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Peptoids as a Chiral Stationary Phase for Liquid Chromatography: Insights from Molecular Dynamics Simulations

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Peptoids as Chiral Stationary Phase for Liquid Chromatography: Insights from Molecular Dynamics Simulations

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chiral stationary phase, enantioselectivity, helix, molecular dynamics, peptoid

Abstract

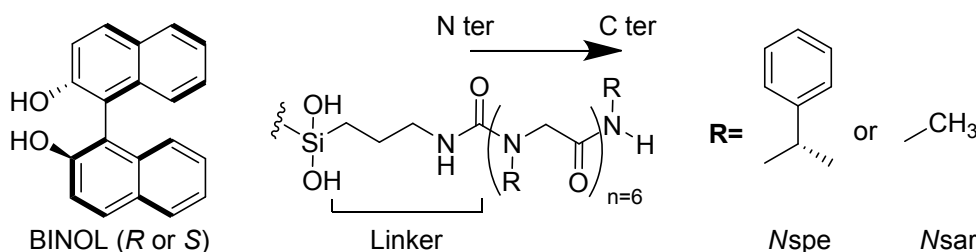
Peptoids are peptide regioisomers with attractive structural tunability in terms of sequence and three-dimensional arrangement. Peptoids are foreseen a great potential for many diverse applications, including their utilization as chiral stationary phase in chromatography. To achieve chiral recognition, a chiral side chain is required to allow specific interactions with a given enantiomer from a racemic mixture. One of the most studied chiral stationary phase, built with (*S*)-*N*-1-phenylethyl (*N*spe) units, was showed successful in resolving racemic mixtures of binaphthyl derivatives. However, there is currently no description at the atomic scale of the factors favoring its enantioselectivity. Here, we take advantage of steered molecular dynamics simulations to mimic the elution process at the atomic scale and present evidence that the predominantly right-handed helical conformation of *N*spe peptoids, and their ability to form stronger hydrogen bonds with the (*S*) enantiomer, are responsible for the chiral recognition of the popular chiral probe 2,2'-bihydroxy-1,1'-binaphthyl.

1. Introduction

The majority of biological molecules such as amino acids and proteins, carbohydrates, or hormones is chiral although only one of the two enantiomers is commonly found in living organisms.¹ In contrast, many chiral synthetic compounds such as drugs are obtained in racemic mixtures.² Enantiomers often display different reactivity in biological systems which are enantioselective.³ This is particularly critical in the pharmaceutical field so that a careful control of the enantiomeric composition is mandatory to avoid medical disasters, such as the infamous thalidomide drug scandal in the late 1950s.³ Various methods have been developed to obtain enantiopure drugs, such as Dutch resolution or asymmetric synthesis.^{4,5} Using the later method,

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3 two kinds of chiral reagents are required if both pure enantiomers are needed. Moreover, this
4 method is limited by the high cost of the catalysts and often requires lengthy synthetic routes.^{6,7}
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6 An alternative relies on the preparation and direct separation of a racemate by chiral stationary
7 phases (CSPs) in chromatography columns.⁸ Nowadays, a large diversity of CSPs is available to
8 carry out enantioselective resolution. These CSPs mainly involve compounds such as
9 cyclodextrins,⁹ polysaccharides,¹⁰ proteins or peptide oligomers.^{11–13} In the latter case, previous
10 studies suggested that specific secondary structures, such as a helical conformation, can promote
11 and enhance enantioselectivity.^{12–15} In 2011, Wu *et al.* investigated peptoids as a new class of
12 chiral selector compounds in stationary phases.¹⁶ Peptoids are peptidomimetic molecules in which
13 the side chain is appended to the nitrogen atom of the amide group instead of the carbon in α -
14 position to the amide carbonyl as it is the case in peptides.¹⁷ These molecules are used in many
15 different applications, ranging from biomedical to nanotechnology,^{18,19} as well as in materials
16 science,^{20,21} because of their ease of synthesis and their resistance to proteolysis compared to their
17 peptide analogues.^{22,23} They also offer a huge versatility of structures by variation of the nature of
18 the side chains; in particular, changing the nature of the side chain around the C terminus extremity
19 was identified as a strategy to improve the chiral recognition.^{24,25} Besides their helical
20 conformation, peptoids have additional attractive features to achieve chiral recognition, thanks to
21 their amide groups that can act as hydrogen bond acceptors and to the wide variety of side chains
22 that can be introduced, such as aromatic rings to create π - π interactions with chiral molecules
23 containing aromatic moieties. In their study, Wu *et al.* have shown that peptoids grafted via their
24 N terminus extremity on silica do exhibit enantioselective properties against chiral binaphthyl
25 derivatives in presence of aromatic, bulky and chiral side chain, such as the (*S*)-1-phenylethyl
26 group (*N*spe, **Scheme 1**).¹⁶ This enantioselectivity has been linked to the fact that peptoids bearing
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Nspe side chains start adopting a helical conformation at a length of about 5 residues, which allows the establishment of specific interactions with a given enantiomer.^{16,26} There is, however, no clear description at the atomistic scale of the origin of these enantioselective properties.



Scheme 1. Primary structure of (A) BINOL (*R* or *S* 2,2'-bihydroxy-1,1'-binaphthyl) and (B) a peptoid chain, represented from N to C terminus, with *Nspe* or *Nsar* side chains and its linker for grafting on silica.

This has motivated the present study which describes the process of chiral recognition of peptoids substituted by *Nspe* side chains grafted on silica by means of molecular dynamics (MD) simulations. Simulations of chiral interfaces can assist experimentalists by shedding light on the recognition mechanism and the interactions involved between the selectors and the analytes to guide synthetic efforts, as recently shown for the well-known Whelk-O1 chiral stationary phase,^{27,28} or even for peptides and saccharides oligomers.^{29–31} To best mimic the conditions reported in the experimental study, we reproduced in our simulations key relevant parameters such as the grafting density and the solvent composition.¹⁶ We considered a peptoid of six units bearing seven *Nspe* side chains (*Nspe*₇ referred to as CSP5 in **Ref. 16**) as host and a binaphthyl derivative as guest (2,2'-bihydroxy-1,1'-binaphthyl or BINOL), see **Scheme 1**.¹⁶ We selected *Nspe*₇ as the enantioselective peptoid because it displays one of the best separation factors towards (*R*)- and (*S*)-BINOL in the experiments carried out by Wu *et al.*¹⁶ Steered molecular dynamics (SMD) have

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3 been performed to drag the enantiomers all along the model elution column and assess on a relative
4 basis their average velocities. Moreover, to test the validity of the computational model, we
5 performed the same simulations using an achiral peptoid bearing methyl side chains (*Nsar*) which
6 behaves as random coil in solution (**Scheme 1**)³² and for which the two BINOL enantiomers are
7 expected to display identical velocities. Our simulations qualitatively reproduce the experimental
8 trend, i.e., the (*S*)-BINOL enantiomer is retained for a longer time by the grafted *Nspe*₇ peptoids
9 and support the initial hypothesis that the helical structure plays a pivotal role in the
10 enantioseparation.
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21 **2. Materials and Methods**

22 *Sample preparation*

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26 An amorphous silica bulk is first generated by heating and cooling down a crystalline supercell
27 of cristobalite, as described elsewhere.^{33,34} We then extract from this structure one slab whose
28 surface dimensions equal to $58.7 \times 58.7 \text{ \AA}^2$, and with a thickness of about 60 Å. The slab was
29 placed horizontally (in the xy plane) in the simulation box, with the two surfaces of the slab
30 forming the walls of the model chromatography column, or more precisely of a single pore of the
31 silica beads which are used in the column. Random defects were further created independently in
32 each slab by removing SiO₂ units from the surface layers in order to increase the roughness of the
33 otherwise atomically flat surfaces. The atomic coordinates were then relaxed to allow local surface
34 reconstruction by thermal annealing. First, a linear ramp in temperature was applied from 300 K
35 to 900 K for 0.5 ns (heating rate: 1.2 K/ps), followed by an annealing at 900 K for 0.5 ns, and
36 finally cooled down to 300 K (1.2 K/ps for 0.5 ns) before a final energy minimization.^{34,35} The
37 pore size of the silica beads used by Wu *et al.* is about 100 Å,¹⁶ whereas the gap used between the
38 two surfaces in our simulation is instead 65 Å in order to save computational time. This is a
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3 reasonable approximation since this thickness is large enough to ensure that peptoids grafted on
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5 opposite surfaces do not interact. The bulk structure and the surface silanol groups of silica were
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7 described using the Clay force field parameters.³⁶
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10 The surface was then decorated with a self-assembled monolayer of oligopeptoid chains.
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12 Namely, we have described the chiral *N*spe and achiral *N*sar peptoids made of 6 monomer units
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14 (**Scheme 1**) by using a previously developed parameterization of the DREIDING force field
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16 specific to peptoids (i.e., the PEPDROID force field), in which the torsional barriers were reduced
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18 artificially to allow for a proper conformational sampling at 298 K (see details in **Supporting**
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20 **Information**).³⁷ Peptoid atomic charges were set using the Gasteiger method in Materials Studio
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22 18.0,^{38,39} as described in the original paper.³⁷ The grafting density is about 0.36 peptoid chain/nm²,
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24 similar to that reported in the experimental study of *N*spe peptoids (details in **Supporting**
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26 **Information**).¹⁶ To achieve this grafting density, 10 peptoid chains (20 in total) were attached on
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28 each silica surface on randomly chosen anchoring sites by connecting them via an alkyl linker to
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30 the silanol groups, see **Figure 1**. The *N*spe peptoid hexamers are grafted on the surface (through
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32 their N terminus extremity, attached to the linker) in their right-handed helical conformation, using
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34 the same initial conformation as described in the theoretical study performed by Armand *et al.*^{16,40}
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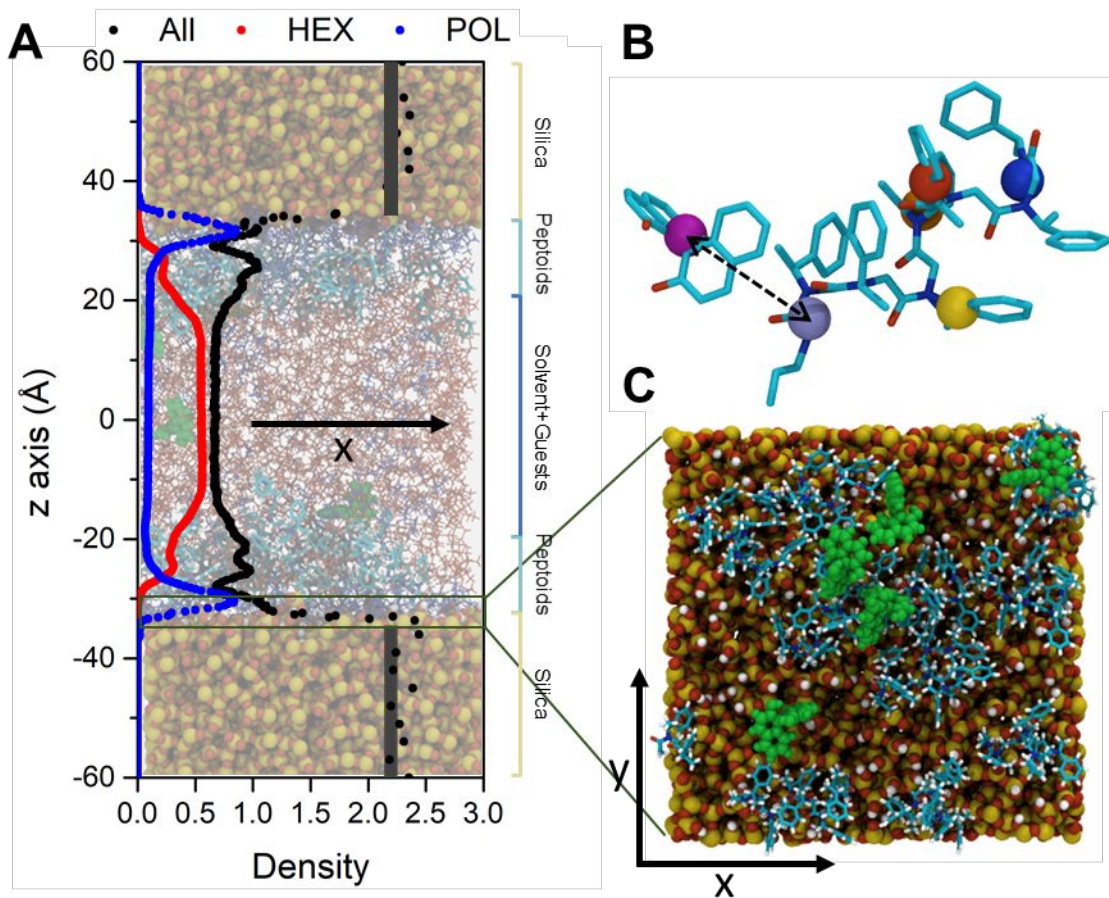


Figure 1. (A) Density profile (black dots) along the z axis of the simulation box. The elution occurs along the x axis. The vertical gray bands correspond to the experimental density of amorphous silica. Partial phase segregation of n-hexane (red dots) and 2-propanol (blue dots) is observed on top of the silica surfaces. (B) Representation of the distances computed between the center of mass of BINOL and the center of mass of each peptoid residue. (C) Top view of the bottom silica surface with grafted peptoids. BINOL molecules are highlighted in green.

The experimental mobile phase is a mixture of n-hexane/2-propanol 70/30 (v/v), which translates in our simulation box into 575 and 425 molecules, respectively, to fill the gap ($\sim 58 \times 58 \times 65 \text{ \AA}^3$) between the two silica surfaces. Solvent molecules are described here using the CGenFF parameters for the (non-)bonded interactions.⁴¹ Atomic charges were generated using the

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3 ParamChem web server.⁴² We chose these parameters because they adequately reproduce the
4 densities of pure solvents as well as the densities of mixtures at different ratios (**see Supporting**
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10 The chiral analytes selected are five (*R*)- and (*S*)-2,2'-bihydroxy-1,1'-binaphthyl (referred to as
11 BINOL in the following). They are also described by the CGenFF parameters, with atomic charges
12 assigned using the ParamChem web server.⁴²
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15 MD simulations on the entire system were performed using the NAMD software using 3D
16 periodic boundary conditions, see **Figure 1**.⁴³ Solvent molecules (n-hexane and 2-propanol),
17 peptoids, guest molecules (BINOL) and the silica atoms closer to the surfaces (within 5 Å) were
18 subjected to thermal motion, while the core of the slab was kept frozen at its equilibrium position
19 to save computational time.⁴⁴ No bond constraints were applied on the system. The simulations
20 were systematically carried out on a system containing only a given BINOL enantiomer (*R* or *S*),
21 since a racemic mixture would either reduce the quality of the statistical analysis made on a given
22 enantiomer if keeping the same total number of molecules or increase too much the number of
23 molecules in the box to guarantee that they behave independently. Each simulation was carried out
24 using a timestep of 1 fs. The particle mesh Ewald (PME) method was used to deal with the
25 Coulomb interactions with a real space cutoff of 10 Å and a switching distance of 9.5 Å.⁴⁵ The van
26 der Waals interactions are treated by a Lennard-Jones potential (12-6) using a 10 Å cutoff with a
27 switching distance of 9.5 Å, and Lorentz-Berthelot mixing rules. The system was first equilibrated
28 with a Langevin thermostat^{46,47} at 300 K and a Langevin barostat⁴⁸ set to 1 atm applied only in the
29 *z* direction (*i.e.*, the length of the box along the *x* and *y* axes remain fixed), until reaching the
30 convergence of the density and the energy of the solvent mixture after about 10 ns (**Figure S4,**
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54 **S5**). Then, steered molecular dynamics (SMD)⁴⁹ simulations of 650 ns for the *Nspe* substrate, and
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3 500 ns for the *Nsar* substrate were carried out in the NVT ensemble for samples containing 5
4 enantiomers (*R* or *S*) using a pulling force of $1.25 \text{ kcal}\cdot\text{mol}^{-1}\cdot\text{\AA}^{-1}$ on a single atom (the hydrogen
5 attached to one of the two carbons in α to the hydroxyl moiety) of each guest molecule along the
6 x direction. The pulling force is used to mimic the elution process along the chromatography
7 column. We chose this value because the flow it generates leads a low deviation from the
8 temperature imposed by the thermostat (see **Supporting Information** for details about the
9 evaluation of the effective temperature); moreover, it keeps the elution efficient (*i.e.*, the net flow
10 is not zero) and the computational cost, which is inversely proportional to the pulling force (the
11 lower the force, the longer the time for the analyte to travel a certain distance), reasonable. The
12 convergence of the simulations was monitored ensuring that the moving average of the velocity of
13 each BINOL inside the simulation becomes constant at long enough simulation times.

28 ***Conformational Analysis***

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31 Since we seek to characterize in a statistical way the conformation of the peptoids involved in
32 the recognition process, we developed a labeling method similar to that proposed by Spencer *et*
33 *al.*⁵⁰ The peptoid backbone is described by 3 dihedral angles per monomer unit (ω , ϕ and ψ), whose
34 combinations give rise to specific secondary structures. For example, a perfect right-handed helix
35 is characterized by a periodic repetition of the pattern ($\omega \sim 0^\circ$, $\phi \sim -80^\circ$, $\psi \sim 180^\circ$) (**Figure S7**).
36 The nomenclature is based on the assignment of a given letter to a range of values for each dihedral
37 angle. Spencer *et al.* describe ψ by the capital Greek letter Z, ϕ by R (right-handed) or S (left-
38 handed) and ω by c (*cis*) or t (*trans*). Accordingly, a helical conformation would be denoted as
39 Z_{RC} -helix. However, this nomenclature is too restrictive since it is mostly focused on helical
40 geometries. In this work, we extended the nomenclature to include a broader range of possible
41 structures and be able to account for slight structural changes. The complete method is described
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3 in the **Supporting Information**. Briefly, we now associate to each monomer unit a given letter
4 based on the value of the dihedral angles; for example, for values characteristic of a right-handed
5 helix, we simply use the single letter “R”. We apply the same method for the different
6 combinations of dihedrals along the peptoid backbone (from N to C terminus) and finally obtain a
7 coded sequence representative of each unit. For sake of illustration, “RRRXX” points to a
8 conformation where the 3 monomer units starting from the N terminus form a right-handed helix,
9 while the last two on the C terminus side, XX, feature any other dihedral combination that is not a
10 right-handed helix. Examples of the most common conformation sequences encountered in the
11 simulations are provided in **Table S4**, while the complete description for each generic name is
12 provided in **Supporting Information (Table S3)**.
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26 **3. Results and discussion**

27 *Steered Molecular Dynamics on (S)-BINOL interacting with Nspe*

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30 The system under study contains 5 (S)-BINOL molecules that were randomly inserted in the
31 solvent layer (**Figure 1A**). A first MD run was conducted using a Langevin piston of 1 atm for 10
32 ns to equilibrate the system which rapidly reached a density close to the experimental value in the
33 bulk (2.23 versus 2.2 g/cm³ for silica and 0.67 versus 0.676 g/cm³ for the solvent),⁵¹ **Figure 1A**).
34 Interestingly, the equilibrated structure displays a certain phase segregation in the density profile
35 between n-hexane and 2-propanol molecules, with the latter forming a layer on top of the silica
36 surface. This is explained by favorable polar interactions between silanol groups and 2-propanol,
37 compared to n-hexane. Such a segregation has also been observed by Monte Carlo simulations
38 performed on alkane-alcohol mixtures, both in the bulk and in confined samples.^{29,52,53}
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51 After equilibration of the system, a steered molecular dynamics (NVT, 650 ns, Langevin
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3 atom of each of the 5 (*S*)-BINOL molecules along the eluting (x) direction. We checked that this
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5 force does not induce a specific orientation of BINOL by measuring the time evolution of the
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7 cosine of the angle θ formed between the C-C bond linking the naphthyl moieties, and the cell
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9 vectors (**Figures S8 and S9**). The value of $\cos(\theta)$ in both the y and z directions oscillates between
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11 -1 and 1, thus indicating that the BINOL molecules sample all possible orientations. As expected,
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13 along the x direction, the value mainly oscillates between 0 and -1 since the pulling force is applied
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15 along this direction. We monitored several other parameters along the SMD, such as the x, y, and
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17 z coordinates of the center of mass of each (*S*)-BINOL, the conformation of each peptoid chain
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19 (20 in total) using the classification described in the section “*Computational Details*”. We also
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21 characterized the hydrogen bonds by measuring the distribution $D - H \cdots A$ distances and angles
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23 using the HBonds plugin (v1.2) from VMD (starting at 2 up to 4 Å by 0.2 Å steps, and at 20° up
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25 to 180° by steps of 20°).⁵⁴ For sake of conciseness, we will discuss in detail the time evolution of
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27 a single (*S*)-BINOL molecule, while other physical observables are computed as the average over
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29 5 molecules. The analysis of other compounds is reported in the **Supporting Information (Figure**
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31 **S10-S15)**.

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38 The displacement of the center of mass of each (*S*)-BINOL along the direction x is punctuated
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40 by several plateaus ranging from 1 to 10 ns, as shown in the inset of **Figure 2 (see also Supporting**
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42 **Information Figures S10-S15)**. These plateaus correspond to periods of time in which BINOL
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44 specifically interacts with peptoids near the surface on the two sides of the pore (for $|z| > 20$ Å), as
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46 shown by the correlation between the plateaus along the x-displacement and the position along z,
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48 highlighted by the green dashed rectangle in **Figure 2**. To better depict this interaction, we
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50 measured the distance between the center of mass of each peptoid and that of the BINOL molecule
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52 along the trajectory, as schematized in **Figure 1B**. If this distance is smaller than 7 Å (the value
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3 computed for a van der Waals contact between a BINOL molecule and a peptoid in a right-handed
4 helix conformation), we consider that a contact is established. Note that we also count one single
5 interaction also when several residues of a given peptoid are simultaneously in contact. This
6 analysis indicates that BINOL interacts more often with the C terminus, i.e., the most exposed
7 side, than with the N terminus grafted on silica (**Figure 3A**). The results have been combined into
8 conformational contact maps featuring the time-evolution of the conformation (color coded) of
9 each individual peptoid chain, together with contact events (**Figure 4**). For example, **Figure 4**
10 shows that the plateau along the x and z coordinates at ~ 75 ns, highlighted in **Figure 2**, is linked
11 to the interaction between BINOL and peptoid chains number 13, 16 and 19 adopting a “RRRXX”
12 conformation (partial right-handed helix, with X a wildcard corresponding to any other letter of
13 the code) during this contact event. We next gathered the conformations of each peptoid chain
14 during the contact events along the simulation to compute their relative abundance, see **Table 1**.
15 In doing so, we found that the main conformations involved in contact events are all derived from
16 a perfect right-handed helix (**Figure S16**). The deviation from the perfect right-handed helix
17 mainly arises at the C terminus side (typically the last two residues), where hydrogen bonds can
18 develop between the BINOL molecule and the amide moiety (**Figure 3A**). This is consistent with
19 the hypothesis of Wu *et al.* that one of the ingredient for the enantioselectivity of *N*spe peptoids
20 against BINOL molecules is the formation of hydrogen bonds.¹⁶ To assess this possibility, we
21 computed the distribution of $D - H \cdots A$ distances and angles between donors (D , consisting in
22 BINOL hydroxyl groups and the -NH group at the peptoid C terminus) and acceptors (A , BINOL
23 hydroxyl oxygen and peptoid amide oxygens, **Figure 5**). Clearly, hydrogen bonds can form for all
24 $D - H \cdots A$ pairs, according to standard geometric criteria (distances lower than 3.5 Å, and angle
25 higher than 150°,⁵⁵ as highlighted with a white frame in **Figure 5**). The exposure of the amide
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hydrogen at the C terminus is then crucial to form hydrogen bonds with (*S*)-BINOL. Moreover, the structural reorganization at the C terminus allows the good positioning of penultimate amide oxygen to form another hydrogen bond with the (*S*)-BINOL, which appears to be the most probable one. As we will see in the next section, the formation of these hydrogen bonds appears to be more frequent for the (*S*)-BINOL than the (*R*)-BINOL.

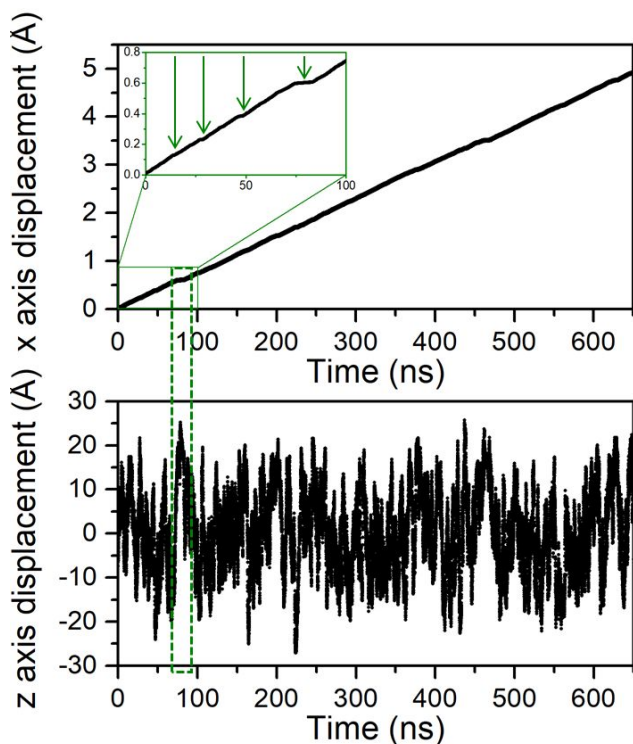


Figure 2. Displacement of a single (*S*)-BINOL molecule along the x (top) and z axis (bottom) over 650 ns. Plateaus are observed along the x displacement as pointed out in the inset by the green arrows, with an associated z displacement towards ± 20 - 25 Å, *i.e.*, close to the peptoids at the silica surface (highlighted for sake of illustration at ~ 75 ns by a green dashed rectangle).

Table 1. Main conformations adopted by *N*_{spe} and *N*_{sar} peptoids only during contact events with (*R*)- and (*S*)-BINOL molecules. The “X” character is used as wildcard and can be any of the previously defined letter (C, T, M, L), except the one in the current sequence. The complete description of the conformations is available in the **Supporting Information**.

Conformation (*R*-BINOL (%) (*S*-BINOL (%))

Nspe

RRRRX	29	34
RRRXX	34	25
RRRRr	16	25
Random coil	14	7

Nsar

Random coil	97	97
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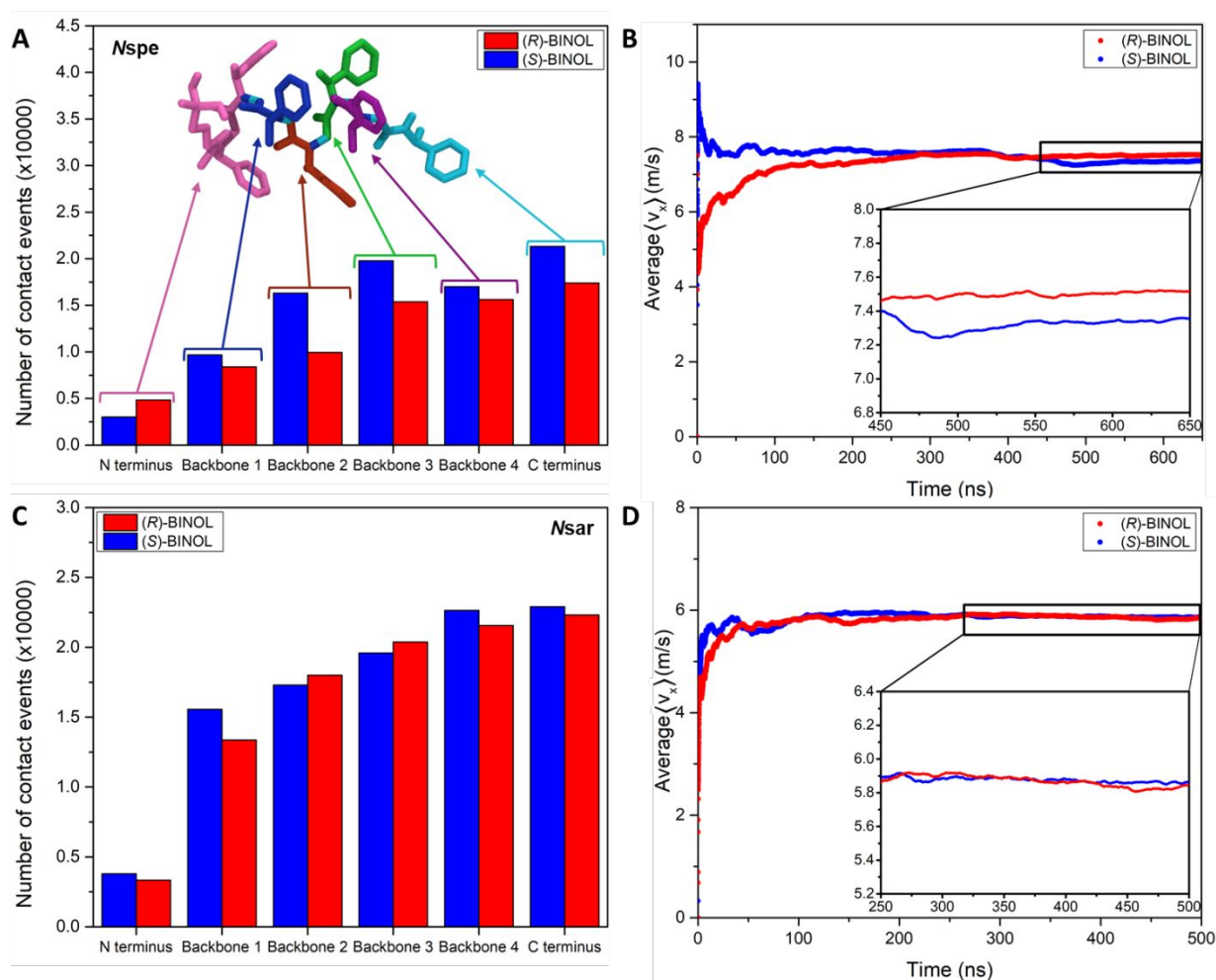


Figure 3. Number of contact events of (*R*)- and (*S*)-BINOL with (**A**) the *Nspe* peptoid residues from the N to C terminus, with most of the interactions occurring on the C terminus side (SMD

run of 650 ns) and (C) the *N*sar peptoid residues yielding a more homogeneous distribution (SMD run of 500 ns). (B) Evolution of the average velocity of (*R*)- and (*S*)-BINOL interacting with (B) the *N*spe peptoids (convergence is reached after 500 ns, as observed in the inset) and (D) with the *N*sar peptoids (convergence is reached after 300 ns).

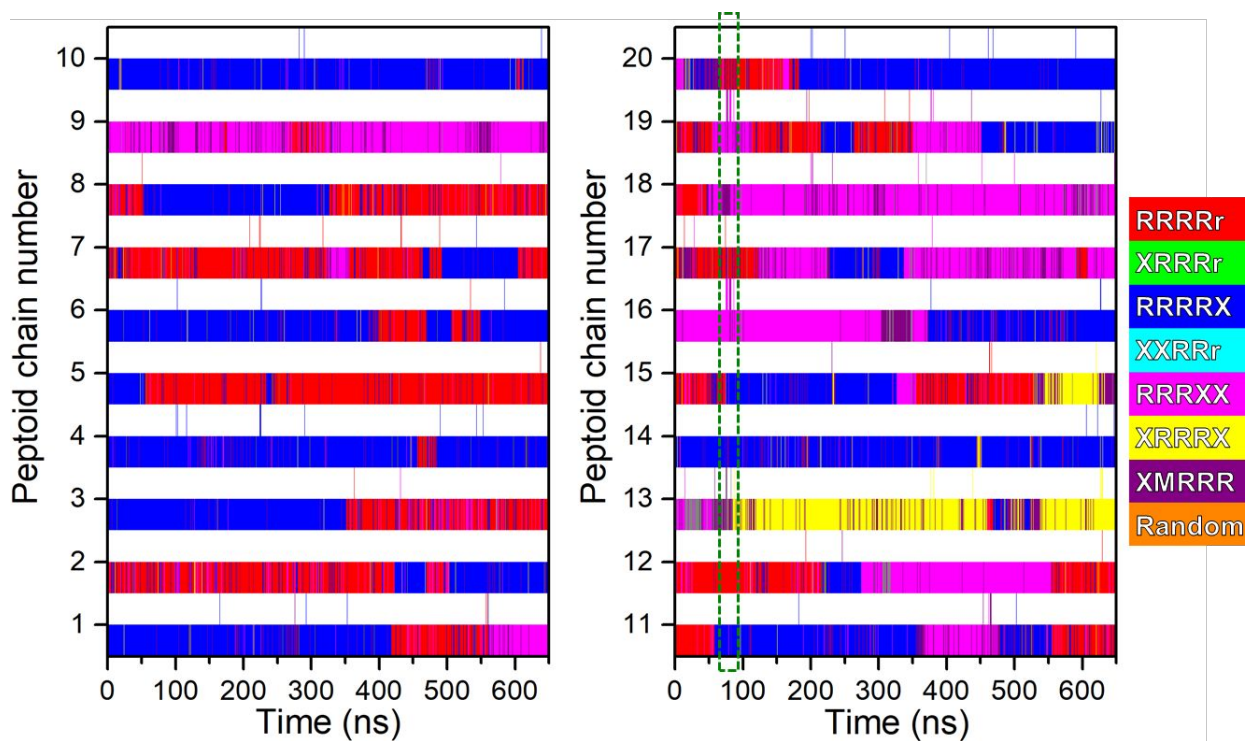


Figure 4. Conformational contact maps of a single (*S*)-BINOL compound with each of the 20 peptoid chains. Each color corresponds to a given peptoid conformation represented by the sequences of letters in the legend, as described in the **Supporting Information**. For every chain number, two colored ribbons are shown, above and below the given number. The lower line depicts the evolution of the conformation along the SMD, while the upper one (mostly white) highlights the conformations occurring when the BINOL molecule is in contact with the peptoid chain.

In order to assess the enantioselectivity, we finally computed the moving average velocity profile for the 5 BINOL molecules, (**Figure 3B**). For (*S*)-BINOL, the velocity reaches an average value of 7.354 m/s upon convergence (after 500 ns). It is worth stressing that this specific value is

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3 tributary of the chosen pulling force and hence cannot be readily compared to experimental values,
4 just as the experimental elution time depends on instrumental parameters such as the flux of
5 solvent. However, the comparison of the velocity of the two enantiomers in the same theoretical
6 (or experimental) conditions will be meaningful (see below). There are so many interactions
7 occurring in the process of chiral recognition that there is a very slow convergence of the average
8 velocity (calculated from time zero up to a given time t), i.e., the quantity displayed in figure 3.
9 Nevertheless, making our analyses only after 500 ns would make us loose the memory of all
10 interactions that have occurred before and that are instrumental to reach the convergence. For sake
11 of illustration, we report in the Figure S42 and FS43 the time evolution of instantaneous velocities
12 averaged among the (R)- and (S)-binol molecules in presence of Nspe and Nsar peptoids. Doing
13 so, we do not distinguish any convergence or specific trend after 500 ns of the instantaneous
14 velocities since the BINOL molecules are submitted to a Brownian motion and interact
15 sporadically with the peptoid chains. As a result, the instantaneous velocities highly fluctuate and
16 the sole consideration of the results beyond 650 ns cannot make us recover the required
17 convergence due to the poor sampling. Accordingly, this indicates that all dynamical processes
18 before 650 ns are truly part of the chiral selection process and that we need the entire trajectory to
19 ensure convergence, as achieved in Figure 3.
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35 ***Steered Molecular Dynamics on (R)-BINOL interacting with Nspe***

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38 With exactly the same setup used for the (S)-BINOL simulation, we next performed a SMD
39 simulation for the pore containing five (R)-BINOL molecules, whose trajectories are analyzed in
40 detail in **Figures S18-S23**. In the case of (R)-BINOL, we obtained a higher average velocity
41 compared to (S)-BINOL (7.515 vs. 7.354 m/s respectively, **Figure 3B**), thus implying that (S)-
42 BINOL is characterized by a larger elution time in our virtual chromatographic column. This is
43 fully consistent with the experimental results obtained by Wu *et al.*¹⁶ The difference in the elution
44 times arises from a different occurrence of contact events experienced by the two enantiomers
45 (**Table 1**). since the main peptoid conformations involved during contact events are the same for
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3 both BINOL enantiomers, though their relative abundances are different. (*R*)-BINOL interacts
4 more frequently with helices largely deviating from the ideal right-handed helix (helices of type
5 “RRRRX” and “RRRXX”, **Table 1**) as well as with random coil conformations. More importantly,
6 (*R*)-BINOL interacts less frequently with the grafted peptoids than the (*S*)-BINOL (**Figure 3A**).
7 Moreover, we do observe a clear difference when comparing the distribution of $D - H \cdots A$
8 distances and angles of the same donor-acceptor couples for (*R*)- and (*S*)-BINOL at the C terminus
9 side of the peptoids (**Figure 5**). The probability of forming hydrogen bonds between (*S*)-BINOL
10 and peptoids is much higher (in the range of 2 to 3.5 Å and angles comprised between 150° and
11 180°) than for (*R*)-BINOL for hydroxyl-amide O2, and N-terminus-hydroxyl oxygen bonds, while
12 it is identical for the hydroxyl-amide O1 interaction.
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26 Besides forming hydrogen bonds, (*S*)-BINOL can interact through π - π interactions inside the
27 cavities formed along the helix backbone, as suggested by Wu *et al.* (**Figure S15A**).¹⁶ In specific
28 helical geometry of type “RRRRX” or “RRRXX”, a pocket is formed at the C terminus side of the
29 peptoid into which the (*S*)-BINOL geometry fits adequately (**Figure S17B**), while such behavior
30 is barely observed along the trajectory for (*R*)-BINOL. By swapping the (*S*)-BINOL in the complex
31 displayed in **Figure S17B** with a (*R*)-BINOL, we observe that (*R*)-BINOL cannot fit equally well
32 inside the cavity (**Figure S17C**).
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42 The consequences of these complex interactions also emerge from the compared analysis of the
43 autocorrelation function of the dihedral angles,⁵⁶ $C_{\alpha}(t) = \langle \cos \alpha(\tau) \cdot \cos \alpha(\tau + t) \rangle +$
44 $\langle \sin \alpha(\tau) \cdot \sin \alpha(\tau + t) \rangle$, with α corresponding to the main peptoid backbone dihedrals ω , ϕ and
45 ψ (**Figures S39, S40, Table S2**). Indeed, we observe a major difference in the behavior of the ω
46 dihedral located at the C terminus extremity when comparing (*R*)- and (*S*)-BINOL simulations. In
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the former case, ω shows a much shorter correlation time, which we attribute to a re-orientation of the C terminus extremity induced by the formation of hydrogen bonds.

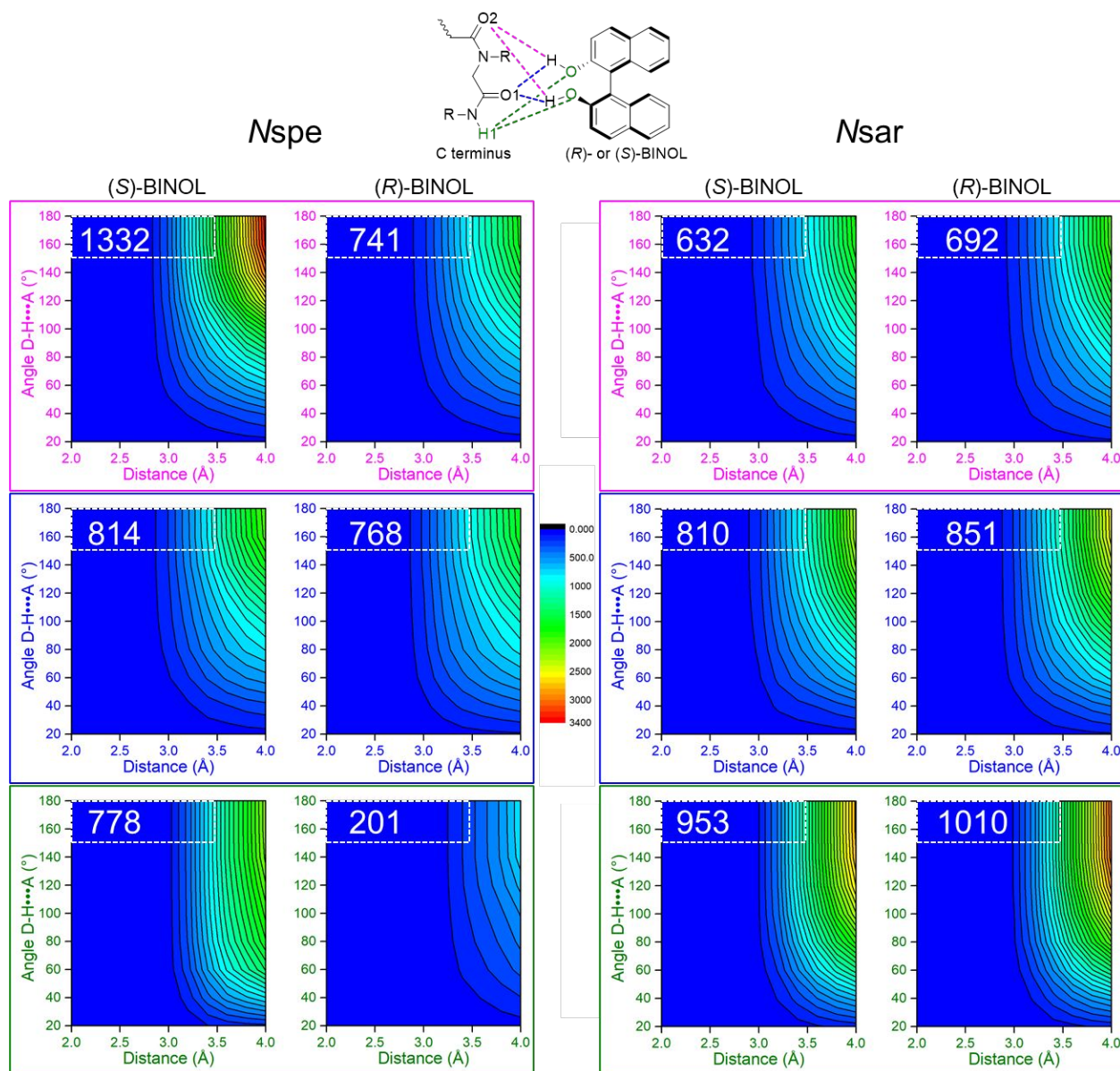


Figure 5. Distributions of angles and distances between donor (D), hydrogen (H) and acceptor (A) of BINOL-peptoid couples. The hydrogen bonds can be formed between the C terminus side (oxygen and hydrogen atoms of amide groups) of peptoids (*Nspe* or *Nsar*) and (*R*)- or (*S*)-BINOL. Each hydrogen bond couple is represented by colored dashed bonds in the molecular representation

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3 and the corresponding heatmap is identified by its colored frame. The dashed white frame inside
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5 the distributions represent the common range used to characterize hydrogen bonds, according to
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7 Van Der Spoel *et al.*⁵⁵ We also report in this frame the maximum number of hydrogen bonds in
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9 this range along the dynamics.
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12 13 *Steered Molecular Dynamics on (S)- or (R)-BINOL: The Nsar case*

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16 In order to substantiate the results for the *Nspe* peptoids chiral stationary phase discussed above,
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18 we performed additional simulations with the same conditions (grafting density, peptoid oligomer
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20 length, solvent composition, etc.) on a model system made this time of achiral peptoids, which in
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22 principle should not exhibit any enantioselectivity. We chose sarcosine, the simplest possible
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24 peptoid unit bearing a methyl side chain, as a building block for an achiral hexamer (*Nsar*, **Scheme**
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26 **1**). Such peptoids are known to behave as flexible polymers and to not adopt any particular
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28 conformation in a variety of solvents (polar and apolar); the main conformation type is thus
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30 labelled as “random coil”.^{32,57} The analysis of the displacements of the (*R*)- and (*S*)-BINOL along
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32 the x and z axes during the simulations with the *Nsar* stationary phase, as well as the
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34 conformational contact maps are reported in **Supporting Information (Figures S25-S38)**. Unlike
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36 *Nspe* hexamers, BINOL enantiomers interact more homogeneously with the units of the sarcosine
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38 chains (except with the hardly accessible N terminus grafted on the silica substrate, **Figure 3C**).
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40 This can be rationalized by observing that, as expected, sarcosine oligomers do not assume chiral
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42 conformations and are more flexible and less sterically hindered than *Nspe* peptoids, which are
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44 mainly helical-like. The higher flexibility of *Nsar* is reflected both by the larger variations in the
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46 average end-to-end distances for sarcosine chains along the dynamics (**Figure S24**) and by the
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48 dihedral autocorrelation functions that indicate fast conformational rearrangements (characteristic
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3 timescale of about 10 ns), compared to the *Nspe* peptoids that can reach up to 150 ns (**Figure S41**,
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5 **Table S3**).

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8 Although sarcosine oligomers behave as random coils, they can still form hydrogen bonds with
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10 BINOL enantiomers. However, compared to the chiral *Nspe* peptoids for which the hydrogen bond
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12 geometrical parameters are different between the two enantiomers, the probability distributions
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14 are very similar for *Nsar* with both BINOL enantiomers (**Figure 5**) and do not show any evidence
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16 of chiral interaction. As a result, no difference is observed in the average velocities of (*S*)- versus
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18 (*R*)-BINOL, owing to the achiral nature of the grafted chains (**Figure 3D**).

21 **4. Conclusions**

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24 We put forward a computational methodology, based on steered molecular dynamics
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26 simulations, for reproducing a liquid chromatography experiment, and applied it to evaluate the
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28 enantioselective properties of chiral *Nspe* peptoids against both 2,2'-bihydroxy-1,1'-binaphthyl
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30 enantiomers (BINOL).¹⁶ Our results show that, during the elution process, (*S*)-BINOL is retained
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32 for a longer time than (*R*)-BINOL in the chromatography column, due to more favorable
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34 interactions with *Nspe* peptoids in conformations derived from a right-handed helix. The geometric
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36 deviation from the perfect right-handed helix that arises on the C terminus side promotes the
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38 exposure of the amide hydrogen of *Nspe* peptoids and triggers the formation of hydrogen bonds
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40 with (*S*)-BINOL. Moreover, the C terminus can form a groove where the (*S*)-BINOL can fit and
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42 bind through π - π interactions. We thus conclude that the formation of hydrogen bonds at the C
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44 terminus side of the helical peptoids, as suggested by Wu *et al.*¹⁶, plays a pivotal role in the chiral
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46 recognition of binaphthyl derivatives, although the origin of the chiral selectivity lies in the right-
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48 handed conformation of *Nspe* peptoids. In a more general perspective, our study delineates how
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3 important is the proper tuning of the chemical structure of the C terminus side, since it could greatly
4 influence the selectivity of peptoids towards a variety of different chiral compounds.
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15 ASSOCIATED CONTENT

16 17 18 **Supporting Information.**

19
20 Additional analyses, figures, tables, computational details and structural description (PDF).
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25 AUTHOR INFORMATION

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34 35 36 37 **Author Contributions**

38
39 S. H., O. M. R. and C. T. have performed the computational studies under the supervision of L.
40
41 M. All authors analyzed the set of data and contributed to the writing of the manuscript. All
42
43 authors have given approval to the final version of the manuscript.
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50 Any funds used to support the research of the manuscript should be placed here (per journal
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Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

(*S*)-*N*-1-phenylethyl, *N*_{spe} ; chiral stationary phase, CSP ; *N*-methyl, *N*_{sar} ; 2,2'-bihydroxy-1,1'-binaphthyl, BINOL ; steered molecular dynamics, SMD ; n-hexane, HEX ; 2-propanol, POL

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