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HPLC separation and VCD spectroscopy of chiral pyrazoles derived from (5*R*)-dihydrocarvone

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Abstract—(4*S*,7*R*)-(−) and (4*S*,7*S*)-(+)-4-isopropylidene-7-methyl-4,5,6,7-tetrahydro-2(1)*H*-indazoles **2a** and **2b** have been successfully separated by using HPLC over a Chiralpak AS column as the stationary phase, yielding up to 700 mg of each diastereomer. Their absolute configurations were determined by using vibrational circular dichroism (VCD) studies. This latter method proved not only very useful for determination of the conformers' distribution, but also for analysis of the 1*H*,2*H* tautomers.

1. Introduction

Since their discovery by Trofimenko in the late sixties,[1] hydrotris(pyrazolyl)borate ligands, also known as scorpionate ligands, have been increasingly used in bio-inorganic, organometallic and coordination chemistry.[2] This last aspect has been extensively developed with a particular interest in the modification of functional groups connected to the pyrazolyl moiety, in order to control or modify the steric and electronic environment surrounding the metal centre. However, only a few chiral analogues have been studied.[3] Chiral pyrazoles are interesting precursors for the preparation of C_3-symmetrical hydrotris(pyrazolyl)borate ligands, which may be used in asymmetric catalysis.[4] Such tripodal ligands also have a potential interest in the design of molecular machines such as the related tripodal hydrotris(indazolyl)borate developed recently by Launay et al. where organometallic molecular turnstiles[5] with suitable functionalization have been used as building blocks in the synthesis of a family of surface-mounted electrically-driven molecular motors (Fig. 1).[6] Indeed, since molecular motors require a unidirectional rotation, the use of a chiral hydrotris(pyrazolyl)borate stator is therefore of major interest in order to highly dissymmetrize the system and obtain such controlled rotational motion.[7] Being able to conceive a unidirectional molecular machine is still a challenge but it is known[8] that the configuration of a chiral molecule may be a way to favour one direction of motion over the other one, as is already seen in the synthetic molecular motor,[9] or in biological motors such as ATP synthase.[10]

Pyrazoles and analogues exist as a 1*H*,2*H* tautomeric mixture. ^{13}C NMR variable temperature in the liquid state and ^{13}C CPMAS NMR spectroscopy in the solid state were two successful methods used to determine the activation barriers, the tautomeric equilibrium and ^{13}C signal assignments.[11] For instance, in benzimidazoles,[12] used as pharmaceuticals such as esomeprazole (a chiral switch of omeprazole, an efficient anti-ulcer agent), the tautomeric equilibrium was only studied by NMR spectroscopy[13] and by X-ray crystallography.[14] Recently, an exhaustive conformational analysis has been conducted on this molecule by using DFT calculations.[15] Interestingly, we herein report that VCD spectroscopy appears to be an alternative method for the study of such tautomerism in chiral molecules and may prove to be particularly useful in the future.

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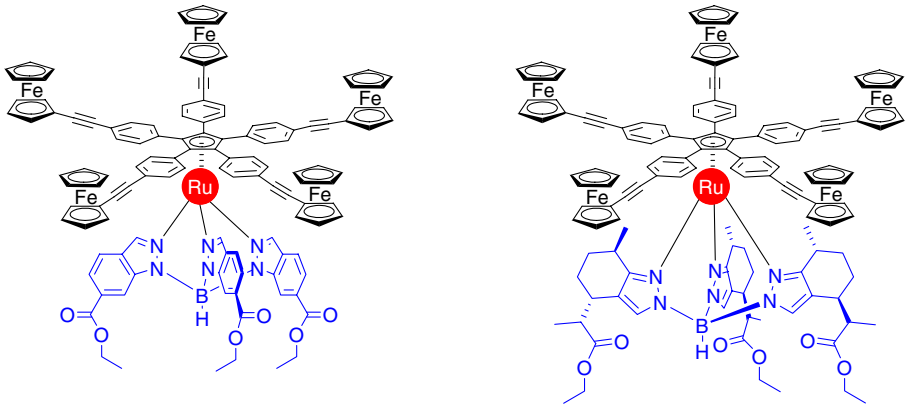


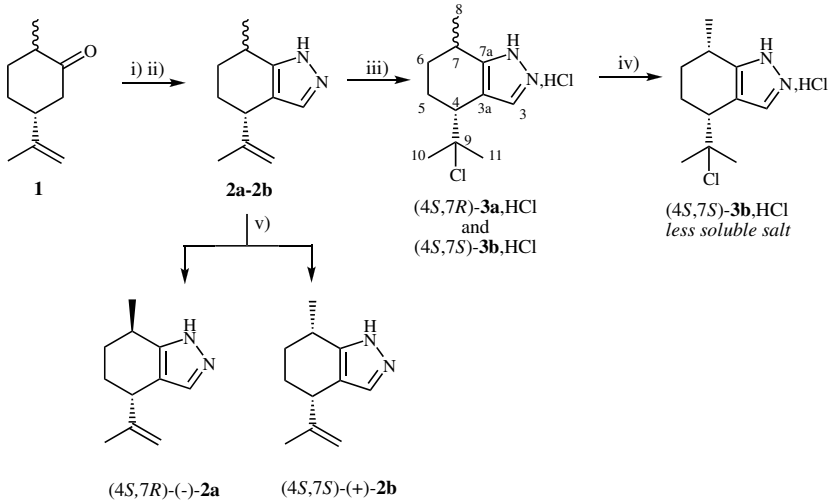
Figure 1. Prototype of a molecular motor with a symmetric tripodal ligand (left) and our target molecule with an enantiomerically pure tripode (right).

2. Results and discussion

In this context, we studied the preparation of enantiopure chiral pyrazoles for the preparation of C_3-symmetrical hydrotris(pyrazolyl)borate ligands. For this purpose, we decided to focus on pyrazoles derived from dihydrocarvone **1**, commercially available as a (2*R*,5*R*)- and (2*S*,5*R*)-diastereomeric mixture. Its olefin moiety can be transformed into a carboxylic or an ester functional group for subsequent immobilization of the molecular motor onto a metallic surface (as depicted in Fig. 1). Diastereomeric pyrazoles **2a** and **2b** (Scheme 1) were prepared from dihydrocarvone by a Claisen condensation, followed by reaction with hydrazine and this resulted in a mixture of (4*R*,7*S*)- and (4*S*,7*S*)-diastereomers **2a** and **2b**.[16] Then, in line with menthylpyrazoles,[3] the separation of diastereoisomers was first investigated by preparing the diastereomeric hydrochloride salts and by studying their separation using fractional crystallization. However, during the preparation of the hydrochloride salts, the addition of HCl onto the double bond was observed. It was nevertheless possible to isolate the (4*S*,7*S*)-hydrochloride salt **3b** in a 30% yield, in an almost diastereomerically pure form, as evidenced by ^{1}H NMR in $CDCl_3$. Its absolute configuration could be determined by using chemical correlation by direct action of HCl on a diastereomerically pure sample of (4*S*,7*S*)-(+)-**2b** (see below).

To avoid HCl addition onto the double bond, the separation of (4*S*,7*R*)- and (4*S*,7*S*)-pyrazole diastereomers **2a** and **2b** was investigated by HPLC methods. Several columns and solvent conditions were tested and finally **2a** and **2b** could be separated by using semi-preparative HPLC using Chiralpak AS (250 * 4.6 mm) as the stationary phase and hexane/isopropanol (95:5), (1 mL/min) as the eluent. This method proved to be very efficient, since it enabled us to obtain up to 700 mg of each diastereomer, with more than 95% *de* (see Scheme 1). The analytical HPLC diagram is given in Figure 2.

Many azoles (benzimidazoles, triazoles, pyrazoles, indazoles, etc) are of pharmaceutical interest. The development of chiral molecules is important in the pharmaceutical industry, since they can be used as chiral switches.[17] How-



Scheme 1. Reagents and conditions: (i) HCO_2Et, Na, EtOH, Et_2O, rt, 20 h, Ar, 81%; (ii) $N_2H_4{\cdot}H_2O$, MeOH, rt, 24 h, 64%; (iii) HCl, CH_2Cl_2, rt, 24 h, 90%; (iv) fractional crystallization in $^iPr_2O$ 30%; (v) separation by semi-preparative HPLC using Chiralpak AS (250 * 10 mm) as the stationary phase.

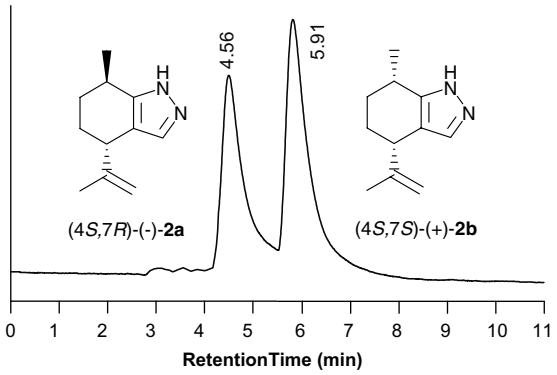


Figure 2. Analytical HPLC using Chiralpak AS (250 * 4.6 mm) as the stationary phase.

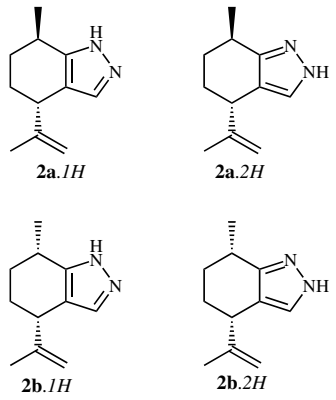


Figure 3. 1*H* and 2*H* tautomers of pyrazoles **2a** and **2b**.

ever, several structural features may arise from these classes of chiral molecules: the existence of several stereoisomers (enantiomers for one stereogenic centre or diastereomers for more than one) requires their careful analysis and quantification by using analytical HPLC measurements. Moreover, for each stereoisomer, two 1*H* and 2*H* tautomers can coexist, (as depicted in Fig. 3 for our pyrazole model molecule). Finally, careful conformational analysis is necessary in order to identify the major conformers. The tautomeric equilibrium in pyrazoles has been extensively studied by Elguero et al. by using NMR spectroscopic methods.[11] However it is not always possible to observe the tautomers, for instance when the equilibrium is too fast on the NMR timescale.

VCD together with conformational analysis could be conducted on our pyrazole model molecule **2** as depicted below. The respective (4*S*,7*R*)-(−)- and (4*S*,7*S*)-(+)-absolute configurations of pyrazole diastereomers **2a** and **2b** could be determined by comparing the experimental and calculated vibrational circular dichroism (VCD) spectra. This careful VCD study also enabled the calculation of the percentage of tautomers 1*H* and 2*H*. The averaged calculated VCD over all tautomers and all conformers reproduced well the experimental VCD spectrum. This comparison between experiment and theory appears to be a reliable method for precisely determining the proportions of each isomer (tautomers and conformers). The fact that the calculations are conducted in vacuum and the experiments are carried out in chloroform does not seem to be a problem for such an evaluation.

Experimental IR and VCD spectra are displayed in Figure 4. For each diastereomer **2a** and **2b**, eight conformations

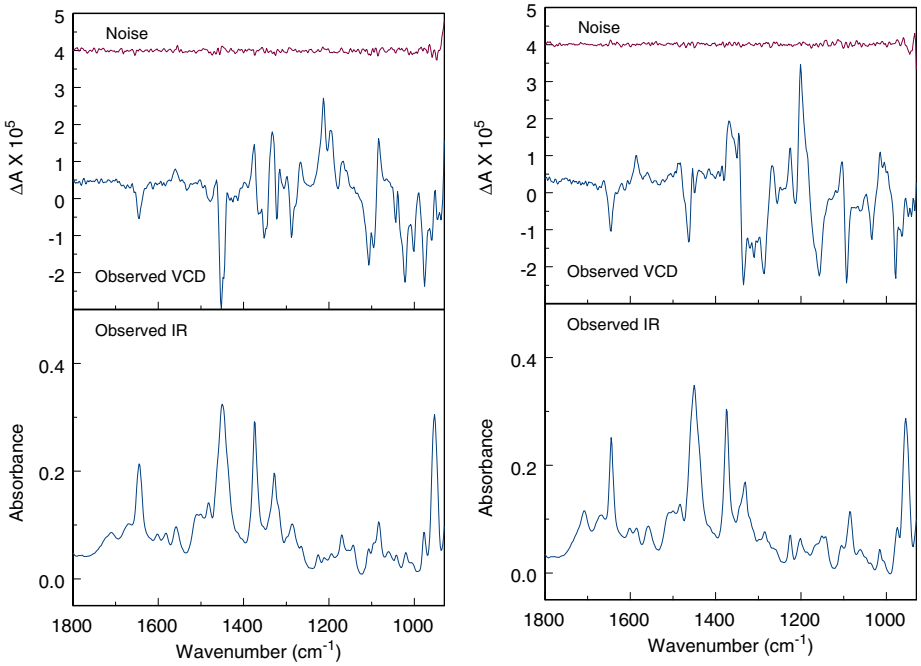


Figure 4. VCD (upper frame) and IR (lower frame) and spectra of pyrazole **2a** [(−)-diastereomer, left] and pyrazole **2b** [(+)-diastereomer, right], 8 mg sample/100 μL $CDCl_3$, 100 μm pathlength, 4 cm^{-1} resolution, 9 h collection, instrument optimized at 1400 cm^{-1}. Uppermost trace for each sample is the VCD noise.

were found. They correspond to two 180° orientations of the isopropenyl group, two puckerings of the CH_2–CH_2 moiety in the 6-membered ring, and the two tautomeric positions of the NH. The optimized conformations, relative energies and Boltzmann populations for **2a** are shown in Figure 5, and for **2b** in Figure 6. For pyrazole **2a**, the dominant conformations are the two tautomers for a single ring pucker and isopropenyl orientation. For **2b**, four conformers are present with large populations, representing the two tautomers of a pair of conformations that differ both in ring pucker and isopropenyl conformation.

In Figure 7, calculated IR and VCD spectra for the two dominant conformers **2a**-A and **2a**-B were compared to experimental data for the (−)-diastereomer, allowing the identification of experimental VCD features that arise from each dominant conformer. In Figure 8, the Bolzmann-population-weighted sums for all eight conformers, and a mixture of 60% **2a**-A and 40% **2a**-B are compared to experiment for the (−)-diastereomer. The good agreement in the VCD pattern between the experimental and theoretical calculations identifies the (−)-diastereomer as diastereomer **2a** and confirms that conformers **2a**-A and **2a**-B are the dominant solution conformations, that is, two tautomeric forms of a single ring-puckering/isopropenyl orientation conformation are dominant in solution.

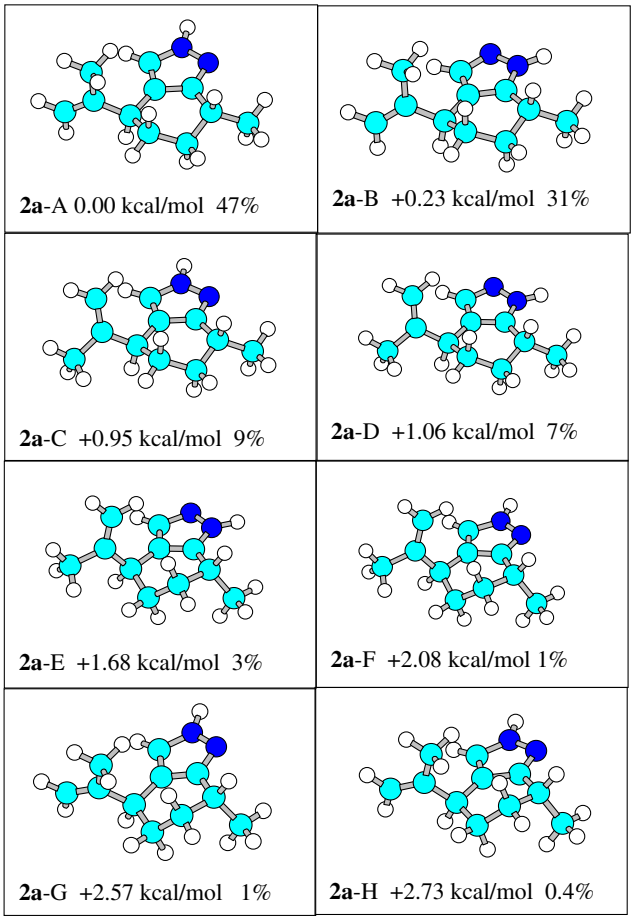


Figure 5. Optimized conformers, relative energies and Boltzmann populations for pyrazole diastereomer **2a**.

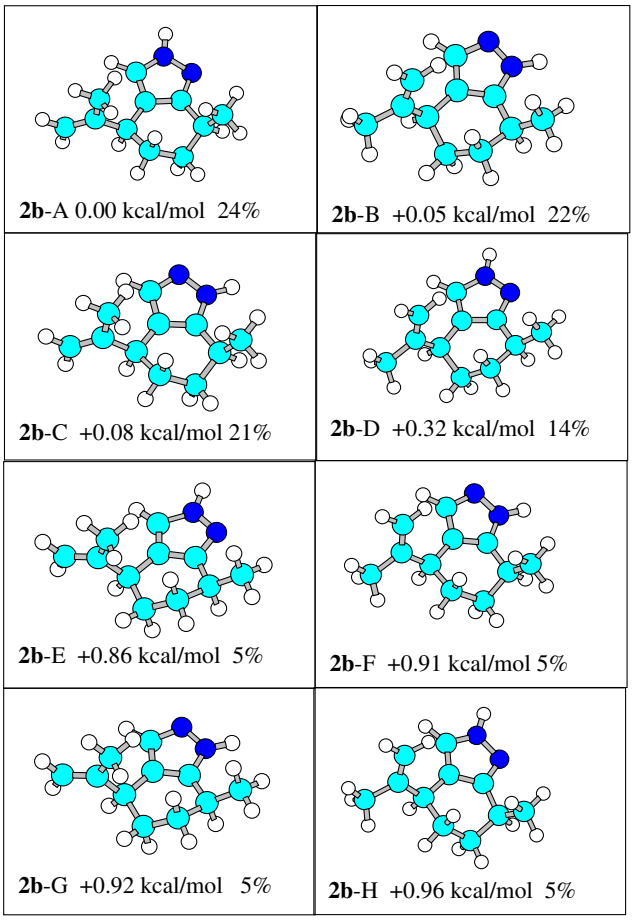


Figure 6. Optimized conformers, relative energies and Boltzmann populations for pyrazole diastereomer **2b**.

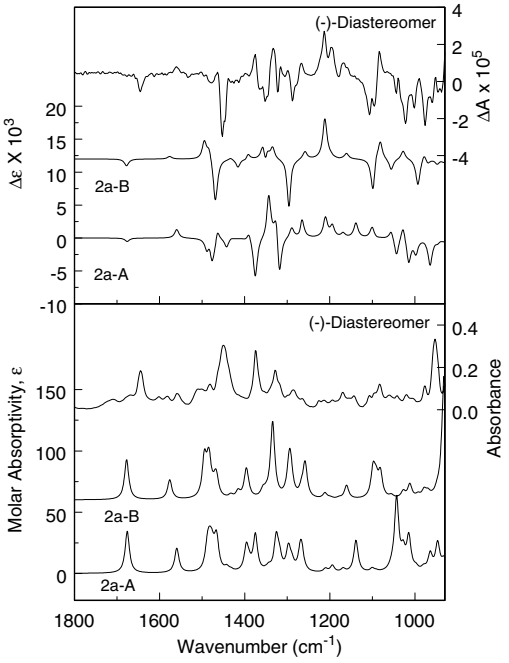


Figure 7. Comparison of VCD (upper frame) and observed IR (lower frame) spectra for (−)-diastereomer (right axes) with calculated spectra for diastereomer **2a** conformers A and B (left axes).

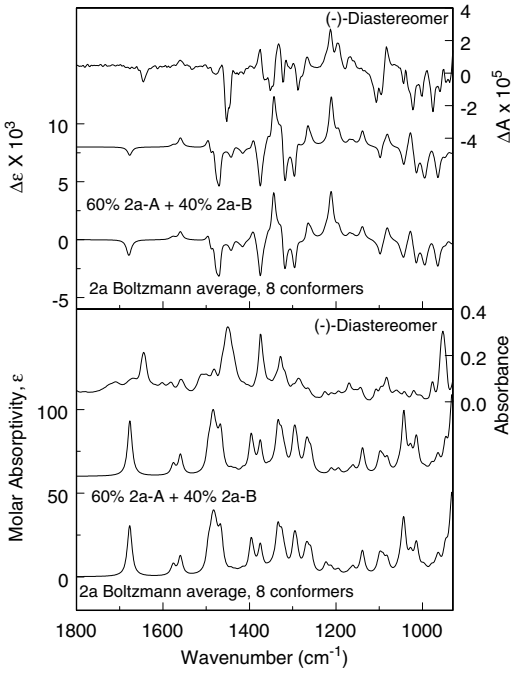


Figure 8. Comparison of the observed IR and VCD spectra for (−)-diastereomer (right axes) with the calculated spectra (left axes, spectra offset for clarity) for 60% **2a**-A + 40% **2a**-B and with the Boltzmann-population-weighted sum of calculated spectra for all eight conformers of **2a**.

For **2b**, the calculated IR and VCD spectra of the four conformers with the highest population (**2b**-A, **2b**-B, **2b**-C and **2b**-D) are compared to the experimental for the (+)-diastereomer in Figure 9, demonstrating the sensitivity of VCD to the conformation and tautomer equilibrium. The Boltzmann-population-weighted sums for all eight conformers

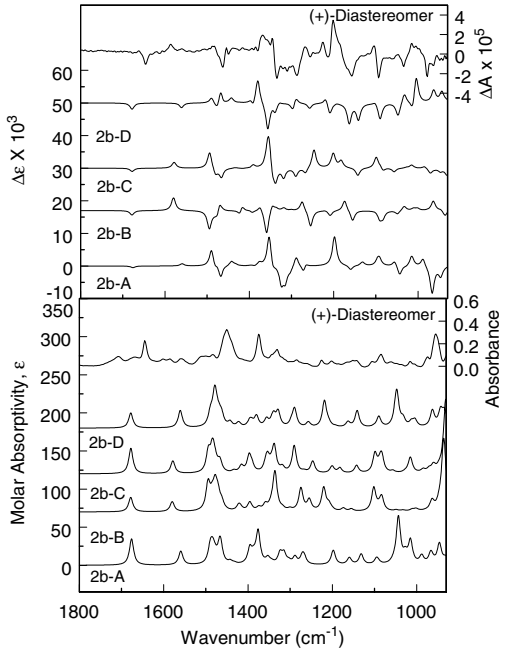


Figure 9. Comparison of the observed IR (lower frame) and VCD (upper frame) spectra for (+)-diastereomer (right axes) with the calculated spectra for diastereomer **2b** conformers A, B, C and D (left axes).

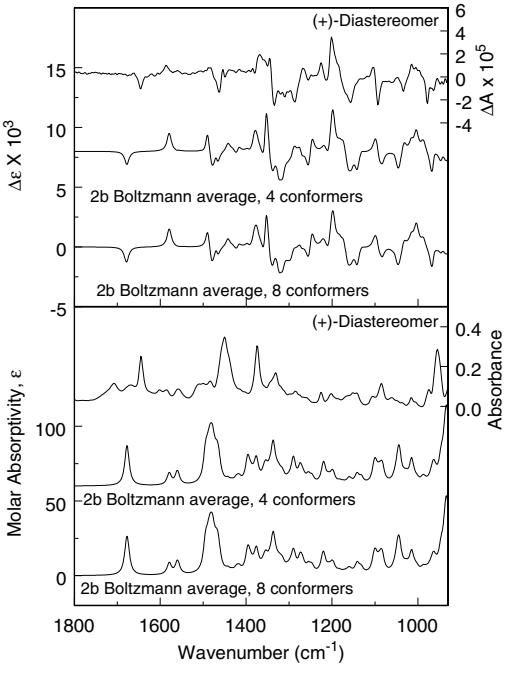


Figure 10. Comparison of the observed IR and VCD spectra for the (+)-diastereomer (right axes) with calculated spectra (left axes, spectra offset for clarity) for the weighted sum of the calculated spectra 30% **2b**-A + 27% **2b**-B + 26% **2b**-C + 17% **2b**-D and with the Boltzmann-population-weighted sum of the calculated spectra for all eight conformers of **2b**.

and for just the four lowest energy conformers (30% **2b**-A + 27% **2b**-B + 26% **2b**-C + 17% **2b**-D) are compared to the experimental data for the (+)-diastereomer in Figure 10. Again, a good agreement between the observed and calculated VCD pattern allows the assignment of the (+)-diastereomer to diastereomer **2b**, with four dominant conformations encompassing the two tautomeric forms of two ring-puckering/isopropenyl orientation combinations.

The distinct differences in the VCD spectra for the pair of diastereomers allow an unambiguous assignment of the absolute configuration for both samples.

3. Conclusion

We have found that chiral diastereomeric pyrazoles can be successfully separated by using semi-preparative HPLC over chiral stationary phases, on a scale of several hundred milligrams. VCD spectroscopy proved to be very powerful for addressing the position of the 1*H*, 2*H* tautomeric equilibrium in the case of rapid exchange at room and low temperature, and is of great help in combination with NMR studies. Work is currently underway for preparing functionalized enantiomerically pure pyrazoles to incorporate such tripodes in molecular motors.

4. Experimental

4.1. Synthesis

^{1}H- and ^{13}C spectra were recorded on a Bruker DPX 200 spectrometer (at 200 MHz for ^{1}H, 50.4 MHz for ^{13}C). Mass

spectra were recorded by the Centre de Spectrométrie de Masse, Université Claude Bernard (Lyon), France. Specific rotations (in deg cm^2 g^{-1}) were measured in a 1 dm thermostated quartz cell on a Jasco-P1010 polarimeter. (4*S*)-Isopropylidene-(7*RS*)-methyl-4,5,6,7-tetrahydro-2(1)*H*-indazole diastereomers **2a**,**b** were prepared according to the literature.[16]

4.1.1. Hydrochloride of (4*S*)-(1-chloro-1-methylethyl)-(7*RS*)-methyl-4,5,6,7-tetrahydro-2(1)*H*-indazole 3a–b,HCl. To a solution of (4*S*)-isopropylidene-(7*RS*)-methyl-4,5,6,7-tetrahydro-2(1)*H*-indazole (300 mg, 1.6 mmol) in CH_2Cl_2 (5 mL) was added 2 mL of concentrated HCl (24 mmol). The mixture was kept overnight under stirring. The product was extracted in dichloromethane, dried over magnesium sulfate and evaporated (360 mg, 86%). ^{1}H NMR ($CDCl_3$): δ 8.31 (diast. **3a**), 8.23 (diast. **3b**) and 8.18 (tautomer) (3s, 2H, H-3), 3.30–3.21 (m, 2H, H-4 and H-7 of diast. **3b**), 3.00–2.81 (m, 1H, H-4 of diast. **3a**), 2.66–2.63 (m, 1H, H-7 of diast. **3a**), 2.11–1.10 (m, 26H). ^{13}C NMR ($CDCl_3$): δ 150.0, 148.5, 131.4, 131.2, 117.3, 116.7, 72.8, 46.1, 45.4, 32.1, 31.3, 28.5, 28.0, 27.4, 26.7, 26.5, 25.6, 22.8, 22.0, 21.8, 20.3, 19.4, 19.3. Using the same procedure, diastereomer (4*S*,7*S*)-(+)-**2b** gave the less soluble salt (see below) (4*S*,7*S*)-**3b**.

4.1.2. Resolution of the mixture of 3a–3b,HCl. The hydrochloride of (4*S*)-(1-chloro-1-methylethyl)-(7*RS*)-methyl-4,5,6,7-tetrahydro-2(1)*H*-indazole **3a**–**b**,HCl (1.26 g; 5 mmol) was dissolved in 40 mL of diethyl ether and stirred overnight. The precipitate and the mother liquor were then separated. Mother liquors enriched in one isomer, (79% **3a**,HCl; 170 mg; 13% yield) were recovered by removing the precipitate obtained by successive crystallizations in diethyl ether.

The precipitate was washed several times with diisopropyl ether and a white solid was obtained as a pure diastereomer **3b**,HCl, as analyzed by ^{1}H NMR (374 mg; 30% yield). ^{1}H NMR ($CDCl_3$) δ 15.8 (br s, 2H, NH), 8.24 (s, 1H, H-3), 7.88 (s, 0.5H, tautomer), 3.21–3.14 (m, 2H, H-4 and H-7), 2.62–2.72 (m, 0.5 H, tautomer), 2.22–2.31 (m, 0.5H, tautomer), 1.87-1.93 (m, 5.5H); 1.74 (s, 3H); 1.51 (d, $J = 6$ Hz, 2H), 1.44 (2s, 6H). ^{13}C NMR ($CDCl_3$) (tautomer mixture): δ 150.0, 148.6, 131.2, 129.1, 129.0, 119.5, 118.5, 116.8, 72.8, 45.4, 32.2, 31.1, 28.5, 28.0, 27.4, 26.2, 25.6, 22.9, 22.0, 21.8, 20.4, 19.5. Mp 130 °C. EI MS $[M-H]^+$ 212.0 exact mass calcd for $C_{11}H_{17}N_2{}^{35}Cl$ 212.2 (3%) and 214.0 exact mass calcd for $C_{11}H_{17}N_2{}^{37}Cl$ 214.2 (1%); $[M-78]^+ = 135.0$ exact mass calcd for $C_8H_{11}N_2$ 135.2 (100%).

4.2. HPLC separations

4.2.1. Analytical separations. The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector and on-line Jasco OR-1590 polarimeter. Hexane and isopropanol, HPLC grade, were degassed and filtered on a 0.45 μm membrane before use. The column used was Chiralpak AS (250 × 4.6 mm) from ChiralTechnologies Europe (Illkirch, France).

Retention times t_R are in minutes, retention factors $k_i = (t_{Ri} - t_{R0})/t_{R0}$ are given. t_{R0} was determined by injection of tri-*tert*-butyl benzene. The sign given by the on-line polarimeter is the sign of the product in the solvent used for the chromatographic separation.[18]

On an analytical scale, the two diastereomers were separated on Chiralpak AS (250 × 4.6 mm) at 25 °C with a hexane/isopropanol (95:5) mixture as mobile phase, a flow-rate of 1 mL/min. The diastereomers were detected by UV at 220 nm and by a polarimeter: $t_{R1}(-) = 4.56$ and $t_{R2}(+) = 5.91$.

4.2.2. Semi-preparative separations. Semi-preparative separations were performed by successive injections on a Knauer unit composed of a Smartline 1000 pump, a Smartline 3900 autosampler, a Smartline 2500 UV-detector and a valve to collect both isomers separately.

On a semi-preparative scale, the two diastereomers were separated on Chiralpak AS (250 × 10 mm) at 30 °C with a hexane/isopropanol (95:5) mixture as the mobile phase, at a flow-rate of 5 mL/min. About 1.2 g of the mixture was solubilized in 120 mL of a hexane/isopropanol (1:1) mixture. The 600 injections of 200 μL were done every 4 min; the diastereomers were detected by UV at 220 nm: the first diastereomer was collected between 1 and 1.8 min, and the second one between 2.1 and 3.2 min. Thus, we collected 500 mg of the first diastereomer and 700 mg of the second one.

(4S,7R)-(−)-**2a**: $[\alpha]_D^{23} = -29.5$ (*c* 0.49, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$): δ 9.8 (ls, 1H, H_1), 7.24 (s,1H, H_3), 4.85 (s, 1H, H_{11}), 4.82 (s, 1H, H_{11}), 3.37 (m, 1H, H_4), 2.84 (m, 1H, H_7), 2.02 (m, 1H, H_6), 1.90 (m, 1H, H_6), 1.57–1.62 (m, 2H,), 1.66 (s, 3H, H_{10}), 1.32 (d, $J = 6.8$ Hz, 3H, H_8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3 (C_9), 147.9 (C_{7a}), 132.6 (C_3) 117.1 (C_{3a}), 111.4 (C_{11}), 41.7 (C_4), 32.1 (C_6), 29.1 (C_7), 28.6 (C_5), 19.9 (C_8), 19.1 (C_{10}). Identical to the literature.[16]

(4S,7S)-(+)-**2b**: $[\alpha]_D^{23} = +15.8$ (*c* 0.51, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.8 (ls, 1H, H_1), 7.25 (s,1H, H_3), 4.83 (s, 1H, H_{11}), 4.65 (s, 1H, H_{11}), 3.35 (m, 1H, H_4), 2.90 (m, 1H, H_7), 1.56–1.84 (m, 4H, H_5 and H_6), 1.76 (s, 3H, H_{10}), 1.25 (d, $J = 7.4$ Hz, 3H, H_8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5 (C_9), 147.6 (C_{7a}), 133.3 (C_3) 116.6 (C_{3a}), 111.9 (C_{11}), 40.0 (C_4), 29.1 (C_6), 27.4 (C_7), 26.0 (C_5), 20.7 (C_{10}), 20.4 (C_8). Identical to the literature.[16]

4.3. VCD studies

Experimental measurement. Samples **2a** [(−)-diastereomer, 32 mg] and **2b** [(+)-diastereomer, 27 mg] were used. Solutions were prepared from 8 mg sample/100 μL $CDCl_3$ solvent and placed in a 100 μm pathlength cell with BaF_2 windows. IR and VCD spectra were measured on a modified Chiral*IR* VCD spectrometer (BioTools, Inc., Jupiter, FL) equipped with dual photoelastic modulators on an external bench. Spectra were obtained with 9 h collection, 4 cm^{-1} resolution and the instrument optimized at 1400 cm^{-1}. Calculations: Structures of the two diastereo-

mers were built with HyperChem (HyperCube, Inc., Gainesville, FL) in the two tautomeric forms, and the possible conformations identified. The optimized geometry, relative energy, vibrational frequencies and IR and VCD intensities for each structure were calculated at the DFT level (B3LYP functional and 6-31G(d) basis set) with GAUSSIAN 03 (Gaussian, Inc., Wallingford, PA).[19] Calculated frequencies were scaled by 0.97 and calculated intensities were converted to Lorentzian bands with 6 cm^{-1} half-width for comparison to experiment.

References

1. (a) Trofimenko, S. *J. Am. Chem. Soc.* **1966**, *88*, 1842–1844; (b) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 6288–6294.
2. (a) Trofimenko, S. *Scorpionates—Polypyrazolylborate Ligands and Their Coordination Chemistry*; Imperial College Press: London, 1999; (b) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943–980; (c) Pettinari, C.; Santini, C.. In *Comprehensive Coordination Chemistry II*; Lever, A. B. P., Ed.; Elsevier: Amsterdam, 2003; Vol. 1, pp 159–210; (d) Reger, D. L. *Coord. Chem. Rev.* **1996**, *147*, 571–595; (e) Etienne, M. *Coord. Chem. Rev.* **1996**, *156*, 201–236; (f) Byers, P. K.; Canty, A. J.; Honeyman, R. T. *Adv. Organomet. Chem.* **1992**, *34*, 1–65.
3. (a) LeCloux, D. D.; Tolman, W. B. *J. Am. Chem. Soc.* **1993**, *115*, 1153–1154; (b) LeCloux, D. D.; Tokar, C. J.; Osawa, M.; Houser, R. P.; Keyes, M. C.; Tolman, W. B. *Organometallics* **1994**, *13*, 2855–2866; (c) Keyes, M. C.; Young, V. G.; Tolman, W. B. *Organometallics* **1996**, *15*, 4133–4140; (d) Keyes, M. C.; Chamberlain, B. M.; Caltagirone, S. A.; Halfen, J. A.; Tolman, W. B. *Organometallics* **1998**, *17*, 1984–1992; (e) Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833–2836.
4. For reviews on coordination chemistry of pyrazole derivatives, see: (a) Monica, G. L.; Ardizzoia, G. A. *Prog. Inorg. Chem.* **1997**, *46*, 151–238; (b) Trofimenko, S. *Prog. Inorg. Chem.* **1986**, *34*, 115–210; (c) Vahrenkamp, H. *Acc. Chem. Res.* **1999**, *32*, 589–596.
5. Carella, A.; Jaud, J.; Rapenne, G.; Launay, J.-P. *Chem. Commun.* **2003**, 2434–2435.
6. (a) Rapenne, G. *Org. Biomol. Chem.* **2005**, *3*, 1165–1169; (b) Carella, A.; Rapenne, G.; Launay, J.-P. *New J. Chem.* **2005**, *29*, 288–290; (c) Carella, A.; Vives, G.; Cox, T.; Jaud, J.; Rapenne, G.; Launay, J.-P. *Eur. J. Inorg. Chem.* **2006**, 980–987; (d) Vives, G.; Sistach, S.; Carella, A.; Launay, J.-P.; Rapenne, G. *New J. Chem.* **2006**, *30*, 1429–1438; (e) Vives, G.; Carella, A.; Launay, J.-P.; Rapenne, G. *Chem. Commun.* **2006**, 2283–2285; (f) Vives, G.; Rapenne, G. *Tetrahedron Lett.* **2006**, *47*, 8741–8744; (g) Vives, G.; Gonzalez, A.; Jaud, J.; Launay, J.-P.; Rapenne, G. *Chem. Eur. J.* **2007**, *13*, 5622–5631.
7. Other kinds of dissymmetrization of the system are possible such as correctly placing an electrode onto the surface where the molecule is grafted see: Carella, A.; Coudret, C.; Guirado, G.; Rapenne, G.; Vives, G.; Launay, J.-P. *Dalton Trans.* **2007**, 177–186.
8. (a) Feringa, B. L. *Acc. Chem. Res.* **2001**, *34*, 504–513; (b) Mandl, C. P.; König, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 1622–1624.
9. (a) Kelly, T. R.; De Silva, H.; Silva, R. A. *Nature* **1999**, *401*, 150–152; (b) Kelly, T. R.; Silva, R. A.; De Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6935–6949; (c) Koumura, N.; Zijistra, R. W. J.; Van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152–154; (d) Ter Wiel, M. K. J.; Van Delden, R. A.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 15076–15086.
10. Walker, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2308–2319.
11. (a) Claramunt, R. M.; López, C.; Santa Maríaa, M. D.; Sanz, D.; Elguero, J. *Prog. NMR Spectrosc.* **2006**, *49*, 169–206; (b) Moreno-Manas, M.; Sebastian, R. M.; Vallribera, A.; Piniella, J. F.; Alvarez-Larena, A.; Jimeno, M. L.; Elguero, J. *New J. Chem.* **2001**, *25*, 329–335.
12. Dunmire, D.; Freedman, T. B.; Nafie, L. A.; Aeschlimann, C.; Gerber, J. G.; Gal, J. *Chirality* **2005**, *17*, S101–S108.
13. Claramunt, R. M.; Lopez, C.; Alkorta, I.; Elguero, J.; Yang, R.; Schulman, S. *Magn. Reson. Chem.* **2004**, *42*, 712–714.
14. Ohishi, H.; In, Y.; Ishida, T.; Inoue, M.; Sato, F.; Okitsu, M.; Ohno, T. *Acta Crystallogr., Sect. C* **1989**, *45*, 1921.
15. Caner, H.; Cheeseman, J. R.; Agranat, I. *Chirality* **2006**, *18*, 10–16.
16. Faure, R.; Frideling, A.; Galy, J. -P.; Alkorta, I.; Elguero, J. *Heterocycles* **2002**, *57*, 307–316.
17. Agranat, I.; Caner, H.; Caldwell, A. *Nat. Rev. Drug Discovery* **2002**, *1*, 753–768.
18. Roussel, C.; Vanthuyne, N.; Serradeil-Albalat, M.; Vallejos, J.-C. *J. Chromatogr., A* **2003**, *995*, 79–85.
19. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Revision D.01 ed.*; Gaussian: Pittsburgh, PA, 2003.