, and any unreacted material.

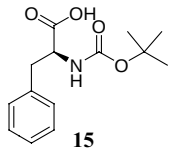
### 2.3. HPLC evaluation of MIPs

The polymers were ground using a mortar and pestle, the particles were sized using USA Standard Testing Sieves (VWR), and the fraction between 20 and 25 μm was collected. The particles were slurry packed, using a Beckman 1108 Solvent Delivery Module, into stainless steel columns (length, 10.0 cm, i.d. 4.6 mm) to full volume (approximately 0.6 g of polymer) for chromatographic experiments, unless otherwise indicated. The polymers were then equilibrated online, prior to HPLC analyses performed isocratically at room temperature (22 °C) using a Hitachi L-7100 pump with a Hitachi L-7400 detector. All HPLC analyses were performed in triplicate under isocratic conditions using the optimal mobile phase found for each polymer. The void volume was determined using acetone as an inert substrate. The separation factors ($\alpha$) were measured as the ratio of capacity factors ($k'_S/k'_R$). The capacity factors were determined by the relation $k' = (R_v - D_v)/D_v$, where $R_v$ is the retention volume of the substrate, and $D_v$ the void volume.

## 3. Results and discussion

### 3.1. Survey of commercially available monomers

The performance of the functional monomers in Table 1 was evaluated using the template *t*boc-L-phenylalanine (*t*boc-L-Phe, **15**, Fig. 3). This template was chosen because



**15**

Fig. 3. Template for evaluating MIP's employing different functional monomers.

it has a single chiral center allowing enantioselectivity, the best probe for MIP selectivity, to be used as a diagnostic of imprinting performance. Molecularly imprinted polymers were synthesized using the L-enantiomer of *t*boc-Phe, and the selectivity of the MIPs was determined by HPLC under isocratic conditions at room temperature. Retention factors ($k'$) were obtained in order to determine separation factors ($\alpha$) of the L- and D-enantiomers of *t*boc-Phe ($\alpha = k'_L/k'_D$). The retention and separation factors for the imprinted polymers are shown in Table 1 in order from highest to lowest selectivity, allowing three key observations to be made. First, the pyridine-based monomers 2-vinylpyridine (2-VPY) and 4-vinylpyridine (4-VPY) show the highest selectivity; second, 2-VPY exhibits higher selectivity than 4-VPY. Third, the best selectivity was obtained by monomers incorporating aromatic amine groups (entries 1–3) versus poor selectivity seen for monomers that have aliphatic amine groups (entries 4–5), in spite of the high binding affinity exhibited by the aliphatic monomers.

### 3.2. Comparison of vinyl-pyridine monomers

One of the most interesting findings from the survey in Section 3.1 is that P-2-VPY gives higher enantioselectivity for the template versus P-4-VPY. To the best of our knowledge, this is the first direct comparison of enantioselectivity by polymers incorporating 2-VPY versus 4-VPY published using normal-phase conditions. The results presented in Table 1 run counter to those found recently

Table 1
Binding and selectivity data for MIPs to *t*boc-L-Phe employing different monomers[a]

| Entry | Polymer | Functional monomer | Treatment | $k'_1$ | $k'_d$ | $\alpha$ |
|---|---|---|---|---|---|---|
| 1 | P-2-VPY | **2** | Imprinted | 1.4 ± 0.01 | 0.80 ± 0.01 | 1.8 |
| | | | Non-imprinted | 0.35 ± 0.003 | 0.35 ± 0.01 | 1.0 |
| 2 | P-4-VPY | **3** | Imprinted | 1.4 ± 0.01 | 0.93 ± 8E-8 | 1.5 |
| | | | Non-imprinted | 0.89 ± 0.04 | 0.89 ± 0.04 | 1.0 |
| 3 | P-1-Vim | **4** | Imprinted | 2.6 ± 0.01 | 2.2 ± 0.01 | 1.2 |
| | | | Non-imprinted | 1.4 ± 0.01 | 1.4 ± 0.01 | 1.0 |
| 4 | P-2-DEMA | **1** | Imprinted | 10.9 ± 0.1 | 9.7 ± 0.1 | 1.1 |
| | | | Non-imprinted | 5.5 ± 0.04 | 5.5 ± 8E-8 | 1.0 |
| 5 | P-3-APM | **5** | Imprinted | 6.4 ± 0.02 | 6.4 ± 0.06 | 1.0 |
| | | | Non-imprinted | 8.1 ± 0.2 | 8.1 ± 0.03 | 1.0 |
| 6 | P-(2-VPY + 2-DEMA) | **2** + **1** | Imprinted | 3.3 ± 0.1 | 3.1 ± 0.04 | 1.1 |

[a] HPLC conditions: flow rate: 1.0 ml/min, UV detection at λ = 257 nm, injections were 5.0 μl of a 1.0 mmol sample, mobile phase = 98/2 (v/v): acetonitrile/acetic acid.

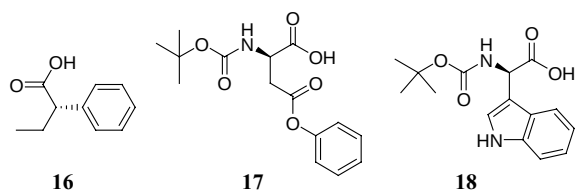



Fig. 4. Templates for comparing MIPs employing 2-VPY vs. 4-VPY.

under reverse-phase conditions, where a 4-VPY functionalized MIP exhibited higher selectivity than 2-VPY for an amine functionalized template [9]. MIPs incorporating 2-VPY have been previously reported to give better selectivity values versus 4-VPY for respective combinations of these two monomers with MAA [14]. In this report, the authors pointed out the difference in p$K_b$ between 2-VPY and 4-VPY (4.98 and 5.62, respectively), and attributed the better performance to greater ionic strength between the template and the more basic 2-VPY. An alternate explanation is that the two different pyridinyl monomers bind similarly to templates; however, the juxtaposition of the polymerizable group and the interactive amine group affects the steric interactions of the template with the structure of the binding site.

To investigate whether the differences between 2-VPY versus 4-VPY are general, several other templates (Fig. 4) were imprinted using both of these functional monomers. HPLC experiments were run as before to determine retention factors and enantioselectivity (Table 2). Combining the data from Tables 1 and 2, it appears that there is no decisive trend for better performance by either 2-VPY or 4-VPY; instead, the results are template specific. Reasons for this can only be speculative at this point, but it is hard to imagine that steric effects do not play a role. An indicator of this is seen in entry 1 of Table 1, where the retention for the non-imprinted 2-VPY is lower than all other control polymers due to sterically encumbered accessibility to binding sites. However,

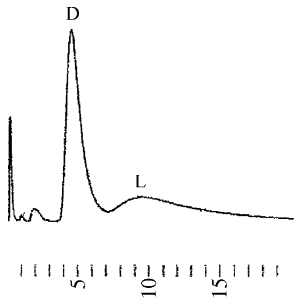



Fig. 5. Chromatograph of resolution for enantiomers of *t*boc-tryptophan using MIP incorporating 4-VPY as functional monomer.

when polymers are *imprinted* using 2-VPY, the template may enforce a cavity between the polymer matrix and the amine binding group which allows access to the analytes. This hypothesis explains the observation that the increase in enantioselectivity by P-2-VPY arises from a lower degree of non-specific interactions relative to P-4-VPY for *t*boc-L-phe.

On the other hand, in cases such as *t*boc-tryptophan (entry 5, Table 2), the imprinting method does not appear to overcome limited steric access, and the 4-VPY monomer is the better choice. This is seen by the improved resolution for the enantiomers of *t*boc-tryptophan in Fig. 5.

### 3.3. Comparison of aromatic versus non-aromatic functional monomers

The MIPs exhibiting the best selectivity consistently appear to be the aromatic amines, and point to the influence of binding group directionality and monomer flexibility on MIP selectivity [19]. In addition to pre-organization of functional groups in the binding site, further fine-tuning is often needed to obtain the desired selectivity. This fine tuning can come from directionality of the binding interactions between the template and functional monomers in MIPs. For example, the aromatic amines are capable of hydrogen

Table 2
Comparison of MIPs to different templates using 2-VPY and 4-VPY monomers[a]

| Entry | Template | Functional monomer | Treatment | $k'_1$ | $k'_d$ | $\alpha$ |
|---|---|---|---|---|---|---|
| 1 | **16** | **1** | Imprinted | 0.44 ± 0.01 | 0.41 ± 0.01 | 1.08 |
| | | | Non-imprinted | 0.77 ± 0.01 | 0.66 ± 0.01 | 1.17 |
| 2 | **16** | **2** | Imprinted | 0.55 ± 0.01 | 0.52 ± 0.004 | 1.05 |
| | | | Non-imprinted | 0.64 ± 0.003 | 0.58 ± 0.0 | 1.09 |
| 3 | **17** | **1** | Imprinted | 0.08 ± 0.01 | 0.08 ± 0.01 | 1.00 |
| | | | Non-imprinted | 0.79 ± 0.01 | 0.75 ± 0.03 | 1.06 |
| 4 | **17** | **2** | Imprinted | 1.37 ± 0.02 | 1.06 ± 0.01 | 1.29 |
| | | | Non-imprinted | 1.07 ± 0.004 | 1.07 ± 0.0 | 1.00 |
| 5 | **18** | **1** | Imprinted | 0.81 ± 0.004 | 0.81 ± 0.004 | 1.00 |
| | | | Non-imprinted | 0.48 ± 0.03 | 0.49 ± 0.006 | 0.99 |
| 6 | **18** | **2** | Imprinted | 2.77 ± 0.04 | 1.36 ± 0.02 | 2.04 |
| | | | Non-imprinted | 1.26 ± 0.003 | 1.26 ± 0.001 | 1.00 |

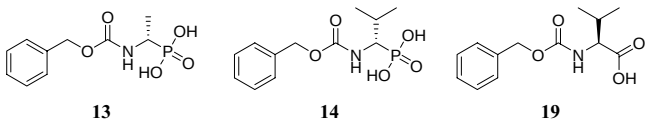
[a] HPLC conditions: flow rate: 1.0 ml/min, UV detection was $\lambda = 254$ nm for **16**, $\lambda = 258$ nm for **17**, and $\lambda = 280$ nm for **18**, injections were 5.0 μl of a 1 mmol sample, mobile phase = 98/2 (v/v): acetonitrile/acetic acid.

bonding and/or electrostatic interactions with the template in a single, coplanar direction. This is what is meant by an interaction having specific directionality. On the other hand, a primary amine on the MIP, provided by monomers such as *N*-(3-aminopropyl)methacrylamide (**5**), presents a charge that can be regarded as spherical in nature, which does not provide directionality, although it does provide a strong binding interaction. Furthermore, these monomers are less conformationally restrained, i.e. the monomers are "floppy", with an associated entropy gain that reduces the selective interactions with the template, which likely result in MIPs with reduced selectivity.

On the other hand, binding affinities are consistently stronger with the aliphatic amine functionalized polymers. This is clearly due to the higher basicity of aliphatic amines with p$K_a$'s in the range 9.0–10.5, versus aromatic amines with p$K_a$'s in the range 5.0–6.5. Therefore, we explored the possibility of combining the high affinity nature of aliphatic amine functionalized MIPs with the selectivity of aromatic amine functionalized MIPs by synthesizing a hybrid MIP incorporating both of these functional groups. Similar approaches have been reported successful for combining acidic and basic functional monomers to enhance MIP selectivity [20]. Thus, the MIP in entry 6 of Table 1 was formulated with equal concentrations of 2-VPY and 2-DEMA; however, the results did not show improvement in binding or selectivity versus MIPs made with 2-VPY and 2-DEMA separately. This is not surprising, since the pre-polymer complex of the hybrid MIP is dominated by 2-DEMA interacting with the template due to its higher basicity, whereas the 2-VPY most likely did not play a role in the imprinting process. The properties of the hybrid MIP reflect those of the P-2-DEMA MIP, e.g. the $\alpha$ values are identical, and the retention factor of the hybrid MIP was half that of the P-2-DEMA MIP. This is to be expected since the concentration of 2-DEMA in the hybrid formulation was half that used to form P-2-DEMA.

### 3.4. Molecular imprinting of aminophosphonic acids

Carboxylic acids are not the only organic acids of interest for separation and detection, phosphates and phosphonic acids represent a large class of bioactive molecules, chemical warfare agents, and pesticides. Most reports of polymers imprinted with phosphates and phosphonic acids made use of these templates as transition state analogs for eliciting catalytic MIPs [21–26]. For these polymers polymerizable imidazole derivatives have been used, including the commercially available 1-vinylimidazole; however, catalysis and not selectivity in these polymers was evaluated. Aqueous phase recognition of phosphates and phosphonates was explored by Sasaki and coworkers, however, the MIPs were made using highly specialized sol–gel materials [27]. With the experience obtained from the study of carboxylate imprinted MIPs, binding and selectivity of MIPs elicited toward phosphate compounds was evaluated using 2-VPY and 2-DEMA.



**13** **14** **19**

Fig. 6. Structures of templates used for aminophosphonic acid binding study.

Polymers were imprinted using chiral aminophosphic acids (Fig. 6), again using enantioselectivity as a performance probe to determine how well phosphate compounds are imprinted. In general, the aminophosphonic acids bound to the MIPs with much higher affinity than the carboxylates, thus a polar aqueous mobile phase was required. Similar to the case of imprinting carboxylates, stronger binding affinities are obtained using 2-DEMA, however, enantioselectivity was only observed for the polymer incorporating 2-VPY. The enantioselectivity for the aminophosphonic acids appears to be modulated by the size of the side chain. For example, comparing entries 1 and 3 in Table 3, the addition of steric bulk on the side chain appears to increase selectivity. This is in agreement with earlier studies on chiral compounds, where selectivity depends on differences in the size and distance of side chains around the chiral center. It also appears that carboxylate compounds imprint better than the phosphonic acid compounds, as shown in entries 3 versus 4 in Table 3. This is likely due to non-specific interactions possible with both phosphate groups that create less specific sites, versus the single interaction elicited by the carboxylate. A pH profile for binding of aminophosphonic acid **13** to 2-VPY functionalized MIPs revealed that selectivity is a function of pH (Fig. 7). This indicates that retention is controlled by an ion-exchange process, similar to a study done previously for MIPs using methacrylic acid as the functional monomer [28]. It has been shown previously for MIPs exhibiting an underlying ion-exchange mechanism that optimum binding affinity and selectivity occur approximately at a pH that maximizes the reciprocal charges on the polymer and solute. This appears to be the case here as well; as shown in Fig. 7, selectivity is observed at pH values lower than approximately 6.8, and is lost at higher pH

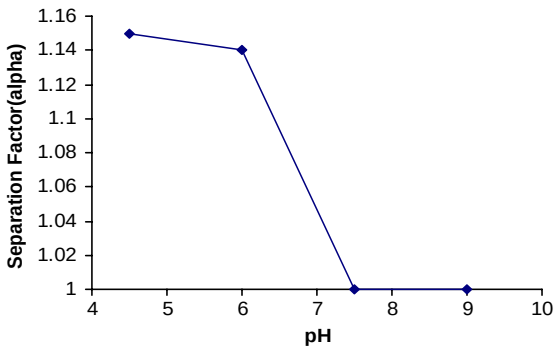



Fig. 7. Study of the effect of pH on separation factors of (1-*tert*-butoxycarbonyl-L-amino-2-methyl-propyl) phosphonic acid imprinted polymer.

Table 3
Binding and selectivity data for aminophosphonic acid and carboxylate templated MIPs[a]

| Entry | Template | Functional monomer | Treatment | $k'_1$ | $k'_d$ | $\alpha$ |
|---|---|---|---|---|---|---|
| 1 | **13** | **1** | Imprinted | 0.31 ± 0.003 | 0.30 ± 0.008 | 1.03 |
| | | | Non-imprinted | 0.0 ± 0.04 | 0.0 ± 0.004 | 1.00 |
| 2 | **13** | **4** | Imprinted | 4.14 ± 0.2 | 4.14 ± 0.2 | 1.00 |
| | | | Non-imprinted | 4.37 ± 0.02 | 4.38 ± 0.05 | 1.00 |
| 3 | **14** | **1** | Imprinted | 0.33 ± 0.0 | 0.29 ± 0.01 | 1.15 |
| | | | Non-imprinted | 0.0 ± 0.004 | 0.0 ± 0.004 | 1.00 |
| 4 | **19** | **1** | Imprinted | 0.33 ± 0.02 | 0.21 ± 0.01 | 1.47 |
| | | | Non-imprinted | 0.11 ± 0.003 | 0.11 ± 2E−9 | 1.00 |

[a] HPLC conditions: column length, 10.0 cm, i.d. 2.1 mm; flow rate: 0.1 ml/min; UV detection at $\lambda = 262$ nm; injections were 5.0 μl of a 1.0 mmol sample; mobile phase: 70/30 (v/v): acetonitrile/50.0 mmol $KHPO_4$ buffer (pH 4.5).

values. As pH values are lowered, there will be an increase in the amount of protonated pyridinium group of 2-VPY, while there will only be a slight decrease in the amount of phosphonate anion. Therefore, optimum results are seen in the pH range where the positively charged pyridinium group is fully protonated, but well above the pH where the phosphonic acid is fully protonated (in the approximate pH range 2–3), maintaining the complementary negatively charged phosphonate anion. None the less, enantioselectivity is much more difficult to achieve for the phosphonic acid templates versus those incorporating carboxylate functionality.

## 4. Conclusion

In order to form carboxylate (and phosphonic acid) binding MIPs, a survey of commercially available amine-based functional monomers has revealed that the best binding occurs with 2-DEMA, while the best selectivity occurs with vinylpyridine monomers. The choice of 2-vinylpyridine or 4-vinylpyridine was investigated for a short series of templates; however, a clear preference for one or the other was not established, rather the results appear to be template specific. The results for the study show an interesting trend in the nature of the interaction between the functional monomer and the template, where higher selectivity is generally observed for MIPs containing aromatic amine-based functional monomers even though higher affinities are achieved by the aliphatic amine monomers. This has been postulated to arise from directional binding between the template and monomer, which is not available to the aliphatic amines. A similar comparison can be made in comparing the different behavior of carboxylate versus phosphonic acid templates, where the phosphonic acid templates exhibit much higher binding affintities. However, comparison of a carboxylate template and an equivalent phosphonic template with regard to shape and steric parameters showed higher selectivity is obtainable by the carboxylate compound. Thus, for eliciting substrate selective MIPs, the vinylpyridine monomers can be considered the commercially available complement to the well-established standard set by methacrylic acid for binding templates incorporating basic functionality.

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