Chapter 5
A Phosphoric Acid-Based Receptor for Amplification of Molecular Chirality

In this chapter a new system for the double amplification of the molecular chirality of simple chiral amines in achiral liquid crystalline media is described. It involves a conformationally flexible phosphoric acid-based receptor that by binding to chiral amines induces chirality in the liquid crystalline matrix. Efficient cholesteric phase formation was shown by several chiral amines that were not able to induce a cholesteric phase by themselves. Solution studies aimed at elucidating the structures of these complexes are discussed. *

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5.1 Introduction

In the previous chapter, a $\beta$-enhancing receptor for the amplification of molecular chirality in liquid crystalline media was reported.\textsuperscript{1} In this system, chiral amino alcohols bind to conformationally flexible biphenol receptors, resulting in a preference for one axially chiral conformation of the receptor. When this complexation and transfer of chirality occur in a liquid crystalline matrix, the induced axial chirality of the receptor is transferred to the LC superstructure, effecting a change from a nematic to a cholesteric LC. In this biphenol-amino alcohol system, the macroscopic stereochemical properties resulted from the molecular chirality of the amino alcohols, as this was the only source of chirality present. Unfortunately, so far this amplification system only worked for amino alcohols. As structural changes in the aromatic groups flanking the binding area did not provide large improvements in the substrate scope and the amplification of chirality, a different approach was taken by introduction of a new primary binding motif. Inspired by several examples in nature as well as synthetic systems, a phosphoric acid functionality was introduced in the binding pocket, as this might facilitate efficient complexation to chiral amines through proton transfer and hydrogen bonding combined with electrostatic interactions.

5.1.1 Phosphate as a Binding Motif

The phosphate backbone of nucleic acids is believed to be able to interact with proteins through hydrogen bonds and salt bridges, both with the polypeptide backbone as well as with basic amino acid side chains.\textsuperscript{2} Similar interactions allow amino glycosides to bind to DNA and RNA, which has led to the development of RNA targeting drugs.\textsuperscript{3,4}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.1}
\caption{Possible interaction models of the phosphodiester backbone of nucleic acids with peptides and amino glycosides.\textsuperscript{2,3,5}}
\end{figure}
The interaction of phosphate groups with neutral and cationic guests has been applied in NMR-based enantiomeric excess determination of chiral amines, for chiral resolving agents, in the induction of chirality in helical polymers and as chiral Brønsted acid organocatalysts for the electrophilic activation of imines. The ability of phosphates to bind to neutral molecules containing the 1,2-diol motif has led to the development of receptors for the molecular recognition of carbohydrates. The binaphthalene-derived macrocyclic multivalent receptors reported by Diederich and coworkers are particularly efficient in the binding of sugars and the discrimination between mono- and disaccharides (Figure 5.2).

Figure 5.2 Association constants for the binding of receptor 5.1 to glycosides 5.2 and 5.3 in CD$_3$CN/CD$_3$OD 88:12.

### 5.2 Phosphoric Acids as Receptors for Amplification of Chirality

In the amplification mechanism reported in the previous chapter, conformationally flexible biphenol receptors like 5.4 were used to amplify the chirality of amino alcohol guests in the liquid crystalline matrix. These structural features were also used in the design of 5.5, resulting in a receptor with a flexible biphenol backbone, a phosphoric acid primary binding site and two 2-naphthyl moieties that feature a dynamic helical structure (Figure 5.3). Using standard synthetic methodologies, the primary binding site of 5.4 was replaced by a phosphoric acid functionality (Scheme 5.1). Using similar protocols, receptor analogue 5.6, devoid of naphthalene side groups, was also synthesized.
5.2.1 Host-guest Complexes in Liquid Crystals

Receptor 5.5 is highly insoluble in various organic solvents, including LC blend E7. However, mixing 5.5 with chiral amines such as 5.7, 5.8 or 5.9 led to soluble mixtures, both in isotropic solution as well as in the liquid crystalline matrix. In contrast to receptor 5.4, 5.5 does not amplify the chirality of amino alcohols (S)-5.7 and (S)-5.8, as no sign of any cholesteric order was ever observed. On the other hand, mixing 5.5 with (R)-α-phenylethylamine 5.9 led to polygonal textures and Grandjean-Cano lines, indicating a cholesteric phase (Figure 5.5a and b).

When (R)-5.9 was mixed with E7 at a similar concentration, in the absence of 5.5, no chiral induction was observed (Figure 5.5c). The interaction of 5.9 with
5.5 should lead to protonation of 5.9, so it could be possible that it is merely the protonated form of 5.9 inducing the cholesteric phase. However, this was ruled out by mixing E7 with 5.9•HCl or the complex of 5.9 with phosphoric acid 5.6 lacking the 3,3'-naphthyl moieties. Compound 5.9•HCl was insoluble in E7 (Figure 5.5d), whereas 5.6•5.9 led to a highly disturbed LC phase (Figure 5.5e). Neither showed any sign of a cholesteric phase.

To assess the chiral induction and substrate scope of receptor 5.5, mixtures with several chiral amines (Figure 5.6) were dissolved in E7 (amine/5.5 = 1.5:1, 0.038 µmol 5.5/mg E7) and the cholesteric pitch was measured using the Grandjean-Cano technique (Table 5.1).

Amines 5.9 and 5.10 induce the shortest pitches, indicating the largest chiral induction (entries 1 and 3). These pitches were slightly shorter than the
previously reported values for amino alcohols, which gave pitches as short as 12 µm. When the enantiomer of 5.9 was applied, a cholesteric phase with opposite helical sign was obtained, again showing that the cholesteric induction is associated with the chirality of the amines (entry 2). Similar but less efficient cholesteric induction was obtained with amine 5.12 and amino ester 5.15 (entries 5 and 8). Unfortunately aliphatic amines 5.13 and 5.14 did not induce a measurable cholesteric pitch, perhaps as a result of a lack of arene interaction possibilities with the receptor. In striking contrast to the primary and secondary amines 5.9 and 5.10, complexation of dimethylated amine 5.11 to receptor 5.5 did not induce a cholesteric phase. This suggests that the additional methyl group creates steric congestion in the binding pocket or a different mode of binding as the protonated form of 5.11 has only one hydrogen available for hydrogen bonding, instead of two or three in the other cases. Both effects could lead to a change in complex conformation with an associated lower helical twisting power. Finally, it was shown that chiral amide 5.16 also induces a cholesteric phase when mixed with 5.5 in E7 (entry 9). Although the obtained pitch is comparable to that obtained with either 5.9 or 5.10, the binding to 5.5 is believed to proceed via a different motif as 5.16 does not contain a basic enough nitrogen, but is capable of forming hydrogen bonds, analogous to the NH···O hydrogen bonds in proteins.

Table 5.1 Pitch of E7 doped with 5.5•amine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Pitch (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-5.9</td>
<td>+10</td>
</tr>
<tr>
<td>2</td>
<td>(S)-5.9</td>
<td>-10</td>
</tr>
<tr>
<td>3</td>
<td>(R)-5.10</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>(R)-5.11</td>
<td>-a</td>
</tr>
<tr>
<td>5</td>
<td>(R)-5.12</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>(R)-5.13</td>
<td>-a</td>
</tr>
<tr>
<td>7</td>
<td>(R)-5.14</td>
<td>-a</td>
</tr>
<tr>
<td>8</td>
<td>(S)-5.15</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>(R)-5.16</td>
<td>16</td>
</tr>
</tbody>
</table>

* No Grandjean-Cano lines were observed.

All these experiments were conducted at a receptor/amine ratio of 1:1.5, to insure complete dissolution of 5.5 and to avoid disturbance of the LC matrix by
large quantities of free amine. As this ratio has an influence on the concentration of chiral complex in the LC, mixtures of 5.5 and 5.9 at varying ratios were added to E7. The receptor/amine ratio varied from 1:1 to 1:5. However, this did not lead to significant variation in the cholesteric pitch, suggesting a large binding constant for the complex of 5.5 and 5.9 in the LC phase (Figure 5.7).

Figure 5.7 Cholesteric pitch vs. equivalents of amine (R)-5.9, using E7 and 1.0 equivalent of receptor 5.5.

5.3 Characterization of the Solution Structure of Host-Guest Complexes

The structure of the complexes of receptor 5.5 with amines 5.9 and 5.10 was studied by 1H NMR and CD spectroscopy, to gain more insight into complex formation and probably the mechanism of the chiral amplification.

5.3.1 1H NMR Complexation Experiments

The complex stoichiometry of 5.5•5.9 was assessed by 1H NMR titration in CDCl3. As receptor 5.5 by itself is insoluble in this solvent, the Job’s plot approach described in the previous chapter could not be applied in this situation. Therefore, the stoichiometry was determined using the solubilization of receptor 5.5 by addition of amine 5.9. The results are shown in Figure 5.8. Without any amine presents, no 1H NMR signals for 5.5 were observed. Upon addition of 0.25 eq. portions of a stock solution of 5.9, the complex went into solution, resulting in an NMR signal for 5.5 and 5.9. By integration of the signals associated with 5.5 and comparing them to an internal standard, the amount of dissolved complex could be estimated. When the relative signal of 5.5 compared to the internal standard was plotted against the number of equivalents of 5.9 added, a gradual increase up to 1 eq. was observed. Addition of more equivalents
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of 5.9 resulted in almost no change in the amount of 5.5 in solution, indicating 1:1 complexation.

**Figure 5.8** Relative amount of receptor 5.5 in solution in response to addition of amine 5.9, as monitored by $^1$H NMR spectroscopy in CDCl$_3$.

$^1$H NMR also provided some insights into the general structure of the complexes. Mixing 5.5 and 5.9 in CDCl$_3$ resulted in large upfield shifts of all aromatic and aliphatic protons of amine 5.9 (Figure 5.9). When 5.9 was mixed with 5.6, this effect was much less pronounced, indicating that it is caused by the shielding of the protons of 5.9 in the complex by the naphthalene moieties present in 5.5.\textsuperscript{12}

**Figure 5.9** $^1$H NMR of 5.9, 5.6•5.9 and 5.5•5.9 in CDCl$_3$. The NMR displays an upfield shift of all designated protons of amine 5.9 upon complexation to 5.5. When mixed with 5.6 this shift is much less pronounced.
The location of the amine in the cleft between the naphthalene moieties was confirmed by a 2D NOESY measurement on a mixture of 5.5 and 5.10 (Figure 5.10).

**Figure 5.10** 2D NOESY spectrum of 5.5•5.10 in CDCl₃. The area marked by the dotted lines shows the NOE cross peaks caused by intermolecular interactions.
This experiment showed considerable interactions between the naphthalenes on 5.5 and both methyl groups (designated \(H_P\) and \(H_N\), see Figure 5.10) on the amine, whereas no significant interactions could be observed between 5.5 and the methylene proton (\(H_O\)) of 5.10. The ortho- and meta-protons on the phenyl substituent of 5.10 also displayed interactions with the naphthalenes on 5.5, in contrast to the para-protons which did not. Unfortunately, due to the overall weakness of the interactions no definitive conclusions regarding the solution structure of the complex could be drawn.

5.3.2 Guest to Host Transfer of Chirality

Circular dichroism spectra of receptor 5.5 with a 100-fold excess of \(\alpha\)-phenylethylamine 5.9 or its mono-methylated analogue 5.10 showed small but significant induced CD signals of 5.5 at 295 and 305 nm, indicating the transfer of chiral information from the amines to the receptor (Figure 5.11).\(^\text{13}\) Although \(^1\)H NMR measurements did confirm binding of dimethylated amine 5.11 to receptor 5.5 in CDCl\(_3\), CD spectroscopy revealed a less pronounced and differently shaped CD signal of 5.5 upon binding to 5.11, as compared to those observed with amines 5.9 and 5.10 (Figure 5.11). This suggests an inefficient transfer of chirality from 5.11 to receptor 5.5, which could reflect its lack in ability to induce a cholesteric phase (vide supra).
The origin of the long wavelength CD band from 285 to 315 nm was determined through comparison of the UV spectra of 5.5 and 5.6 with and without added amine (R)-5.9 (Figure 5.12). The absence of this band in both UV spectra of receptor 5.6 shows that the observed circular dichroism originates from a chiral arrangement of or around the naphthalene moieties on 5.5.

**Figure 5.12** UV spectra of receptors 5.5 and 5.6, with and without added amine (R)-5.9. Shown are the spectra of 5.5 (dotted line), 5.5(R)-5.9 (dashed-dotted line), 5.6 (black line) and 5.6(R)-5.9 (dashed line). These spectra were recorded using the same concentrations and ratios of amine and receptors as in Figure 5.11.

### 5.4 Conclusions

In this chapter, a new receptor for the amplification of molecular chirality of simple chiral amines in liquid crystalline media has been presented. Binding of the chiral amine to the conformationally flexible phosphoric acid-based receptor induces chirality in the receptor, possibly expressed in a chiral conformation. Solution studies showed a 1:1 binding of the amine guests to the phosphoric acid host. This then probably leads to an excess of one of the chiral conformers of the receptor, as observed by circular dichroism spectroscopy. When this conformational change takes place in the LC matrix it causes a transition from the nematic to the cholesteric phase. With this approach it was possible to generate cholesteric phases employing several amines that are not capable of inducing cholesteric phases by themselves. This could ultimately lead to LC-based materials for the detection of small chiral organic molecules. Moreover, preliminary results show that it is also possible to amplify the chirality of amides, which could have implications for the detection of peptides and their role in chiral amplification phenomena.
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5.5 Experimental Section

For general remarks, see Section 3.7.

^1H NMR experiments

All NMR experiments were performed at 20 °C.

Stoichiometry determination.

The 1:1 binding stoichiometry of the 5.5•5.9 complex was determined using the following setup. An NMR tube was filled with 4.8 mg 5.5, 0.5 ml CDCl\textsubscript{3} and 5 μl acetone as internal standard, generating a suspension. No ^1H NMR signals for 5.5 were observed. Upon addition of 0.25 eq. portions of a stock solution of 5.9 (5.05 mg in 0.4 ml CDCl\textsubscript{3}), the complex went into solution, resulting in an NMR signal for 5.5 and 5.9. By integration of the signals associated with 5.5 and comparing them to the acetone signal, the amount of dissolved complex could be estimated.

^1H NMR of complexes 5.5•5.9 and 5.6•5.9.

Conditions: 5.5•5.9, [5.5] = [5.9] = 0.04 M in CDCl\textsubscript{3}; 5.6•5.9, [5.6] = [5.9] = 0.04 M in CDCl\textsubscript{3}.

2D NOESY of 5.5•5.10.

The 2D NOESY spectrum of 5.5•5.10 was recorded at 500 MHz on a Varian Unity Plus Varian-500, using a mixture of 5.5 (0.045 M) and 5.10 (0.045 M) in CDCl\textsubscript{3}. The mixing time was set to 0.7 s.

CD and UV measurements

CD spectra were recorded on a JASCO J-715 spectropolarimeter using UVASOL grade CHCl\textsubscript{3} (Merck) in a 1.0-mm quartz cell at ambient temperature (20-25°C). For all, [5.5] = 4.04·10\textsuperscript{-4} M, [amine] = 4.04·10\textsuperscript{-2} M (100 eq.). UV spectra were recorded on a Hewlett-Packard HP 8453 FT spectrophotometer, using the same conditions as stated for the CD measurements.

Synthesis

$^{31}$P NMR spectra were recorded on a Varian Mercury Plus, operating at 162 MHz, in DMSO-d\textsubscript{6} or CDCl\textsubscript{3}. Chemical shift values are denoted in δ values (ppm) relative to residual solvent peaks (DMSO-d\textsubscript{6}, $^1$H δ = 2.50, $^{13}$C δ = 39.52; CHCl\textsubscript{3}, $^1$H δ = 7.26, $^{13}$C δ = 77.0 ppm), or external H\textsubscript{3}PO\textsubscript{4} ($^{31}$P, δ = 0.0 ppm).

For the synthesis of 5.4, see Section 4.7.
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4,8-Di-naphthalen-2-yl-6-oxo-5,7-dioxa-6λ5-phosphadibenzo[a,c]cyclohepten-6-ol (5.5).

The synthesis of 5.5 was adapted from a literature procedure.14 Triethylamine (10.4 ml, 75.3 mmol) was added to a stirred solution of 5.4 (1.10 g, 2.51 mmol) in dry CH2Cl2 (50 ml). POCl3 (0.5 ml, 5.52 mmol) was added and the mixture was stirred for 3 h at 40°C. Subsequently the solvent was removed in vacuo, giving a yellow solid. This solid was suspended in a 1:1 mixture of THF and water (60 ml), which was then heated under reflux for 4 h. The resulting mixture was cooled to room temperature and the layers were separated. The aqueous layer was extracted twice with CH2Cl2. The combined organics were washed twice with water, dried over Na2SO4 and the solvent was removed in vacuo yielding a brown solid. Recrystallization from chloroform yielded 5.5 as a white solid (815 mg, 1.63 mmol, 65%). m.p. >330°C (dec.); 1H NMR (DMSO-d6, 400 MHz) 8.23 (s, 2H), 7.93 (m, 8H), 7.67 (dd, J1 = 7.6 Hz, J2 = 1.1 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.54 (dd, J1 = 3.3 Hz, J2 = 6.2 Hz, 4H), 7.50 (dd, J1 = 7.7 Hz, J2 = 7.7 Hz, 2H); 13C NMR (DMSO-d6, 100 MHz) 145.4 (d, Jp-c = 9.1 Hz), 134.6, 134.0 (d, Jp-c = 3.7 Hz), 132.9, 132.2, 131.6, 130.1, 129.8, 128.5, 128.2, 127.8, 127.5, 127.4, 126.32, 126.27, 125.9; 31P NMR (DMSO-d6, 162 MHz) 0.46 (s); MS (EI): m/z 500 (M+, 100%), 436 (M-PO2H, 4%), 420 (M-PO3H, 10%); Anal. Calcd. for C32H21O4P: C, 76.79; H, 4.23; Found C, 76.85; H, 4.29; FT-IR (KBr, cm⁻¹) ν 3053, 2430, 2062, 1632, 1419, 1348, 1213, 1125, 1047, 966, 858, 820, 783, 741, 638, 579, 529, 479, 446. Phosphoric acid 5.5 is insoluble in CDCl3. However, addition of 1 eq. of amine 5.9 or 5.10 led to a soluble complex, revealing small hydrocarbon peaks in the 1H NMR spectrum at 1.26 and 0.85 ppm. This residue in the analytically pure sample could not be removed by repeated recrystallization or column chromatography, but was found not to interfere with the complex formation as no interactions were visible between this residue and 5.5 in the 2D NOESY spectrum of the complex of 5.5 with 5.10 (vide infra).
According to a literature procedure,\textsuperscript{15} 1.00 g (5.38 mmol) 2,2'-biphenol gave 0.65 g 5.6 (2.62 mmol, 48\%) as a white solid. Spectral data were in accordance with literature values. m.p. 272\textdegree C (dec.); \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) 7.63 (dd, \(J_1 = 7.6\text{ Hz}, J_2 = 1.6\text{ Hz}, 2\text{H}\)), 7.49 (d, \(J_1 = 7.7\text{ Hz}, J_2 = 0.9\text{ Hz}, 2\text{H}\)), 7.39 (d, \(J_1 = 7.5\text{ Hz}, J_2 = 1.1\text{ Hz}, 2\text{H}\)), 7.28 (ddd, \(J_1 = 8.0\text{ Hz}, J_2 = 8.0\text{ Hz}, J_3 = 1.2\text{ Hz}, 2\text{H}\)); \textsuperscript{31}P NMR (162 MHz) 1.53 (s); MS (EI): m/z 248 (M+, 100\%), 184 (M-PO\textsubscript{2}H\textsubscript{2}, 2\%), 168 (M-PO\textsubscript{3}H\textsubscript{3}, 31\%); HRMS calcd for C\textsubscript{12}H\textsubscript{9}O\textsubscript{4}P: 248.0238; Found 248.0251; FT-IR (KBr, cm\textsuperscript{-1}) \(\nu = 3063, 2433, 2057, 1650, 1435, 1227, 1135, 1046, 935, 789, 760, 614, 525, 444\).
was tested. To check if the difference in pitch as described in Table 5.1 was not a result of a difference in clearing temperature between the complexes, the clearing temperatures of mixtures of E7 with complexes 5.5•5.9, 5.5•5.10, 5.5•5.11 and 5.5•5.16 where determined. In all four cases the same clearing temperature was observed (Tcl = 58.4 ± 0.3 °C). As the clearing temperature of E7 with only amines 5.9, 5.10 or 5.11 (Tcl = 59.2 ± 0.2 °C), is higher than for the complexes the lack of cholesteric induction by the sole amines can not be ascribed to a depression in clearing temperature.

5.6 References and Notes

10 Only addition of extremely large amounts (1:1 compared to E7) of (R)-5.9 led to a chiral phase, judging from the polygonal line texture observed under the microscope.
11 In water, the pKₐ of phosphoric acids generally lies around 2, whereas the pKa of protonated alkyl amines ions lies around 10. Therefore, phosphoric acid 5.5 is expected to nearly fully deprotonate the mentioned amines.
12 Due to the insolubility of receptor 5.5 in CDCl₃ without added amine, and the absence of a significant shift in the proton resonances of 5.5 upon complexation to
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one or more equivalents of amine 5.9 as described in Figure 5.8, no statements regarding the difference in chemical shift between the bound and unbound forms of 5.5 can be made at this point.

13 See also Chapter 4, Section 4.5.3 for details. At this point it can not be excluded that at least part of the CD signal originates from the chiral environment generated by the chiral amine, instead of a truly chiral conformation of the receptor.

