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# 1 Emergence of molecular recognition phenomena in a simple model 2 of imprinted porous materials

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7 Polymerization in the presence of templates, followed by their consequent removal, leads to  
8 structures with cavities capable of molecular recognition. This molecular imprinting technology has  
9 been employed to create porous polymers with tailored selectivity for adsorption, chromatographic  
10 separations, sensing, and other applications. Performance of these materials crucially depends on the  
11 availability of highly selective binding sites. This parameter is a function of a large number of  
12 processing conditions and is difficult to control. Furthermore, the nature of molecular recognition  
13 processes in these materials is poorly understood to allow a more systematic design. In this work we  
14 propose a simple model of molecularly imprinted polymers mimicking the actual process of their  
15 formation. We demonstrate that a range of molecular recognition effects emerge in this model and  
16 that they are consistent with the experimental observations. The model also provides a wealth of  
17 information on how binding sites form and function in the imprinted structures. It demonstrates the  
18 capability to assess the role of various processing conditions in the final properties of imprinted  
19 materials, and therefore it can be used to provide some qualitative insights on the optimal values of  
20 processing parameters. © 2009 American Institute of Physics. [DOI: 10.1063/1.3140204]

21

## 22 I. INTRODUCTION

23 Molecular recognition is a process of strong and specific  
24 noncovalent binding between a molecule and a substrate.  
25 This mechanism is vital for a number of biological processes  
26 including enzymatic reactions, defensive mechanisms, and  
27 genetic information replication. Recently, however, a tech-  
28 nology has been developed to synthesize abiogenic porous  
29 structures capable of biomimetic molecular recognition. At  
30 the heart of this technology is the molecular imprinting pro-  
31 tocol, where self-assembly of the precursors and polymeriza-  
32 tion of the material take place in the presence of additional  
33 template molecules. The templates are subsequently removed  
34 leaving in the final structure cavities, or imprints, which are  
35 structurally complementary to the template species. These  
36 cavities function as selective binding sites, capable of recog-  
37 nition and rebinding of the original template species. The  
38 first observation of molecular recognition in abiogenic struc-  
39 tures dates back to 1931, when Polyakov<sup>1</sup> prepared sol-gel  
40 materials in the presence of benzene, toluene, and xylene and  
41 observed a particular affinity of the resulted structures to-  
42 ward the original additives or related ligands. It was hypoth-  
43 esized that the produced silica materials acquired some kind  
44 of *steric memory* toward the guest species. However, the true  
45 potential of this approach was realized with the first molecu-  
46 larly imprinted polymers (MIPs) prepared in 1970s.<sup>2</sup> In MIP  
47 synthesis, the polymerizing mixture consists of cross-linker  
48 component, responsible for the structural integrity of the  
49 polymer, and functional monomers, which form associations  
50 with the functional groups of the template molecule. Thus, in  
51 addition to steric effects, the resulting binding site also fea-

tures very specific complementary interaction patterns. The 52  
basic steps of this technique are shown in Fig. 1. For ex- 53  
ample, one of the earliest MIPs was prepared using meth- 54  
acrylic acid as the functional monomer and ethylene glycol 55  
dimethacrylate as the cross-linking monomer, with two small 56  
drug molecules, theophylline and diazepam, as the template 57  
species.<sup>3</sup> These structures were able to differentiate between 58  
close analogs of the template, exhibiting properties similar to 59  
the natural antibodies. This demonstrated the remarkable po- 60  
tential of molecular imprinting. Rich polymeric chemistry 61  
and a large number of possible building components opened 62  
an opportunity to design highly functionalized materials for 63  
chromatographic separations, sensing, artificial immunoas- 64  
says, catalysis, and other applications implemented over the 65  
last 20 years.<sup>2</sup> 66

Despite these successes, synthesis of MIPs remains an 67  
intricate and vastly empirical process.<sup>4</sup> It has been well es- 68  
tablished in a number of studies that MIPs have few selective 69  
binding sites and a large number of relatively nonselective 70  
sites.<sup>5</sup> This heterogeneity of binding sites is an intrinsic fea- 71  
ture of the imprinting technique. The performance of a MIP 72  
crucially depends on this characteristic, and it is important to 73  
be able to control it. For this we need a detailed understand- 74  
ing of how specific binding sites form and function. 75

Recent experimental and theoretical studies suggest that 76  
very selective, high quality binding sites result from strong 77  
associations between the functional monomers and template 78  
species.<sup>6–10</sup> For example, in the aforementioned study by 79  
Vlatakis *et al.*,<sup>3</sup> methacrylic acid forms ionic interactions and 80  
hydrogen bonds with amino and polar functional groups of 81  
the template. Naturally, most of the recent design efforts 82  
have been focused on screening for appropriate functional 83

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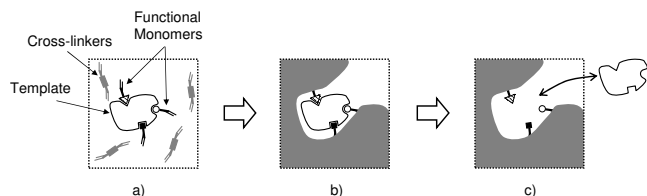


FIG. 1. A schematic depiction of the polymer imprinting principles. (a) A mixture of components is equilibrated and functional monomer-template complexes are formed; (b) polymerization stage; (c) after template extraction, a cavity is left capable of rebinding the template.

monomers associated with it. This leads to binding sites of different types and quality, depending on the number of monomers associated with the site. This model is clearly well suited to explore binding site distributions in MIPs and how this characteristic depends on the relative concentrations of the template and monomer species and on the strength of the template-functional monomer association. It was also applied to a specific case of enantioselective recognition of racemic components. It is also important to note that a number of atomistic models of MIPs have started to emerge recently.

In this work, we aim to develop a more general, computationally efficient model, which would satisfy the following criteria. The model should reflect the process of MIP formation and feature complex interconnected three dimensional porous space characteristic for MIPs. The model should exhibit molecular recognition and provide a tool to investigate the relation between various processing conditions (such as relative concentration of species), porous morphology, and the binding site distribution. Several elements of this strategy have been already developed. Van Tassel *et al.* proposed a series of models, where all species were represented as hard spheres or Lennard-Jones particles. The first step of the model involves an equilibrated mixture of template and matrix components (matrix here and throughout the article is a generic term for the polymer components). The mixture is then quenched and the template particles are removed. The resulting structure of the quenched matrix component serves as the model porous material. The advantage of the model is that it also allows for a theoretical treatment within the replica Ornstein-Zernike formalism. It has been shown that the presence of a template enhances adsorption and that the magnitude of the effect strongly depends on the template/matrix composition ratio and on the size of the template. However, as expected, no molecular recognition effect could be captured in a system of simple particles. Recently, the model of Van Tassel *et al.* was extended to molecular species. Using both computer simulations and integral equation approaches, a range of systems with either purely repulsive or more complex patterns of interaction was considered. The adsorption of rigid linear chains, clusters, and molecules of other shapes in matrices templated with these species was investigated and a number of nontrivial effects were observed. Molecular recognition was also observed for systems interacting with Lennard-Jones-like potentials; however, this observation was limited to one specific system in a narrow range of conditions and therefore it lacks generality.

## II. METHODOLOGY

### A. Computational strategy

In the first step a mixture of the MIP components (template, cross-linker, and functional monomer) is equilibrated under specified conditions. When equilibrium is reached, the system is quenched (i.e., molecules are frozen in their positions and orientations), this stage imitates polymerization in the actual MIP synthesis. The porous structure formed by the quenched configurations of the matrix species (cross-linkers

monomers, which would form stable complexes with the template molecule of interest. This, however, is only one of many factors that play a role in the final characteristics of a MIP. First of all, not all of the formed complexes become selective binding sites. Some of the complexes may be destroyed during the polymerization process, and others may evolve into inaccessible binding sites either because of a trapped template molecule inside or because they become spatially isolated from the remaining porous space during the polymerization. Furthermore, several scenarios are possible where specific and accessible binding sites are not able to perform their rebinding function. For example, during the adsorption or rebinding process, one or more molecules can form associations with the interaction groups of the binding sites in an arrangement different from the original predecessor complex. In general, recognition events in a binding site are strongly affected by the state of the neighboring binding sites and pores. All of these factors may contribute to the diminished performance of a MIP and are intimately linked to the various properties of the imprinted material such as density, concentration of the interaction groups on the surface, and so on. As a result MIP performance depends not only on the stability of the complexes between functional monomers and templates in the prepolymerization mixture but also on a number of other processing conditions such as relative concentration of the components, choice of solvent, and polymerization temperature. The number of optimization parameters is large, they are not independent of each other and their mutual effects are quite intricate. Clearly, design of MIPs with tailored functionalities requires some rational strategies.

Computational methods and theoretical approaches have been playing an increasingly important role in the development of these strategies with a number of fundamental models of MIPs recently proposed. For example, Yungerman and Srebnik considered a model of a polymerizing Lennard-Jones fluid templated with rigid dimers, also made of two Lennard-Jones sites. Polymerization was modeled as the formation of harmonic bonds between the particles representing monomers. This model allowed the authors to investigate porosity and pore size distribution in the final structure as function of the template concentration and degree of polymerization. Wu *et al.* recently proposed a simple two dimensional square lattice model of MIPs. In the model each lattice site can be either empty or occupied by a cross-linker, functional monomer, or template species. Each functional monomer can form an association with only one out of four adjacent lattice sites. Template sites can have up to four

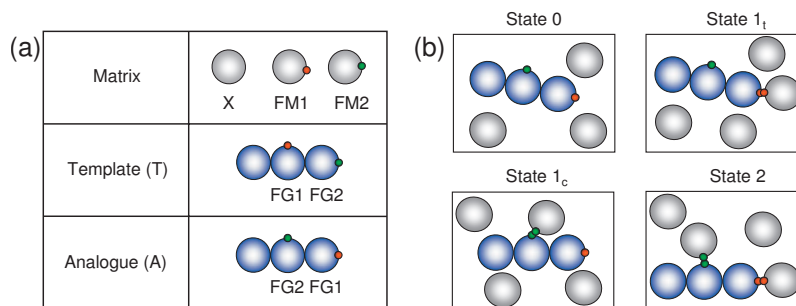


FIG. 2. (Color) (a) Summary of the species considered in this work. Matrix species include cross-linker  $X$  and functional monomers  $FM1$  and  $FM2$ , which feature surface interaction sites shown in red ( $FM1$ ) and green ( $FM2$ ); template ( $T$ ) is a rigid chain of three tangent hard spheres with surface interaction sites in the arrangement as shown. Functional group  $FG1$  (red interaction site) can associate with functional monomer  $FM1$ , functional group  $FG2$  (green interaction site) can associate with functional monomer  $FM2$ . Analog  $A$  has the location of the functional groups exchanged. (b) Schematic depiction of the possible complexes between the template and functional monomers in the prepolymerization mixture. Each complex is described by the number of associations formed between the template and functional monomers (states 0, 1<sub>t</sub>, 1<sub>c</sub>, 2), with subscripts  $t$  and  $c$  signifying the terminal and central location of the engaged functional group, respectively.

188 and functional monomers) models the MIP after template  
189 extraction. This simulated MIP is then used in the adsorption  
190 simulations.

## 191 B. Molecular model

192 In a series of earlier studies, Sarkisov and Van Tassel<sup>32,33</sup>  
193 applied the strategy described above to a range of systems  
194 where rigid molecules were constructed from a basic build-  
195 ing block, such as a hard sphere or a Lennard-Jones-like  
196 particle. For example, the template could be represented as a  
197 rigid chain of several hard spheres, whereas the polymer was  
198 represented simply as a fluid of hard spheres.

199 In order to capture the molecular recognition phenom-  
200 ena, we need to go beyond these types of interactions. In  
201 experiments, formation of the very specific binding sites re-  
202 sults from strong associations between the template molecule  
203 and functional monomers. The nature of these associations is  
204 complex and includes both hydrogen bonds and electrostatic  
205 contributions. To a significant extent, molecular recognition  
206 is a process of reforming of these associations in the binding  
207 site. Thus, the idea of this work is to extend the model of  
208 Sarkisov and Van Tassel to incorporate a simple description  
209 of associations forming between functional monomers and a  
210 template molecule. The inspiration for our approach comes  
211 from an earlier model of water proposed by Kolafa *et al.*<sup>35,36</sup>  
212 In their model, water is represented as a hard sphere deco-  
213 rated with four additional interaction sites in a tetrahedral  
214 arrangement. These interaction sites, located close to or at  
215 the surface of the hard sphere, are small compared to the  
216 central hard sphere particle and are able to associate with  
217 each other via a short range square-well potential. Associa-  
218 tions between water particles in this description feature the  
219 directionality, short range, and strength of hydrogen bonds.  
220 Using this approach we construct the species involved in our  
221 model as shown in Fig. 2(a). In this study, a cross-linker  
222 molecule is a hard sphere of size  $\sigma$  (species  $X$ ). A functional  
223 monomer in this model is represented as a hard sphere of  
224 size  $\sigma$  with an interaction site on the surface as shown in Fig.  
225 2(a). We consider functional monomers of two types,  $FM1$   
226 and  $FM2$ , but the model is not limited to this specific case. A  
227 template molecule (species  $T$ ) is a rigid linear chain of three

tangent hard spheres of the same size  $\sigma$ . Two of these  
228 spheres also feature surface interaction sites in the arrange-  
229 ment as shown in Fig. 2(a) and can be viewed as functional  
230 groups ( $FG1$  and  $FG2$ ). Functional monomer  $FM1$  can asso-  
231 ciate with functional group  $FG1$ , whereas functional mono-  
232 mer  $FM2$  can associate with functional group  $FG2$ . The as-  
233 sociation between interaction sites is modeled via a square-  
234 well potential of the following form: 235

$$u(r)/k_B T = \begin{cases} -\varepsilon/k_B T, & r \leq \sigma_{SW} \\ 0, & r > \sigma_{SW}, \end{cases} \quad (1) \quad 236$$

where  $u(r)$  is the interaction energy between two interaction  
237 sites,  $r$  is the distance between the two sites,  $\varepsilon$  determines the  
238 well depth of the potential and is equal to  $10k_B T$  (typical  
239 magnitude for hydrogen bonds),  $\sigma_{SW}$  is the size of the  
240 interaction site and is equal to  $0.15\sigma$ , and  $k_B$  and  $T$  are the  
241 Boltzmann constant and temperature as usual. No functional  
242 monomers can associate with each other, and the same is true  
243 for the functional groups. 244

245 One of the key objectives of this study is to test whether  
246 the proposed model is capable of molecular recognition. This  
247 function would manifest itself in the ability of the model  
248 imprinted matrix to preferentially adsorb the original tem-  
249 plate species and distinguish them from analogous species  
250 that have similar structure and composition but different ar-  
251 rangements of the functional groups. An example of such an  
252 analog, where the location of the functional groups is ex-  
253 changed, is also shown in Fig. 2(a).

## C. Characterization of prepolymerization complexes and binding sites 254 255

In the model presented here, associations form between  
256 the functional monomers and the functional groups of the  
257 template. In the prepolymerization mixture composed from  
258 the species presented in Fig. 2(a), a template molecule can be  
259 observed in one of four possible states. These states are  
260 shown in Fig. 2(b). In the first state, labeled 0, the template  
261 molecule does not form any associations. States (or com-  
262 plexes) 1<sub>t</sub> and 1<sub>c</sub> are characterized by a single association  
263 with either the terminal or the central functional group of the  
264 template engaged in the association, respectively. (We 265

266 choose this notation, instead of using FG1 and FG2, since  
 267 the location of these groups in the template and analog mol-  
 268 ecules is swapped.) Finally, the template can have associa-  
 269 tions established with both functional groups and this corre-  
 270 sponds to state (or complex of type) 2. Computer simulations  
 271 allow us to monitor the population of these complexes during  
 272 the equilibration of the matrix and relate these characteristics  
 273 to various parameters of the system, such as composition and  
 274 density. Once the system is quenched (imitating polymeriza-  
 275 tion), the complexes are frozen in their instant configura-  
 276 tions. Template removal transforms these complexes into  
 277 binding sites.

278 Let us consider behavior of these binding sites during an  
 279 adsorption process, where we use template as the adsorbate.  
 280 Again, adsorbed molecules can be observed in different  
 281 states, similar to those depicted in Fig. 2(b), depending on  
 282 the number of associations they form with the matrix. It is  
 283 important to recognize that not all of these states correspond  
 284 to molecules located in the binding sites formed during the  
 285 imprinting. For example, a situation is possible where an  
 286 adsorbing molecule is able to form two associations with the  
 287 matrix in an arrangement that does not correspond to any  
 288 particular complex in the prepolymerization mixture. Thus,  
 289 to distinguish the states of the adsorbed molecules from  
 290 those in the prepolymerization mixture, we introduce a clas-  
 291 sification of adsorbed states similar to that in Fig. 2(b) and  
 292 based simply on the number of associations the adsorbed  
 293 molecule forms with the matrix. Specifically, molecules that  
 294 form two associations with the matrix are denoted as state  $2^a$   
 295 (“a” stands here for an adsorbed molecule here); a molecule  
 296 with only one association made by the terminal functional  
 297 group is in state  $1_t^a$ ; a molecule with only one association  
 298 made by the central functional group is in state  $1_c^a$ ; finally a  
 299 molecule with no associations is classified as state  $0^a$ . It is  
 300 instructive to know how many of the molecules in state  $2^a$   
 301 are actually located in the binding sites resulted from the  
 302 complexes of type 2 in the prepolymerization mixture. Com-  
 303 puter simulations allow us, given a particular state on the  
 304 adsorption isotherm, to examine the binding state of each  
 305 molecule.

#### 306 D. Simulation details

307 The first stage of the proposed computational strategy  
 308 considers an equilibrium mixture of the template, functional  
 309 monomer, and cross-linker components. Equilibration of the  
 310 system is performed in the canonical  $NVT$  ensemble using  
 311 the classical Metropolis sampling protocol. The number of  
 312 canonical Monte Carlo steps (translations and rotations) re-  
 313 quired for the equilibration is between  $3 \times 10^8$  and  $6 \times 10^8$   
 314 (depending on the system), of these approximately  $5 \times 10^7$   
 315 are used to generate average properties of the system. For  
 316 each system, a total of three different matrix realizations are  
 317 generated.

318 Simulations of adsorption are performed using the grand  
 319 canonical Monte Carlo. In this ensemble, temperature  $T$ , vol-  
 320 ume of the system  $V$ , and the chemical potential  $\mu/k_B T$  of  
 321 the adsorbing species are specified. A point on the adsorption  
 322 isotherm corresponds to a simulation with approximately  $10^8$

steps performed, with each step being either an insertion, 323  
 deletion, translation, or rotation attempt. Translations and ro- 324  
 tations are accepted with the acceptance probability, 325

$$P_{\text{trans,rot}} = \min(1, e^{-\beta[U_{\text{new}} - U_{\text{old}}]}), \quad (2) \quad 326$$

where  $\beta = 1/k_B T$ ,  $U_{\text{old}}$ , and  $U_{\text{new}}$  are the configurational en- 327  
 ergies of the system before and after the attempted move, 328  
 respectively. To increase the efficiency of insertion and dele- 329  
 tion moves, we implement a volume biased sampling method 330  
 as described by Snurr *et al.*<sup>37</sup> in the context of adsorption in 331  
 zeolites. In this method the system is divided into small 332  
 cubelets. A probe hard sphere particle is placed in the center 333  
 of each cubelet and tested for overlaps with the particles of 334  
 the structure. If no overlaps are registered, this cubelet is 335  
 saved in a list of accessible cubelets. Insertions are then per- 336  
 formed by random selection of a cubelet from the list. A 337  
 molecule of adsorbate is randomly placed within the selected 338  
 cubelet, with this move accepted or rejected based on the 339  
 following biased probability criterion: 340

$$P_{\text{ins}} = \min\left(1, \frac{q^{\text{rot}} e^{\beta \mu V_C}}{(N+1)\Lambda^3}\right), \quad (3) \quad 341$$

where  $N$  is the number of adsorbate molecules in the system 342  
 and  $V_C$  is the total volume of all accessible cubelets. Note 343  
 that the de Broglie wavelength  $\Lambda$  and the ideal gas rotational 344  
 partition function  $q^{\text{rot}}$  are implicitly set to  $\sigma$  and 1, respec- 345  
 tively. In order to preserve the microscopic reversibility, the 346  
 acceptance criterion for particle deletions also has to be bi- 347  
 ased, 348

$$P_{\text{del}} = \min\left(1, \frac{N\Lambda^3}{q^{\text{rot}} e^{\beta \mu V_C}}\right). \quad (4) \quad 349$$

These simulations are carried out for a range of increasing 350  
 values of chemical potential. The adsorbed density of the 351  
 species as a function of the chemical potential constitutes an 352  
 adsorption isotherm. 353

### III. RESULTS 354

In this study, we explore six different MIP systems and 355  
 their parameters are given in Table I. MIP1 has characteris- 356  
 tics, such as the overall density, similar to those in the earlier 357  
 studies of Sarkisov and Van Tassel.<sup>33</sup> This system features 358  
 2400 cross-linker particles and 400 functional monomer par- 359  
 ticles of each type. The system is imprinted with 400 tem- 360  
 plate molecules. Therefore, the ratio of functional monomers 361  
 ( $N_{\text{FM1}} + N_{\text{FM2}}$ ) and functional groups ( $N_{\text{FG1}} + N_{\text{FG2}}$ ) is stoichi- 362  
 ometric in the system. The prepolymerization mixture is 363  
 placed in a cubic box of  $20\sigma$  in size. The overall reduced 364  
 density of the system,  $\rho^* = (N_{\text{total}}/V)\sigma^3$ , is 0.55 (here  $N_{\text{total}}$  365  
 $= N_X + N_{\text{FM1}} + N_{\text{FM2}} + 3N_T$  is the total number of hard sphere 366  
 particles present in the system,  $N_X$  and  $N_T$  is the number of 367  
 cross-linker and template particles,  $V$  is the volume of the 368  
 system). 369

The first step of the proposed protocol involves simula- 370  
 tion of an equilibrium mixture of the cross-linker, functional 371  
 monomers, and template components. Figure 3 summarizes 372  
 the distribution of complexes observed in this prepolymer- 373  
 ization mixture. About 25% of templates are able to form 374

TABLE I. Summary of the compositions and densities  $\rho^* = (N_{\text{total}}/V)\sigma^3$  for the systems studied in this work. Here,  $N_{\text{total}}$  is the total number of hard sphere sites in the system, whereas  $N_X$ ,  $N_{\text{FM1}}$ ,  $N_{\text{FM2}}$ , and  $N_T$  are the number of cross-linker  $X$ , functional monomer FM1, functional monomer FM2, and template  $T$  particles, respectively.

MIP	$N_X$	$N_{\text{FM1}}$	$N_{\text{FM2}}$	$N_T$	$\rho^*$
1	2400	400	400	400	0.5500
2	1800	300	300	300	0.4125
3	3000	500	500	500	0.6875
4	2800	200	200	400	0.5500
5	1600	800	800	400	0.5500
6	0	1600	1600	400	0.5500

375 associations with two functional monomers. Other states of  
 376 the template molecules (bound to just one monomer, either  
 377 FM1 or FM2, or not bound to any functional monomers) are  
 378 also observed with roughly the same probability of 25% for  
 379 each state. The final configuration of this mixture is saved,  
 380 the template species are removed, and the resulting structure  
 381 represents a model MIP. The most intriguing aspect of this  
 382 study is to establish whether this model material is capable  
 383 of molecular recognition. For this we perform single compo-  
 384 nent adsorption simulations of the template and analog. The  
 385 analog, as depicted in Fig. 2(a), features exactly the same  
 386 building blocks and the overall geometry as the template,  
 387 however, the location of the interaction sites is reversed,  
 388 compared to the template. Thus, higher adsorbed density of  
 389 the template compared to the analog at the same correspond-  
 390 ing chemical potential would signify molecular recognition  
 391 in the model MIP. Figure 4(a) shows adsorption isotherms  
 392 for the template and analog. Indeed, adsorption densities for  
 393 the template are higher throughout the whole range of chemi-  
 394 cal potentials. A more intuitive way to characterize selectiv-  
 395 ity of a MIP is the separation factor  $S$ , which is the ratio of  
 396 the adsorbed template and analog densities at the same  
 397 chemical potential. This factor is plotted in Fig. 4(b). For the  
 398 whole range of chemical potential, this factor is greater than  
 399 1, signifying the preferential adsorption of the template com-  
 400 pared to the analog. As expected, this factor is decreasing at  
 401 higher loadings, as the highly specific binding sites become  
 402 occupied at lower chemical potentials and the remaining po-  
 403 rous space does not exhibit any preferential adsorption. This  
 404 trend is very similar to what is typically observed in experi-

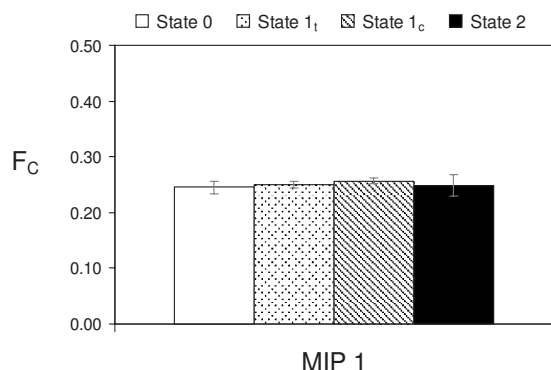


FIG. 3. Equilibrium distribution of the template-functional monomer complexes in MIP1 system prior to polymerization.  $F_C$  is the fraction of complexes of each type.

ments, and even the values of the separation factor are com-  
 405 parable to the typical experimental values in MIP studies.<sup>5</sup>  
 406 Hence, we establish that the presented model is able to cap-  
 407 ture molecular recognition effect. Computer simulations al-  
 408 low us to generate a detailed look at the state of each ad-  
 409 sorbed molecule and its environment throughout the whole  
 410 adsorption process. Specifically, for each state on the adsorp-  
 411 tion isotherm, we have complete information about how  
 412 many molecules form two associations with the matrix, just  
 413 one association with the matrix, or have no associations  
 414 formed at all. Figure 5(a) summarizes the distribution of ad-  
 415 sorbed molecules among different states of association along  
 416 the adsorption isotherm for MIP1. For example, at the  
 417

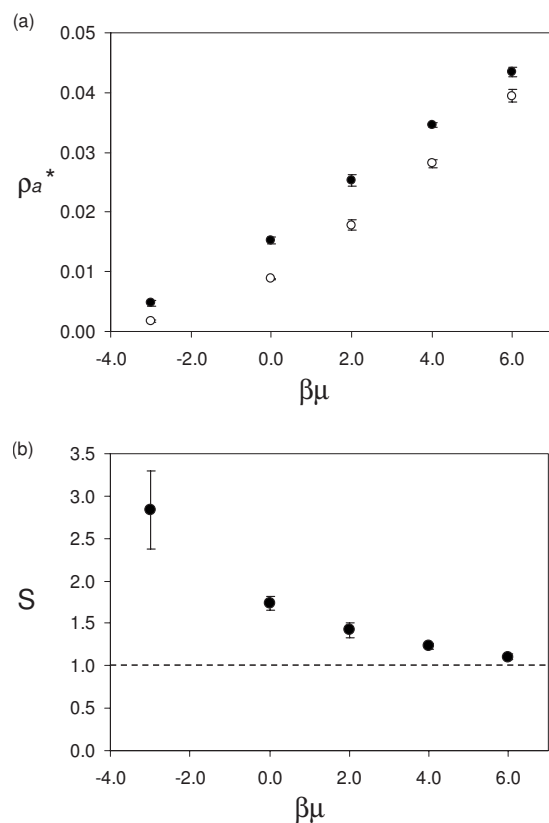


FIG. 4. (a) The adsorption isotherms for MIP1, adsorbate density  $\rho_a^* = (N_a/V)\sigma^3$  as a function of the adsorbate chemical potential  $\beta\mu$ .  $N_a$  is the number of adsorbed molecules. Closed symbols correspond to the adsorbed template density  $\rho_{a,T}^*$  and open symbols correspond to the adsorbed analog density  $\rho_{a,A}^*$ . (b) Separation factor  $S = \rho_{a,T}^*/\rho_{a,A}^*$  as a function of the chemical potential  $\beta\mu$  for MIP1.

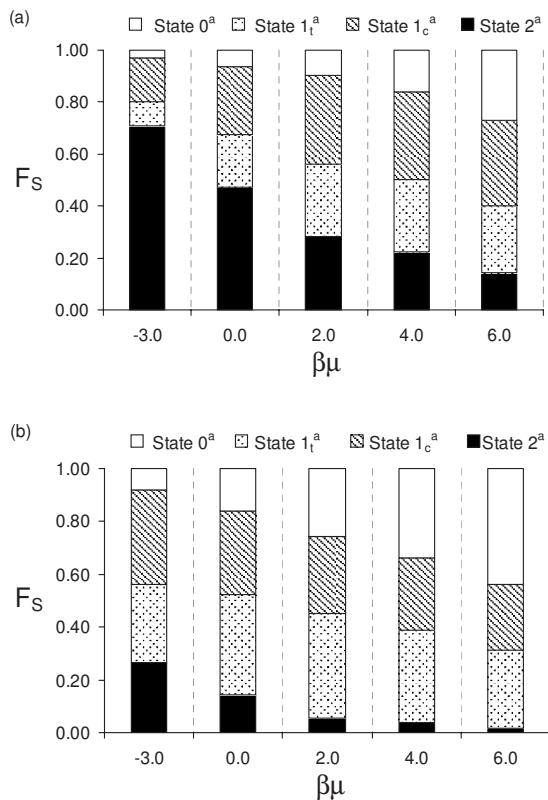


FIG. 5. Fraction  $F_S$  of adsorbed molecules in each binding state as a function of the chemical potential  $\beta\mu$  in MIP1 for the template (a) and analog (b).

418 chemical potential  $\beta\mu = -3.0$ , there are about 70% of ad-  
 419 sorbed molecules in 2<sup>a</sup> state, 9% in 1<sub>t</sub><sup>a</sup> state, 18% in 1<sub>c</sub><sup>a</sup> state,  
 420 and 3% not forming any associations (state 0). Overall, at  
 421 lower values of the chemical potential, the majority of the  
 422 adsorbed molecules form two associations with the matrix.  
 423 As the loading of the material increases, progressively more  
 424 and more molecules are able to form only one association  
 425 with the matrix or no associations at all. Interestingly, at the  
 426 highest loading the distribution of binding sites among dif-  
 427 ferent association states resembles the distribution of com-  
 428 plexes in the prepolymerization mixture. It is also instructive  
 429 to apply similar analysis to the analog adsorption in the same  
 430 material. Figure 5(b) shows distribution of adsorbed mol-  
 431 ecules among different binding states for the analog in MIP1.  
 432 The most important feature of this result is a significant frac-  
 433 tion of analog molecules that are able to form two associa-  
 434 tions with the matrix despite the porous space being specifi-  
 435 cally tailored to recognize the interaction pattern of the  
 436 template.

437 In order to investigate the effect of density on molecular  
 438 recognition in MIPs, we consider two variations of MIP1.  
 439 Both of the systems feature the same mole fractions of the  
 440 components as MIP1; however, MIP2 has lower overall den-  
 441 sity than MIP1 (75% of MIP1) and MIP3 has higher overall  
 442 density than MIP1 (125% of MIP1). It is important to note,  
 443 that as we increase the density of the material, some of the  
 444 binding sites may become inaccessible; however, at this  
 445 stage we do not address this issue. Analysis of the prepoly-  
 446 merization states of these systems as shown in Fig. 6, reveals  
 447 that higher density leads to a noticeably higher proportion of

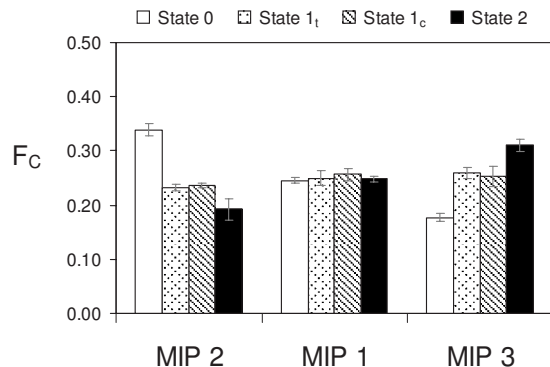


FIG. 6. Equilibrium distribution of the template-functional monomer complexes in MIP2 and MIP3 systems prior to polymerization, compared to this distribution in MIP1.  $F_C$  is the fraction of complexes of each type.

type 2 complexes observed in the mixture. High density of 448  
 the mixture also induces stronger complementarity between 449  
 the template and the resulting binding site. All these factors 450  
 lead to higher selectivity in MIP3 compared to the materials 451  
 of lower density. Figure 7 summarizes adsorption isotherms 452  
 and separation factors for all three materials. Although, ca- 453  
 pacity of MIP3 is lower compared to other materials due to 454  
 the reduced porosity, this system exhibits significantly higher 455  
 separation factors reaching more than 7 at the lowest value of 456  
 the chemical potential shown in the figure. 457

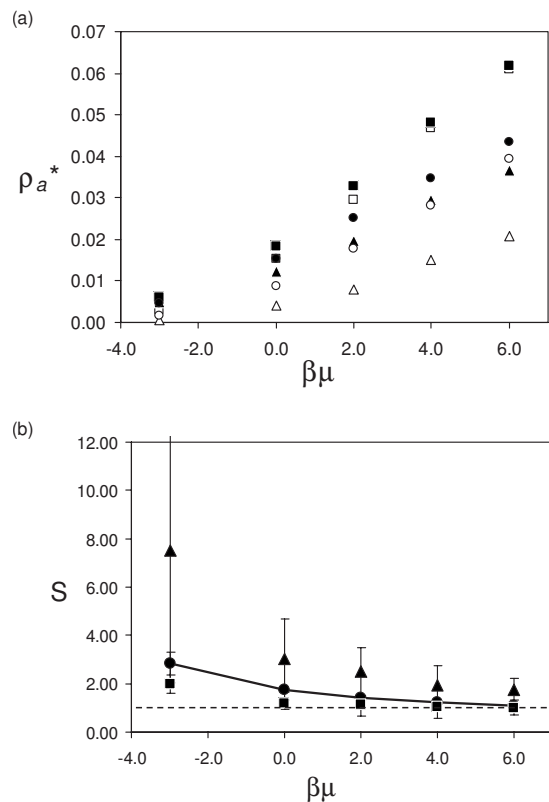


FIG. 7. (a) The adsorption isotherms for MIP1 (circles), MIP2 (squares), and MIP3 (triangles), adsorbate density  $\rho_a^* = (N_a/V)\sigma^3$  as a function of the adsorbate chemical potential  $\beta\mu$ .  $N_a$  is the number of adsorbed molecules. Closed symbols correspond to the adsorbed template density  $\rho_{a,T}^*$  and open symbols correspond to the adsorbed analog density  $\rho_{a,A}^*$ . Error bars are not shown for clarity. (b) Separation factor  $S = \rho_{a,T}^*/\rho_{a,A}^*$  as a function of chemical potential  $\beta\mu$  for MIP1 (circles and solid line), MIP2 (squares), and MIP3 (triangles).

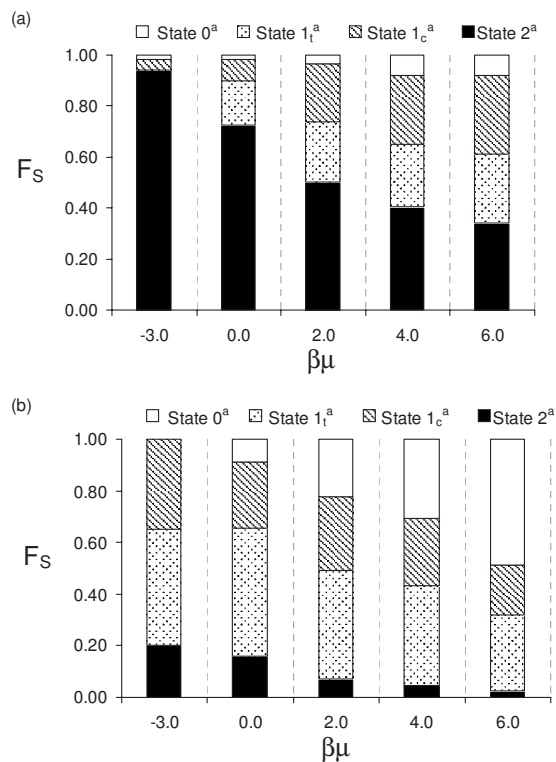


FIG. 8. Fraction  $F_S$  of adsorbed molecules in each binding state as a function of the chemical potential  $\beta\mu$  in MIP3 for the template (a) and analog (b).

458 We perform analysis of the states of the template and  
 459 analog molecules adsorbed at each point on the isotherm and  
 460 observe that for MIP3 templates are predominantly adsorbed  
 461 in type 2<sup>a</sup> states for a significant part of the isotherm (Fig. 8).  
 462 Although, some analogs also appear to be bound in type 2<sup>a</sup>  
 463 state, the fraction of these is relatively small throughout the  
 464 isotherm. Thus, higher density leads to more specific binding  
 465 sites and more pronounced molecular recognition.

466 Composition of the prepolymerization mixture is also a  
 467 crucial optimization parameter. Both relative amounts of  
 468 cross-linker and functional monomer (X:M ratio) and func-  
 469 tional monomer and template (M:T ratio) are important and  
 470 are not independent from each other. It has been observed in  
 471 a number of studies that selectivity of MIPs goes through a  
 472 maximum as these ratios are varied in a systematic way (for  
 473 a comprehensive review of these effects, we recommend a  
 474 recent article by Spivak<sup>38</sup>). Here we study the effect of X:M  
 475 ratio by changing the relative amounts of cross-linker and  
 476 functional monomer, while maintaining the overall density of  
 477 the system and the amount of the template constant. (Here  
 478  $X=N_X$ ,  $M=N_{FM1}+N_{FM2}$ ). We change the number of func-  
 479 tional monomers simply by turning the cross-linker particles  
 480 into functional monomers as required. The reference MIP1  
 481 has a 3:1 ratio of cross-linker to functional monomer. Three  
 482 variations on this ratio are explored. MIP4 features lower  
 483 number of functional monomers (X:M ratio of 7:1), MIP5  
 484 has double the number of functional monomers (X:M ratio of  
 485 1:1), and MIP6 has quadruple the number of functional  
 486 monomers (X:M ratio of 0:1) compared to MIP1. Prepoly-  
 487 merization mixture of MIP6 consists of functional monomers  
 488 and templates only, with no cross-linker particles. Therefore,

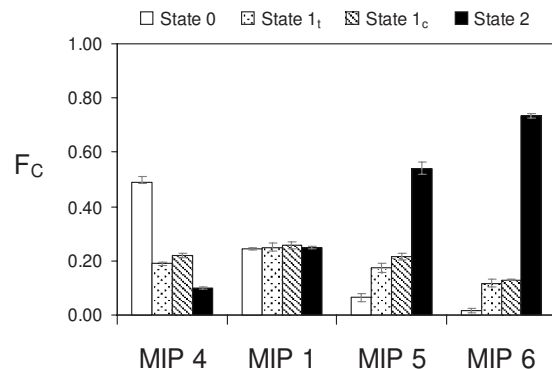


FIG. 9. Equilibrium distribution of the template-functional monomer complexes in MIP4, MIP5, and MIP6 systems prior to polymerization, compared to this distribution in MIP1.

we investigate a range of regimes from the one correspond- 489  
 ing to the deficit of functional monomers (MIP4) to the other 490  
 extreme where the whole polymer is constructed solely from 491  
 the functional monomer (MIP6). As we increase the number 492  
 of functional monomers in the system, the fraction of type 2 493  
 complexes also increases and this is shown in Fig. 9. In 494  
 MIP6, for example, almost 75% of template molecules are in 495  
 state 2 in the prepolymerization mixture. Furthermore, at a 496  
 given value of the chemical potential, the selectivity of ma- 497  
 terials goes through a maximum, with MIP5, corresponding 498  
 to X:M ratio of 1:1, exhibiting the highest selectivity. Figure 499  
 10 summarizes this behavior for three different values of the 500  
 chemical potential. This behavior is particularly pronounced 501  
 at the lower values of the chemical potential where adsorp- 502  
 tion takes place predominantly in very selective binding 503  
 sites. The explanation of this maximum in selectivity is as 504  
 follows. At a low concentration of the functional monomer, 505  
 there are simply not enough functional monomers to form 506  
 complexes of type 2 with all the available templates. As this 507  
 concentration is increased, the equilibrium is shifted toward 508  
 formation of type 2 complexes, leading to a larger number of 509  
 highly specific 2<sup>a</sup> binding sites. However, in the other ex- 510  
 treme situation abundance of functional monomers leads not 511  
 only to a larger number of type 2 complexes but also to a 512  
 significant number of free functional monomers. Therefore, 513

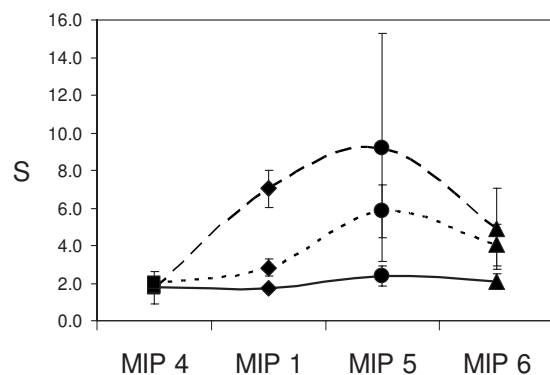


FIG. 10. Selectivity of model MIP structures as a function of cross-linker to functional monomer (X:M) ratio. From left to right: MIP4 X:M=7:1 (squares), MIP1 X:M=3:1 (diamonds), MIP5 X:M=1:1 (circles), and MIP6 X:M=0:1 (triangles). The data are plotted at three different values of the chemical potential  $\beta\mu = -5.0$  (broad-dashed line),  $\beta\mu = -3.0$  (dashed line), and  $\beta\mu = 0.0$  (solid line).



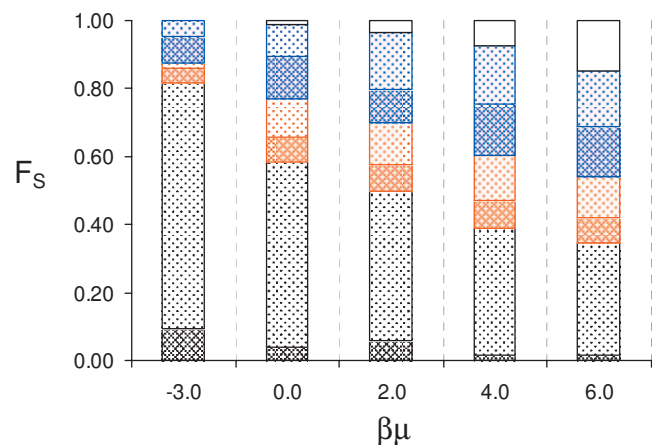


FIG. 11. (Color) Fraction  $F_S$  of adsorbed template molecules in each binding state as a function of the chemical potential  $\beta\mu$  in MIP5. Color of each bar corresponds to a particular adsorbed state: gray for  $2^a$ , blue for  $1_c^a$ , red for  $1_i^a$ , and white for  $0^a$  states, respectively. Lighter shades correspond to molecules located in the binding sites, formed from the prepolymerization complexes. Darker shades correspond to molecules forming alternative associations with the matrix.

groups in real MIPs and prove to be crucial for molecular recognition to emerge in the model. Our previous models based on simpler, less specific interactions were insufficient to capture this effect.

At the heart of the model is the general simulation protocol aimed to closely mimic various stages of MIP formation and function. Equilibration of the prepolymerization mixture of components followed by quenching of the mixture and removal of the template leads to realistic imprinted structures featuring complex interconnected porous space. Thus, this approach makes it possible to explore all elements relevant to MIP performance, such as molecular recognition effects, binding sites structure, heterogeneity and distribution, pore size distribution, and connectivity within the framework of a single model. This realism of the model ensures that it is able to capture a number of experimentally observed trends. Specifically, it generates realistic values of separation factors that diminish with increased loading in accordance with experimental observations. Furthermore, the model predicts that with higher density of the material the quality of imprinting improves, leading to more specific binding sites, and hence, higher selectivity of the model MIP. We briefly explored predictions of the model for other processing conditions such as the ratio of cross-linker to functional monomer in the prepolymerization mixture. The model predicts a maximum in the selectivity of model materials, as this ratio is varied. At low concentration of the functional monomers, there is simply not enough monomers to form complexes with all available templates. On the other hand, very high concentrations of the functional monomer result in predominantly nonspecific binding. This is in agreement with experimental observations, although an additional factor noticed in experiments is lower rigidity and robustness of the polymer network at high concentrations of the functional monomer.<sup>39</sup> In general, this is an encouraging result as the model demonstrates the capability to assess the role of various processing conditions in the final properties of MIPs, and therefore it can be used to provide some qualitative insights on the optimal values of processing parameters.

We expect that the model can make a particular important contribution to our understanding of molecular recognition mechanisms in MIPs. In the range of conditions explored in this work, we consistently observe that the analog molecules are able to form very favorable associations with the matrix even though the porous space is imprinted to recognize the interaction pattern of the template. This is an important contribution to a diminished selectivity of MIPs, highlighted by this model.

Several aspects of the model require further development. In the current version the polymerization process is modeled simply by quenching molecules of the prepolymerization mixture in their instant locations and orientations. A more realistic approach would involve some mechanism of association between cross-linkers and functional monomers. This model would be able to generate connected and self-sustaining polymer networks. This can be easily implemented using the same language of surface interaction sites that we use to describe functional monomer–functional group associations. Furthermore, in this study we do not ad-

additional opportunities open for the analog to form two associations (state  $2^a$ ) upon adsorption. This limits the effect of the imprinting on the structure and the resulting MIP exhibits less specific binding.

It is also interesting to examine the nature of binding states of adsorbed molecules in the imprinted materials. Specifically, we would like to assess how many molecules in a particular state are actually located in the binding sites evolved from the corresponding complexes in the prepolymerization mixture. For this, in Fig. 11, we consider the most selective material MIP5 and, in addition to the original distribution of adsorbed molecules among various binding states, we also delineate between *rebinding* to the original binding sites (lighter patterns) and forming new associations, not observed during the prepolymerization (darker patterns). For example, at the chemical potential  $\beta\mu = -3.0$  about 81% of all adsorbed molecules are in  $2^a$  state (gray patterns), but about 9% are in  $2^a$  binding sites that did not form from type 2 complexes during the imprinting process. About 5% of molecules are in state  $1_i^a$  (red patterns), but only 1% are in the binding sites formed from  $1_i$  complexes, and about 14% of adsorbed molecules are in  $1_c^a$  state (blue patterns), but only 4% are located in the binding sites formed from  $1_c$  complexes. This analysis indicates that about 10% of the most specific binding sites identified from a typical binding site distribution method, such as the Freundlich isotherms, may not have originated from imprinting.

#### IV. CONCLUSIONS

In this article we propose a simple model of imprinted porous materials. For the first time, molecular recognition effect emerges in the model of MIPs. Molecular species in this model are treated as either hard spheres or rigid clusters of hard spheres. Some of the hard spheres also feature small interaction sites capable of associating with each other in a prescribed manner. These associations aim to imitate interactions between the functional monomers and functional

609 dress the accessibility of the binding sites, and this is an  
 610 important factor to be investigated in our future work. It is  
 611 also important to explore molecular recognition effects as a  
 612 function of molecular geometry. Our preliminary studies on  
 613 the systems with a single type of functional monomer and a  
 614 single functional group (the analog then differs from the tem-  
 615 plate by the location of the functional group) suggest that the  
 616 main conclusions of this work remain valid for this simpler  
 617 case; however, the magnitude of the observed separation fac-  
 618 tors is lower. Therefore, the main focus of the future work  
 619 will be on more complex systems, where one might expect a  
 620 richer spectrum of behavior.

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