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NMR enantiodiscrimination by cyclic tetraamidic chiral solvating agents

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Abstract—Cyclic tetraamidic chiral selectors are efficient chiral solvating agents (CSAs) for NMR spectroscopy, which enantiodiscriminate several classes of chiral substrates, mainly endowed with a π-acidic aromatic ring. The great potential of DOSY techniques in the investigation of enantiodiscrimination phenomena, also in complex mixtures, was clearly demonstrated.

1. Introduction

The attractiveness and popularity of NMR methods for determining enantiomeric purities using chiral solvating agents (CSAs) are clearly shown by the effort over the last twenty years to design more and more efficient and versatile CSAs.[1–5] These range from simple low molecular mass organic compounds to more complex systems able to form supramolecular diastereoisomeric adducts with the enantiomeric pairs. Enantioselective chromatography also made important contributions in this field: efficient CSAs have been proposed based on chiral selectors employed to produce chiral stationary phases (CSPs) for HPLC or GC, as in the case of quinine,[6] amino acid derivatives[7] or cyclodextrins and their derivatives.[8–17] Recently, chiral A_2B_2 tetraamidic cyclic receptors have led to the production of new CSPs with significantly high performances in the enantioseparation of chiral substrates having a π-acidic moiety.[18] The efficiency of the said CSPs was very much dependent on the nature of the diamine employed in the preparation of the cyclic receptors, since the **CSP-1** formed from (1*R*,2*R*)-1,2-diphenylethylendiamine was more efficient than the **CSP-2** obtained by using (1*R*,2*R*)-1,2-diaminocyclohexane (Scheme 1).

These interesting results prompted us to inquire into the capability of **1** (Scheme 1), a $CDCl_3$ soluble analogue of **CSP-1**, to act as a CSA to induce NMR nonequivalences in the nuclei of enantiomers of chiral substrates, comparing its efficiency to that of **2** (Scheme 1), which is the basis of **CSP-2**. This investigation also enabled us to exploit the potentialities of DOSY (Diffusion-Ordered SpectroscopY) techniques[19,20] in the analysis of enantiodiscrimination processes in solution.

2. Results and discussion

2.1. ^{1}H NMR enantiodiscrimination experiments

The enantiodiscrimination experiments were carried out by comparing the ^{1}H NMR spectra of the pure racemates **3**–**15** (Scheme 2) (3.6 mM, $CDCl_3$) and their mixtures with the chiral auxiliaries **1** and **2**.

When the chiral auxiliary induced anisochrony in the proton nuclei of the two enantiomers, we measured the nonequivalence $\Delta\delta$, which is the difference between the chemical shifts of corresponding protons of the two enantiomers of the chiral substrates. This parameter reflects the enantiodiscriminating efficiency of the CSA.

In the presence of the chiral auxiliary **1**, the proton resonances of the valine derivative **3** undergo splittings (Table 1 and Fig. 1a), which range from about 0.01 ppm

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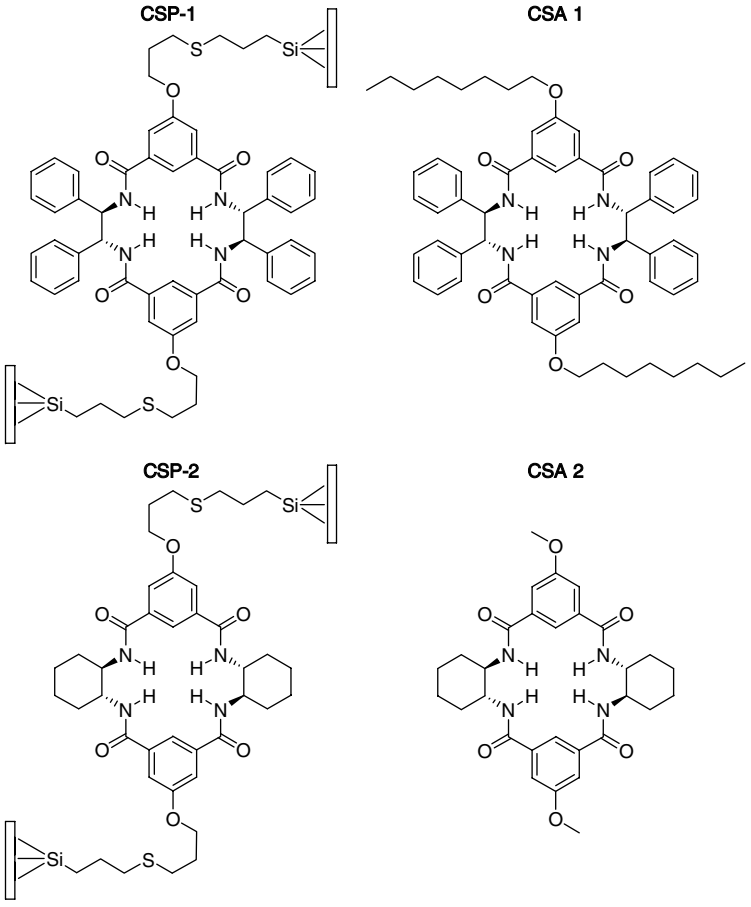
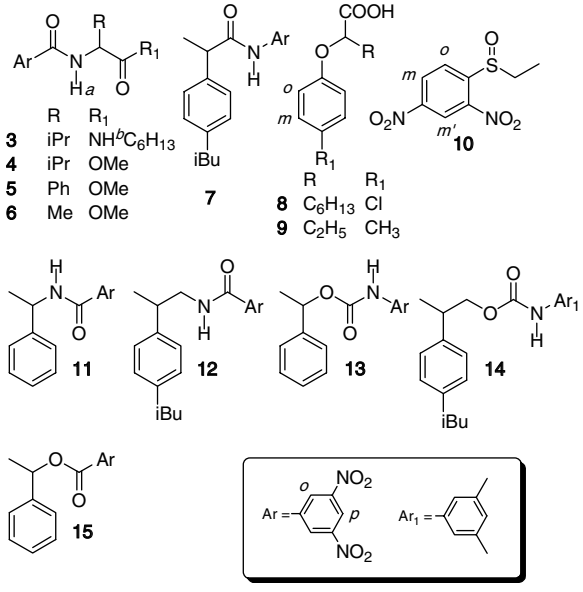


Scheme 1. CSP and CSA structures.



Scheme 2. Racemic compounds **3**–**15**.

for the *para*-proton of 3,5-dinitrophenyl moiety to 0.13 ppm for the amide proton bound to it.

Relevant nonequivalences are measured also for the other NH proton bound to the hexyl chain (Table 1 and Fig. 1a). These nonequivalences significantly increase on lowering the temperature to −20 °C (Table 1), whereas further temperature decreases do not affect them. The other valine derivative **4**, whose amine group is derivatized as 3,5-dinitrobenzamide, but with the carboxyl function derivatized as the methyl ester, shows analogous nonequivalences of 3,5-dinitrophenyl and NH protons, but the doublings are, in this case, strongly dependent on the temperature. As an example, the splitting of the *para*-aromatic proton is 0.019 ppm at 25 °C, and increases to 0.090 ppm at −40 °C.

Taking into consideration the other amino acid derivatives **5** and **6**, having derivatizing groups analogous to **4**, we can observe that both the presence of the phenyl group of **5** and the methyl group of **6** are responsible for a smaller degree of enantiodiscrimination (Table 1).

The proton resonances of derivatized chiral carboxyl acids and α-aryloxyacids are significantly split giving rise to nonequivalences, which in the case of **7**, reach about 0.05 ppm at 25 °C and 0.33 ppm at −40 °C for the NH amide proton. The α-aryloxyacid **9** with a *p*-methyl group shows smaller nonequivalences than **8**, which has a *p*-chloro substituent on the aromatic ring (Table 1).

3,5-Dinitrobenzoyl derivative **11** of a simple aromatic amine is enantiodiscriminated by **1** with nonequivalences,

Table 1. Nonequivalences ($\Delta\delta = |\delta_S - \delta_R|$, ppm, 600 MHz, $CDCl_3$, 25 °C) measured on the proton signals of compounds **3**–**11** (3.6 mM) in the presence of equimolar amount of **1** and of **2** (in parenthesis)

Compound	Proton	25 °C	0 °C	−20 °C	−40 °C
3	H_{para}	0.010 (0.003)	0.015	0.019	n.d.[a]
	H_{ortho}	0.032 (0.028)	0.041	0.046	0.050
	NH-a	0.131 (0.088)	0.171	0.191	n.d.[a]
	NH-b	0.064 (0.057)	0.086	0.099	0.092
4	H_{para}	0.019 (0.012)	0.033	0.054	0.090
	H_{ortho}	0.009 (0.003)	0.013	0.017	0.024
	NH	0.100 (0.057)	0.163	n.d.[a]	n.d.[a]
5	H_{para}	0.009	0.021	0.037	0.065
	H_{ortho}	—	—	—	0.018
	NH	n.d.[a]	0.065	0.110	0.182
6	H_{para}	0.009	0.016	0.026	0.044
	H_{ortho}	0.010	0.015	0.021	0.034
	NH	0.079	0.101	n.d.[a]	0.114
7	H_{para}	0.007	0.015	0.025	0.044
	H_{ortho}	0.003	0.014	0.019	0.029
	NH	0.046	0.106	0.180	0.326
8	H_{meta}	0.031 (—)	0.039	0.036	0.026
	H_{ortho}	0.041 (0.002)	0.045	0.031	—
9	H_{meta}	—	0.005	0.010	0.016
	H_{ortho}	0.005	0.014	0.030	0.051
10	$H_{meta'}$	0.031 (0.019)	0.051	0.075	0.100
	H_{meta}	0.117 (0.014)	0.195	0.284	0.427
	H_{ortho}	0.046 (0.046)	0.074	0.109	0.135
11	H_{para}	0.003	0.004	0.004	n.d.[a]
	H_{ortho}	0.003	0.005	0.008	0.015
	NH	0.026	0.038	0.052	0.115

[a] n.d. = not determined.

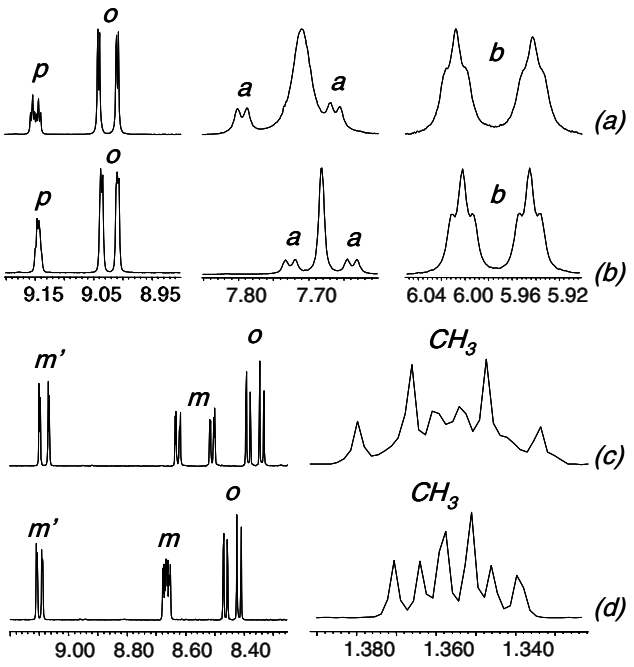


Figure 1. ^1H NMR (600 MHz, $CDCl_3$, 25 °C) spectral regions of mixtures CSA/(±)-compound: (a) **1/3**; (b) **2/3**; (c) **1/10**; (d) **2/10**.

which are lower than those measured for acid derivatives and ranging as in the case of **11** between 0.03 ppm at 25 °C and 0.12 ppm at −40 °C for the NH proton.

Benzamide **12**, with the stereogenic centre in position beta with respect to the NH, did not produce doublings as well as other carbinol derivatives such as **13**–**15**. In any case the presence of the π-acid aromatic ring in the chiral substrates is a prerequisite for enantiodiscrimination by **1** and **2**.

An interesting case is chiral sulfoxide **10**, which shows significantly high nonequivalences of the aromatic protons. At 25 °C, these are 0.03 ppm, 0.05 ppm and 0.12 ppm for the *m*′, *o*, *m* protons, respectively, and increase at −40 °C to 0.1 ppm for *m*′, 0.14 ppm for *o* and 0.43 ppm for *m*.

The other chiral auxiliary **2**, obtained from 1,2-diaminocyclohexane, also shows enantiodiscriminating ability with respect to the same classes of chiral compounds discussed in relation to **1**, but its enantiodiscriminating efficiency is lower than that of **1** (Table 1 and Fig. 1).

2.2. Enantiodiscrimination DOSY experiments

DOSY techniques[19,20] make it possible to measure diffusion coefficients (*D*) in solution. For spherical particles of hydrodynamic radius R_H in a solvent of viscosity η, the diffusion coefficients are given by Eq. 1

$$D = \frac{kT}{6\pi\eta R_H} \quad (1)$$

where k is the Boltzmann constant and T is the temperature.

These NMR methods have, therefore, considerable potential not only in the field of analysis of complex mixtures, but also in the detection of enantiodiscriminating phenomena.[8] In fact, the enantioselective interaction between a chiral selector and two enantiomers gives rise to formation of diastereoisomeric solvates characterized by lower diffusion coefficients than the pure compounds, as a consequence of their different sizes.

In the rapid exchange conditions, the diffusion coefficient D is the weighted average of its value in free (D_f) and complexed (D_c) states:

$$D = X_f D_f + X_c D_c \quad (2)$$

where X_f and X_c are the molar fractions of the free and complexed species, respectively.

Thus, even if the molecular sizes of the two diastereoisomeric solvates are similar in principle, the two enantiomers can be differentiated on the basis of their different bound fractions.

In order to investigate this kind of application of DOSY techniques, we first compared the DOSY maps of the pure compounds **1** and **6** (3.6 mM) with those of the equimolar mixtures **1**/(*R*)-**6** and **1**/(*S*)-**6** (Table 2). For the pure receptor we measured a diffusion coefficient of 5.24×10^{-6} cm^2 s^{-1}, which remained nearly unchanged in the two mixtures **1**/(*R*)-**6** and **1**/(*S*)-**6**. By contrast, the diffusion parameter of the amino acid derivative was 10.40×10^{-6} cm^2 s^{-1} in pure **6** and changed to 9.96×10^{-6} cm^2 s^{-1} for **1**/(*R*)-**6** and 9.61×10^{-6} cm^2 s^{-1} for **1**/(*S*)-**6** (Table 2). These results confirm the fact that the molecular diffusion of the complex is mainly (but not only) affected by the properties of the chiral auxiliary, that is, the component with greater molecular size, and the two enantiomers can be differentiated on the basis of their bound fractions.

Table 2. Diffusion data of pure **6** (3.6 mM) and of **6** in the presence of equimolar amounts of **1**

	D ($\times 10^{-6}$ cm^2 s^{-1})	K^I (M^{-1})	K^{II} (M^{-1})
6	10.40		
(*R*)-**6**/**1**	9.96	28	19
(*S*)-**6**/**1**	9.61	58	41

Association constants calculated by diffusion data (K^I) and by chemical shifts (K^{II}).

Thus, by using the NMR approach proposed for the analysis of the diffusion properties of cyclodextrin inclusion complexes,[21,22] we made the approximation that the diffusion coefficients of the two enantiomers in the bound states were equal to that of the chiral auxiliary ($D_c \cong D_{CSA}$ in Eq. 2) and used Eq. 3 to calculate the molar fractions of the two bound enantiomers (X_c).

$$X_c = \frac{D - D_f}{D_c - D_f} \quad (3)$$

The values obtained were 0.085 and 0.15 for (*R*)-**6** and (*S*)-**6**, respectively, allowing by a single point determination, the two association constants of the two 1:1 diastereoisomeric solvates to be estimated as $K_R = 28$ and $K_S = 58$ M^{-1} (Table 2).

In order to check the validity of this approach, we calculated the two association constants independently, by using the Foster–Fyfe method[23] of analysis of chemical shift dependence on the concentration of solutions containing a fixed amount of every enantiomer and increasing excesses of the receptor. By this procedure we determined association constants of 19 M^{-1} (K_R) and 41 M^{-1} (K_S) (Table 2). The differences between the two sets of data could be due to the fact that, probably, the molecular sizes of the chiral auxiliary and each enantiomer are not sufficiently differentiated to validate fully the above assumption that the global diffusion is controlled by the chiral auxiliary. However, in spite of this fact, we hypothesize that the molecular sizes of the two diastereoisomeric solvates in the complexed forms (D_c^R and D_c^S) are equal, on the condition of equal complexation stoichiometries. Therefore, in Eq. 3 the quantities $D_c - D_f$ are the same for the mixtures containing the two enantiomers and the ratios between their diffusion shifts ($D - D_f$) directly give the ratios of their bound fractions X_c, without knowing the association constants or the concentration of the solution analyzed. As a matter of fact, the above ratio was 0.56 in excellent agreement with the value of 0.52 calculated by using the association constants values determined by chemical shifts measurements.

The trend of diffusion shifts (Table 3) caused by the chiral auxiliary in the two enantiomers was according to chemical shifts variations ($\Delta\delta$, complexation shifts) (Table 3), lower for **1**/(*R*)-**6** relative to **1**/(*S*)-**6**.

Table 3. Diffusion shifts ($\Delta D = D - D_f$) and complexation shifts ($\Delta\delta = \delta_{obs} - \delta_f$) for the two enantiomers of **6** (3.6 mM) in the presence of equimolar amount of **1**

	ΔD	$\Delta\delta$			
		NH	H_p	H_o	CH
(*R*)-**6**/**1**	−0.44	42.2	−15.6	2.4	−3.9
(*S*)-**6**/**1**	−0.79	95.6	−21.5	−4.9	−6.8

In this regard, we must remark that, even though diffusion shifts are not so high as chemical shift variations, the latter cannot be used to extract directly the ratios between the bound fractions of the two enantiomers in the analyzed solutions, as, in principle, chemical shifts of corresponding nuclei of the two complexed stereoisomers could be significantly different as the consequence of the different stereochemical arrangements of the two diastereoisomeric solvates. In this respect diffusion coefficients can be considered global parameters featuring the whole molecule, whereas chemical shifts are local parameters. Given the above results, we checked also the possibility of analyzing mixtures containing the

chiral auxiliary and more than one racemic substrate in order to detect directly in the mixture differences in the extent of immobilization of the chiral compounds due to interaction with the chiral auxiliary. Thus we took into consideration the mixture containing **1** (10.8 mM) and equimolar amounts (3.6 mM) of all racemic compounds **3**, **6** and **15**. We compared first the DOSY maps of the solution containing the mixture of the three racemates (without the chiral auxiliary) and each pure component and negligible variations of the diffusion coefficients of the three components due to their co-presence were detected, revealing that the diffusion shifts observed in the mixture **1**/(**3**+**6**+**15**) can be attributed to the interaction with the chiral auxiliary. In the presence of the chiral auxiliary, compound **15** (which was not enantiodiscriminated by **1**) showed the lowest diffusion shift of -0.74×10^{-6} cm^2 s^{-1} (Table 4 and Fig. 2), (*R*)-**6** and (*S*)-**6** showed diffusion shifts of -1.07×10^{-6} and -1.84×10^{-6} cm^2 s^{-1}, respectively (Table 4) and, finally, the variations experienced by (*S*)-**3** and (*R*)-**3** diffusion coefficients were -1.31×10^{-6} and -0.76×10^{-6} cm^2 s^{-1} (Table 4).

Table 4. Diffusion data (D and $\Delta D = D - D_f$, $\times10^{-6}$ cm^2 s^{-1}) of the mixture containing the chiral auxiliary **1** (10.8 mM) and all the racemates **3**, **6** and **15** (3.6 mM)

	D_f	D^R	ΔD^R	D^S	ΔD^S
3	8.10	7.34	−0.76	6.79	−1.31
6	10.40	9.33	−1.07	8.56	−1.84
15	10.60	9.86	−0.74	9.86	−0.74

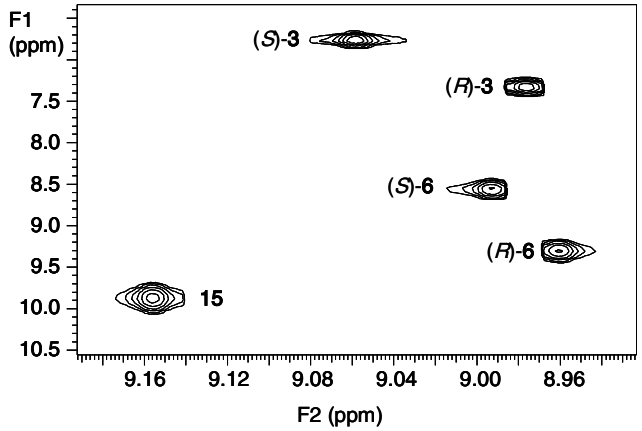


Figure 2. DOSY map (600 MHz, $CDCl_3$, 25 °C) of **1** (10.8 mM) in the presence of **3**, **6** and **15** (3.6 mM): spectral region corresponding to the *ortho* protons of 3,5-dinitrophenyl moiety.

The similarity of the diffusion coefficients of pure **6** and **15** reflects their comparable molecular sizes and, hence, the ratios of the measured diffusion shifts in the presence of **1** can be correlated to the ratios of the bound fractions: both enantiomers of **6** have enhanced affinity for **1** relatively to **15** and, as already observed, (*R*)-**6** is less associated to **1** than (*S*)-**6** is (Fig. 2) as the ratio between their bound fractions, calculated on the basis of the ratio between their diffusion shifts was 0.58, that is, very similar to the value obtained for the corresponding mixture containing the single enantiomers and the chiral auxiliary. The same trend is shown (Table 4) by the two enantiomers of **3**, that is (*S*)-**3** shows enhanced diffusion shift (-1.31×10^{-6} cm^2 s^{-1}) with respect to (*R*)-**3** (-0.76×10^{-6} cm^2 s^{-1}). It is noteworthy that the fact that the diffusion shifts of **3** are lower relative to the values obtained for **6** does not mean that **3** is less tightly bound to **1** relatively to **6**, as a matter of fact we must take into account that the diffusion coefficient of pure **3** is remarkably lower of the same parameter of **6**, reflecting the differences in their molecular sizes. As a further remark, the relative magnitudes of the diffusion shifts for the two enantiomers of **3** are not only according to the chemical shifts variations (Table 5) but also to chromatographic data; as in the chromatographic enantioseparation of **3** using **CSP-1**, (*S*)-**3** was more retained than (*R*)-**3**.[18]

Table 5. Complexation shifts ($\Delta\delta = \delta_{obs} - \delta_f$) for the two enantiomers of **3** (3.6 mM) in the presence of equimolar amount of **1**

	$\Delta\delta$		
	NH_b	H_o	CH
(*R*)-**3**/**1**	47.9	−4.2	−5.9
(*S*)-**3**/**1**	90.3	16.9	−21.0

3. Conclusion

In conclusion, as found in earlier studies,[6,7] a similar enantiodiscriminating trend in chiral selectors employed in chromatography and NMR spectroscopy was observed. The same classes of compounds are enantiodiscriminated with similar structural effects. In the present case, the chiral selector **1**, which in HPLC is more efficient than **2**, is itself the one producing the highest nonequivalences in solution within the same classes of compounds. Therefore the considerable synergy of the combined chromatography-NMR approach has been confirmed: chiral auxiliaries employed in HPLC or GC can constitute the basis of efficient complexing agents for NMR, offering efficient alternatives to the analytical chromatographic enantioseparation of compounds, which can be considered remarkably attractive in view of the speed and low costs involved: some milligrams of the chiral compounds, dissolved in less than 1 mL of deuterated solvent, can be analyzed in a few minutes by recording an ^{1}H NMR routine spectrum. It is noteworthy that even though several other efficient CSAs are available[1–5] for the analyses of π-acid substrates, however **1** and **2** have very favourable spectroscopical properties, as a matter of fact, in virtue of their symmetry, the sharp proton resonances of the two chiral auxiliaries leave free wide spectral regions, where the signals of the chiral substrates to be analyzed can be detected without significant interference. Furthermore, the nonequivalences measured are remarkable also at very low concentrations (3.6 mM), reducing the needed amount of chiral auxiliary.

Finally, the NMR analysis in solution of mixtures of chiral selectors and enantiomeric pairs provides information about their enantiodiscriminating potentialities,

which in turn, can constitute a reasonable starting point for their application in enantioselective chromatography. In this last field, DOSY techniques clearly proved their validity, as they enable us to analyze the behaviour of a selected chiral auxiliary directly with respect to complex mixtures of chiral compounds, giving a complete picture of its enantiodiscriminating efficiency and versatility.

4. Experimental

4.1. General methods

NMR measurements were performed on a Varian INOVA600 spectrometer operating at 600 MHz for ^{1}H using a 5 mm broadband inverse probe with *z*-axis gradient. The sample temperature was maintained at 25 °C. All ^{1}H NMR chemical shifts are referenced to TMS as external standard. DOSY experiments were carried out by using a stimulated echo sequence with self-compensating gradient schemes, a spectral width of 8000 Hz and 64 K data points. Typically, a value of 100 ms was used for Δ, 1.0 ms for δ and g was varied in 30 steps (16 transients each) to obtain an approximately 90–95% decrease in the resonance intensity at the largest gradient amplitudes. The baselines of all arrayed spectra were corrected prior to processing the data. After data acquisition, each FID was apodized with 1.0 Hz line broadening and Fourier transformed. The data were processed with the DOSY macro (involving the determination of the resonance heights of all the signals above a pre-established threshold and the fitting of the decay curve for each resonance to a Gaussian function) to obtain pseudo two dimensional spectra with NMR chemical shifts along one axis and calculated diffusion coefficients along the other.

The solutions for the association constants determination by the Foster–Fyfe method[23] were prepared keeping the concentration of the substrate at 0.1 mM and ranging that of the chiral auxiliary from 2 to 15 mM.

4.2. Materials

Compounds **1** and **2** were prepared, respectively, starting from 5-octyloxyisophthaloyl and 5-methoxyisophthaloyl chlorides and the required diamines following the procedure described in Ref. 18.

Compound **1**. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ ppm 0.85 (CH_3, 6H, t), 1.19–1.30 (CH_2, 16H, m), 1.35 (CH_2, 4H, m), 1.68 (CH_2, 4H, m), 3.86 and 3.94 (CH_2O, 4H, m), 5.52 (CH, 4H, br s), 7.23 (Ph-para, 4H, br s), 7.24 (Ph-*ortho*, 8H, br s), 7.26 (Ar, 4H, s), 7.27 (Ph-*meta*, 8H, br s), 7.81 (NH, 4H, br s), 8.12 (Ar, 2H, s). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ ppm 14.3 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 60.9 (CH), 68.7 (CH_2), 116.2 (CH), 118.6 (CH), 127.8 (CH), 128.1 (CH), 128.7 (CH); quaternary C: 135.6, 138.3, 159.5, 167.8. Anal. Calcd for $C_{60}H_{68}N_4O_6$: C, 76.57; H, 7.28; N, 5.95. Found: C, 76.40; H, 7.21; N, 6.15.

Compound **2**. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) δ ppm 1.42 and 1.86 (CH_2, 8H, m), 1.48 and 2.27 (CH_2, 8H, m), 3.84 (CH_3O, 6H, s), 3.93 (CH, 4H, m), 7.16 (Ar, 4H, s), 7.47 (NH, 4H, d), 7.52 (Ar, 2H, s). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C) δ ppm 24.9 (CH_2), 32.1 (CH_2), 55.3 (CH), 55.6 (CH_3), 115.2 (CH), 118.2 (CH); quaternary C: 136.3, 159.6, 168.7. Anal. Calcd for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.51; H, 6.55; N, 10.36.

Acknowledgements

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