NMR and molecular modeling of the dimeric self-association of the enantiomers of 1,1′-bi-2-naphthol and 1-phenyl-2,2,2-trifluoroethanol in the solution state and their relevance to enantiomer self-disproportionation on achiral-phase chromatography (ESDAC)†

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Molecular modeling of the homo- and heterochiral dimeric self-associates of the enantiomers of 1,1′-bi-2-naphthol and 1-phenyl-2,2,2-trifluoroethanol in solution has been performed in order to understand their NMR behavior and in light of the phenomenon of "enantiomer self-disproportionation on achiral-phase chromatography" (ESDAC). For 1,1′-bi-2-naphthol in C_6D_6, distinct NMR signals for each enantiomer arise for some spins in non-racemic mixtures—the phenomenon of self-induced diastereomeric anisochronism (SIDA). The linear divergence of these split signals across an enantiomeric titration (a series of samples in which the percentage of one enantiomer is varied from 50–100% whilst maintaining a constant total concentration), as well as the near linear migration of certain signals in $CDCl_3$ across a similar enantiomeric titration, where signals were not observed to be split, is consistent with the calculated small energy differences between the homo- and heterochiral associates. For an enantiomeric titration of 1-phenyl-2,2,2-trifluoroethanol in *n*-hexane, NMR signals also remained unsplit but the noticeable migration of some revealed a skew indicative of a preference for the heterochiral associate. This was duly reflected in the calculations which provided a ΔG value favoring the heterochiral associate by 2.4 kJ mol^{-1}. The relevance of these results to evaluating the likely occurrence of ESDAC is considered.

Introduction

Chiral compounds can respond asymmetrically to an achiral environment. The apparent system chirality emanates from the analytes themselves due to the formation of homo- and heterochiral aggregates.[1] In spectroscopy, values for non-racemic mixtures can deviate from interpolation between the pure enantiomers and their racemic mixture and such nonlinear effects[2] have been observed by several methods including NMR. Indeed, racemic mixtures, non-racemic mixtures, and enantiomers are all considered, albeit incorrectly,[1] to have identical NMR spectra by many practitioners. Without association this holds, however, there are cases[3–5] of distinct signals for each enantiomer for non-racemic mixtures (self-induced diastereomeric anisochronism, SIDA). Assuming the formation of aggregates that exchange rapidly on the NMR timescale, the following relationships provide an explanation for the SIDA phenomenon:

$$\delta_R = x_{R,\mathrm{free}}\delta_{\mathrm{free}} + x_{R,\mathrm{hom}}\delta_{\mathrm{hom}} + x_{R,\mathrm{het}}\delta_{\mathrm{het}}$$
$$\delta_S = x_{S,\mathrm{free}}\delta_{\mathrm{free}} + x_{S,\mathrm{hom}}\delta_{\mathrm{hom}} + x_{S,\mathrm{het}}\delta_{\mathrm{het}}$$

(where $\delta_{R/S}$ are the observed chemical shifts, $\delta_{\mathrm{free/hom/het}}$ are the chemical shifts of the free, homo-, and heterochiral states, and $x_{R(S)\mathrm{free/hom/het}}$ represent the mole fractions for each enantiomer separately). Since enantiomer distributions will differ in non-racemic mixtures and chemical shift differences ($\Delta\delta$) exist between the homo- and heterochiral states, distinct population-weighted averaged δs arise and, in principle at least, this is always the case. In systems for which association can occur but distinct signals are lacking, the chemical shift differences ($\Delta\delta$) may simply be too small, coupled with minor mole fractional changes between the various states for each enantiomer in relation to variances arising from environmental influences. This applies when the equilibrium between single molecules and dimers strongly favors single molecules with the result that the $\Delta\delta$ need to be ever larger for distinct signals to arise.

For the chromatography of non-racemic mixtures over achiral stationary phases, association may result in individual enantiomers and their racemic mixture exhibiting discernible R_fs in extreme cases, but more usual are accounts of optical purity changes across an eluting peak with the result that the optical state of any collected sample is thus dependent on peak fractionation. This result is under-appreciated by workers, based on anecdotal accounts and the surmise of Soloshonok,[6] despite being described in Eliel *et. al*.'s treatise[1] on stereochemistry. But this is not altogether unsurprising given that "enantiomer self-disproportionation on achiral-phase chromatography"[7] (ESDAC) reports are limited with only 18 described[6,8–10] unique occurrences with a further 8 treatments.[11]

Other instances of enantiomer self-disproportionation under other circumstances exist, *e.g.* sublimation,[12] ultra-centrifugation,[13] and these, together with crystallization events,[14]

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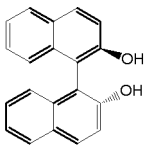
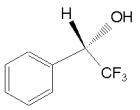
provide tantalizing suggestions as to the origin of homochirality.[14,15]

It is the dangers, or possible applications, posed by ESDAC that moved us to evaluate the solution-state association of enantiomers in order to identify susceptible systems. Thus, we have examined by NMR and molecular modeling 1,1′-bi-2-naphthol[11a,c–e,16] (**1**) and 1-phenyl-2,2,2-trifluoroethanol[6] (**2**), both of which exhibit exceptional ESDAC behavior. Their commonality is the likelihood to form H-bonded dimeric associates and it is this presumption and previous reports[1,6,9] that suggest the use of non-polar solvents to enable the formation of dimers and hence any implication for ESDAC.



R-(+)-1,1'-bi-2-naphthol (**1**)



S-(+)-1-phenyl-2,2,2-trifluoroethanol (**2**)

Results and discussion

NMR samples of **1** in $CDCl_3$ were prepared in which the percentage of one enantiomer was varied from 50–100% whilst maintaining a constant total concentration (herein enantiomeric titration). $CDCl_3$ was tried since strong ESDAC results have been obtained using $CHCl_3$. Distinct enantiomer signals in the non-racemic mixtures were not observed though some signals migrated across the titration. The migrations are attributed to shifting of the single molecule–dimer equilibrium, hence the presence of dimers is implicit by this result. But the dimer amounts are insufficient to express discrete signals for the enantiomers arising from $\Delta\delta$ and mole fraction changes. Plots of δ vs. enantiomer composition for various migrating signals provided curves that were monotonic and deviated only slightly from a linear interpolation between the racemic mixture and the pure enantiomer. This near-linear behavior, although it precludes a definitive indication of the homo- ($\mathbf{1}_{2hom}$) vs. heterochiral ($\mathbf{1}_{2het}$) dimer preference, nevertheless implies that ΔG between $\mathbf{1}_{2hom}$ and $\mathbf{1}_{2het}$ is small.[5]

An enantiomeric titration of **1** was then undertaken in C_6D_6 for which, for non-racemic mixtures, distinct signals were observed for some nuclei (Fig. 1). The $\Delta\delta$ between the *R* and *S* signals increased progressively with displacement from the racemic mixture, though they were minor in comparison to the δ migrations of the signals due to shifts in the single molecule–dimer equilibrium. Indeed, so small was the difference even at the last step that, except for C-1, distinct carbon signals or just the presence of a shoulder could only be discerned for those signals displaying differentiation by not applying any exponential broadening. The largest $\Delta\delta$ were observed for the OH signal (13.6 ppb), H-3 (6.3 ppb), and C-1 (14.8 ppb); this compares to a $\Delta\delta$ between the signals of the racemic mixture and the pure enantiomer accordingly of 739.2, 96.2, and 213.5 ppb, respectively. But whilst the major signals migrated monotonically and yielded a plot that was almost co-linear to an interpolation between the δs of the racemic mixture and its enantiomer, the minor peaks diverged, linearly, away from the interpolation line. This is exemplified by a plot for δ_{H3} portrayed in Fig. 2. The significance of this result is that linear divergences should occur when *K* for the equilibrium between homo- and heterochiral associates is small in value.[5]

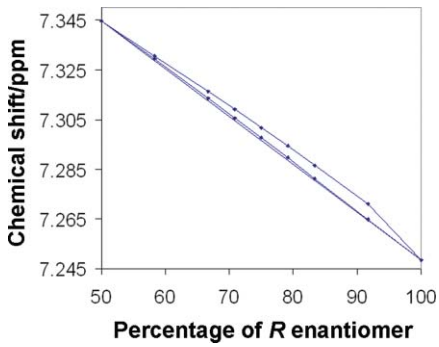


Fig. 2 In respect to an interpolation between δ_{H3} for racemic **1** and the enantiomer, δ_{H3} of the major enantiomer migrates practically co-linearly whilst δ_{H3} of the minor enantiomer diverges in a linear fashion.

Modeling of $\mathbf{1}_{2hom}$ and $\mathbf{1}_{2het}$ at the B3LYP/T(D)ZP level of theory was then performed (optimized structures presented in Fig. 3). For $\mathbf{1}_{2hom}$, the OH pairs from separate molecules directly oppose one another and alternate in direction, forming a symmetrical arrangement. On the other hand, the OH groups in $\mathbf{1}_{2het}$ are

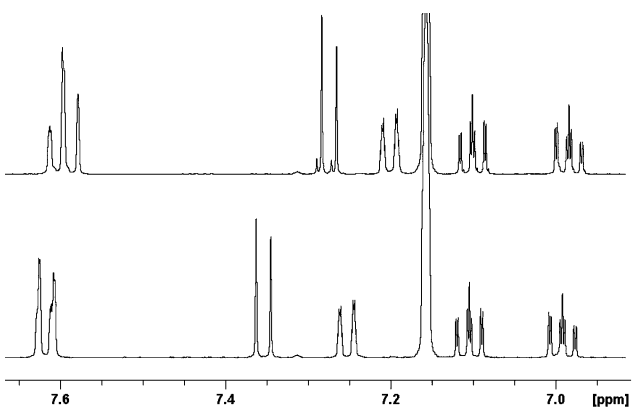


Fig. 1 ^{1}H NMR for racemic **1** (lower trace) and the prepared sample of 91.67% *R* (upper trace) showing signal migration and distinct δs for the enantiomers, *e.g.* H-3 (*ca.* 7.27 ppm).

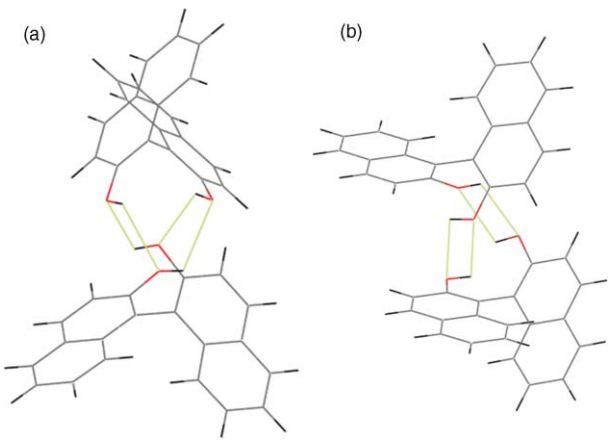


Fig. 3 a The optimized structure of the heterochiral complex of 1,1′-bi-2-naphthol ($\mathbf{1}_{2het}$). b The optimized structure of the homochiral complex of 1,1′-bi-2-naphthol ($\mathbf{1}_{2hom}$).

interspaced and form an alternating, interlocking sequence employing all Hs and Os of the four OH groups. Each OH is a donor to one of the other OHs in the other molecule but an acceptor for the remaining one, thus forming a continuum of H-bonding.

Calculation of ΔG with inclusion of the solvent provided $\mathbf{1}_{2hom}$ as the more stable entity by 0.1 kJ mol^{-1} in C_6H_6 but $\mathbf{1}_{2het}$ instead prevailed by the same amount in $CHCl_3$. These values are below the level of interpretability (and hence do not reliably indicate true associate preference), but both results indicate that there is little difference between the associates energetically and this is entirely consistent with the NMR observations in the two solvents. The latter result also agrees with previous experimental evaluations[11a,d] in that solvent and for which the excess enantiomer was observed to elute before the racemic mixture. The same elution order resulted from this work with benzene as the eluent, thereby this is either a case of the limitations of the modeling (since a reversal of elution order would be expected based on the calculated energies), or there is some moderation by the stationary phase. However, a prediction of the chromatographic elution order between the excess enantiomer and the racemic mixture based on the $\mathbf{1}_{2hom}$ or $\mathbf{1}_{2het}$ preference (to effect the enantiomeric distribution) is compounded in this instance by the potential for intramolecular H-bonding in **1**, leaving the likely chromatographic elution order between the dimer and the free molecule unclear. Nevertheless, the small difference in stabilities between $\mathbf{1}_{2hom}$ and $\mathbf{1}_{2het}$ for both solvents is consistent with NMR measurements where in C_6D_6 the linear divergence of signals for the two enantiomers indicates[5] a small magnitude of the value for K and in $CDCl_3$ a near-linear progression of signals was observed over the course of the enantiomeric titration.

For the enantiomeric titration of **2** in *n*-hexane, the ^{1}H, ^{19}F, and ^{13}C spectra of the non-racemic mixtures contained only single sets of signals though migrations across the enantiomeric titration were again evident for some signals, particularly for those nuclei close to the H-bonding centers. Since peaks migrated without splitting, it implies that the single molecule–dimer equilibrium is strongly shifted towards the single molecules, in particular with respect to the $\Delta\delta$ between $\mathbf{2}_{2hom}$ and $\mathbf{2}_{2het}$ associates. This is similar to **1** in $CDCl_3$ solution, but unlike **1** the preference between $\mathbf{2}_{2hom}$ and $\mathbf{2}_{2het}$ is now available from plots of δ vs. enantiomer%. For example, the trend for C-1 shown in Fig. 4 shows a distinct bend (a flattening out of δ values) towards the δ_{rac} value, this is interpreted as evidence that $\mathbf{2}_{2het}$ is energetically preferred. This interpretation is based on the following reasoning: only if $\mathbf{2}_{2hom}$ and $\mathbf{2}_{2het}$ are degenerate will the curve be linear (*cf.* the case of **1** where only slight energy differences were found); otherwise if $\mathbf{2}_{2het}$ is preferred, then there will be a deviation above the interpolation line if $\delta_{rac} > \delta_{enant}$, or below it if $\delta_{rac} < \delta_{enant}$ and conversely if $\mathbf{2}_{2hom}$ is preferred. Moreover, there will be a bend towards the favored complex, *i.e.* towards the racemic mixture δ value in the case of a $\mathbf{2}_{2het}$ preference and towards the enantiomer δ value in the case of a $\mathbf{2}_{2hom}$ preference since in the former case these associations will dominate non-racemic mixtures as they become more racemic. Conversely for a $\mathbf{2}_{2hom}$ preference, homochiral associations will predominate above the statistical distribution as the non-racemic mixtures approach greater enantiomeric purity and so the δ trend will flatten out as it tends towards the enantiomeric value. Behavior like this mimics the behavior of distinct spins for the enantiomers in an enantiomeric titration.[5]

Similar and consistent trends were observed for other spins in the molecule though the bends were not necessarily as apparent and therefore they rely to a degree on $\Delta\delta$ as well as on the relative size of the energy difference between $\mathbf{2}_{2hom}$ and $\mathbf{2}_{2het}$. Although single molecules should be heavily favored over dimers in this system regardless of enantiomeric composition, an equilibrium shift can nonetheless still be sufficient to cause signal migration. The conundrum that signals can migrate due to an equilibrium shift in an already heavily favored equilibrium, but not split to exhibit distinct signals for the two enantiomers due to alterations in the mole fractions of the homo- and heterochiral associates, is rationalized on the basis that $\Delta\delta$ between free molecules and dimers can be considerable but $\Delta\delta$s between the stereoisomeric $\mathbf{2}_{2hom}$ and $\mathbf{2}_{2het}$ are likely to be minor by comparison. This is especially so for the latter with the flexibility of H-bonds.[17]

Modeling at the B3LYP/TZVP level of theory provided structures for $\mathbf{2}_{2hom}$ and $\mathbf{2}_{2het}$ which were very similar (optimized structures are presented in Fig. 5) with both forming a complex consisting of one CF_3 group from one of the molecules and the two OHs from both molecules. For the unit in which the CF_3 group did not participate in H-bonding, the OH group acted as both H-acceptor and H-donor (to the CF_3) whereas the OH group of the other molecule participated only as a H-donor. The contacts

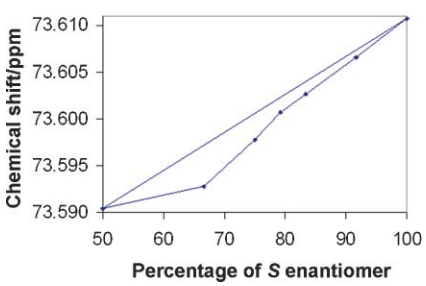


Fig. 4 A plot of δ_{C1} vs. percentage *S* enantiomer for **2**.

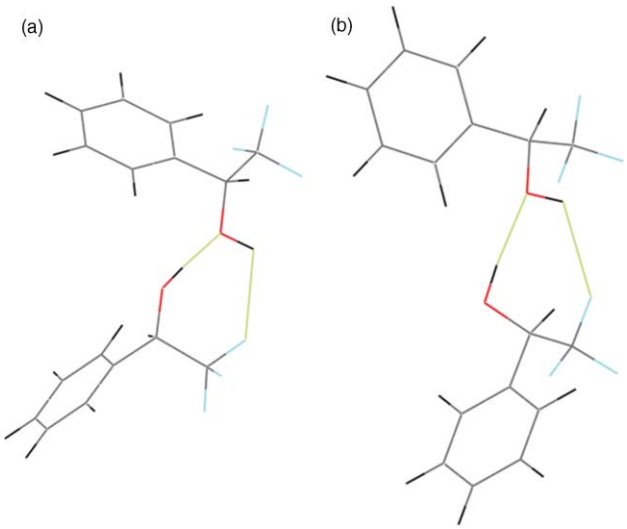


Fig. 5 a The optimized structure of the heterochiral complex of 1-phenyl-2,2,2-trifluoroethanol ($\mathbf{2}_{2het}$). b The optimized structure of the homochiral complex of 1-phenyl-2,2,2-trifluoroethanol ($\mathbf{2}_{2hom}$).

consisted of a strong bond between H and O (1.89 Å for $\mathbf{2}_{2het}$ and 1.90 Å for $\mathbf{2}_{2hom}$) and a weaker association between H and F (2.54 Å for $\mathbf{2}_{2het}$ and 2.38 Å for $\mathbf{2}_{2hom}$). Though **2** has been intensely modeled before,[18] the considered structures were not relevant to this system and conditions.

Calculation of ΔG with inclusion of the solvent provided $\mathbf{2}_{2het}$ as the more stable entity in both chromatography solvents[6] *n*-hexane (2.4 kJ mol^{-1}) and ethyl acetate (2.3 kJ mol^{-1}). This much more substantial result is consistent with the chromatography in which early fractions were observed to be more racemic. Dimers with OHs involved in H-bonding would be expected to elute faster rather than be adsorbed onto the polar surface of the substrate in comparison with the single molecules. Therefore if the heterochiral complex $\mathbf{2}_{2het}$ is preferred over the homochiral complex $\mathbf{2}_{2hom}$, the faster-eluting dimers will be enriched in it, *i.e.* the early fractions will be more racemic compared to the overall enantiomeric composition of the sample. Furthermore, in the NMR only a single set of signals was observed, with a clear bend towards the racemic mixture for a plot of δ vs. enantiomer% for migrating signals, therefore these calculations substantiate the abovementioned claims, in particular with respect to the larger calculated energy difference between the homo- and heterochiral associates in comparison to **1**.

Changes resulting in disruption of the H-bonding should cause gravitation of the δs of the racemic mixture and the enantiomer to the same terminal values, *i.e.*, $\Delta\delta$ should reduce progressively as alterations are made. To confirm this, three specific adjustments were undertaken on 50 and 100% enantiopure samples: serial dilution of the samples (for **1** and **2**), variable temperature measurements (at 25, 40, and 60 °C for **2**), and the incremental introduction of a polar solvent (ethyl acetate was used for **2**). In all cases, as the δs gravitated towards terminal values the $\Delta\delta$ were markedly reduced, in some instances to below the level of reproducibility based on the solvent and internal reference signals, thereby confirming the presence of H-bonding based associations and an equilibrium shift towards single molecules. Following the variable temperature runs, re-measurement at 25 °C realized $\Delta\delta$ in the main comparable to the original $\Delta\delta$ even if the absolute δs were not reproducible. Ostensibly, if the δs of the individual species were known, approaches such as these could provide support for the preferred complex based on the comparative rates of change of the δs. However, the demands of such measurements given the small changes in δ may preclude a reliable analysis for this aspect and additional work is also required to eliminate other effects that could account for the $\Delta\delta$, such as conformational changes, temperature dependence of the solvent dielectric constant, *etc.*

The longitudinal relaxation time, T_1, or the diffusion coefficient, *D*, can both potentially indicate a shift in the single molecule–dimer equilibrium with the advantage that the observed nuclei need not be located near the site of complexation. However, T_1s and *D*s for the racemic and enantiomeric solutions of **1** provided differences that lay below the level of reproducibility and were thus not amenable to interpretation, but diffusion was noted to be significantly slower in C_6D_6 *cf.* $CDCl_3$ after accounting for the higher viscosity of C_6D_6 thereby alluding to a greater extent of dimerization in C_6D_6. This is consistent with the C_6D_6 solutions of non-racemic mixtures exhibiting distinct signals whilst the $CDCl_3$ solutions did not ($\Delta\delta$ changes between $\mathbf{1}_{2hom}$ and $\mathbf{1}_{2het}$ due to the differing solvents notwithstanding).

Conclusions

ESDAC might be more common than is realized and might be simply being overlooked due to a lack of anticipation by workers, and similarly SIDA might also be actually more prevalent. What this work demonstrates is that NMR examination of samples under appropriate conditions may allude to the presence of dimers, either by the observation of discrete signals for the enantiomers or by the migration of unsplit signals over the course of an enantiomeric titration. The implications that such observations may have regarding the potential occurrence of ESDAC can thereby alert workers to the need to check for the phenomenon if it is likely to impact their work, either negatively or for gainful exploitation of the chiral bias. Modeling at the appropriate level, either in conjunction with NMR or without in the absence of suitable samples for NMR analysis, also provides a means of evaluation and the success of the modeling is apparent by the consistency with the NMR results in all cases.

Experimental

NMR methods

Spectra were acquired on a Bruker Avance NMR spectrometer equipped with a normal configuration dual coil probe operating at 400, 376, and 100 MHz for ^{1}H, ^{19}F, and ^{13}C nuclei, respectively at 25 °C using TMS (for both ^{1}H and ^{13}C, $\delta = 0$ ppm) and C_6H_5F ($\delta_{C6H5F} = -115.97685$ ppm; secondary to $^{19F}\delta_{CF3CO2H} = -78.5$ ppm in $CDCl_3$, [2–3% v/v] at 25 °C) as internal standards. Acquisitions were run locked when a suitable deuterium source was present, *e.g.* when either using, or after the addition of, either $CDCl_3$ or C_6D_6, or were run unlocked in HPLC-grade *n*-hexane (no-D NMR[19]). Spectra were acquired whilst being spun and shimming was performed until $\nu_{\frac{1}{2}}$ for the ^{1}H signal of TMS was less than 0.5 Hz. ^{1}H, ^{13}C, and ^{19}F spectra were acquired with digital resolutions of 0.1135, 0.3668, and 0.1479 Hz pt^{-1}, respectively, zero-filled to 0.0142, 0.0458, and 0.0185 Hz pt^{-1}, respectively, providing digital resolutions of 0.04, 0.5, and 0.05 ppb, respectively; 1 or 0 Hz, as appropriate, of line broadening was applied to the ^{13}C spectra only. Processing was always performed in a methodical manner with respect to phasing, calibration, peak picking, *etc.* Diffusion coefficients were measured using the bipolar pulse pair longitudinal eddy current delay (BPPLED) sequence[20] employing sinusoidally-shaped gradients without sample spinning. The gradient strength was incremented linearly in 16 steps from 1.07 – 50.83 G/cm; the diffusion delay, Δ, was set to 50 ms, δ to 2 ms, the gradient pulses to 1 ms, the eddy current delay, Te, to 5 ms, and the *Aq* and post-acquisition delay (PAD) times together totaled 13.4 s. Longitudinal relaxation rates, T_1, were measured using inversion–recovery with 15 recovery times ranging between 0.002–40 s and a total time for relaxation (*Aq* + PAD) of 53 s. Diffusion coefficients and longitudinal relaxation rates were calculated using curve-fitting procedures available in the standard Bruker Software Package *XWIN-NMR 3.5*. Aliquots of solvents or solutions were dispensed into the NMR tubes by analytical-grade syringes with particular attention being paid to syringe washing and drying/wetting. The equilibrium time in the NMR (*ca.* 10 min minimum) for temperature stabilization and equilibration after sample make-up[21] prior to insertion in the

magnet were also factors given due consideration. NMR tubes were tightly capped and when not in use samples were stored together as sets at –20 °C or at 25 °C in a sealed container with an atmosphere saturated with the solvent in use. Spin analysis was performed using Perch[22] iteration software for the extraction of ^{1}H chemical shifts and $J_{H,H}$s reported in signal assignments and the extraction of ^{1}H chemical shifts for enantiomeric analysis in cases of overlapped signals or higher order multiplets. For manually extracted signals, particular lines of multiplets were chosen for convenience and then used for analysis even if the δ did not coincide with the top of a line.

Computational methods

The homo- and heterochiral dimers of **1** and **2** were optimized using the Turbomole program package[23–25] and B3LYP functional.[26–28] From the Turbomole basis set library, the triple-zeta plus polarization (TZP)[29] basis set was used for oxygen whilst for the remaining atoms the double-zeta plus polarization (DZP)[29] basis set was used in the case of **1** whilst the triple-zeta valence-polarized (TZVP)[29] basis set was used for all atoms of **2**. A number of homo- and heterochiral complexes were optimized for each of **1** and **2** but the one described in each instance was the most stable one obtained for each. In some cases, different starting geometries yielded the same optimized final geometries as presented. Vibrational analysis was carried out for the optimized structures in order to prove that all optimized structures are real minima on the potential energy surface (no imaginary frequencies were obtained for any of the final structures reported) and to obtain the thermodynamic contributions. The calculated frequencies were scaled by a factor of 0.9614.[30] Solvent effects were included by using the Conductor-like Screening Model (COSMO)[31] method ($\varepsilon_{\text{chloroform}}$, 4.81; $\varepsilon_{\text{benzene}}$, 2.28; $\varepsilon_{n\text{-hexane}}$, 1.69; $\varepsilon_{\text{ethyl acetate}}$, 6.02).

Sample preparation

Stock solutions of the enantiomers of **1** and **2** were made up precisely (identical concentrations for the two enantiomers of each pair in each particular solvent) and then dispensed accordingly into NMR tubes to result in total solutions of 0.6 mL ranging from 50% (racemic mixture) through to 100% of one enantiomer. The stock solution volumes depended on the number of samples to be made up but the excess amount was generally of the order of 2–3 mL to minimize evaporation errors. For the serial dilutions, aliquots (25–1,500 μL) were added sequentially to the NMR tubes and when the tubes were near full, portions were transferred to new tubes and the dilution continued with. The approximate stock solution concentrations of each enantiomer were (for **1**): C_6D_6, 10.1 mg/mL; $CDCl_3$, 10.5 mg/mL; and (for **2**): *n*-hexane, 37.5 mg/mL.

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Notes and references

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