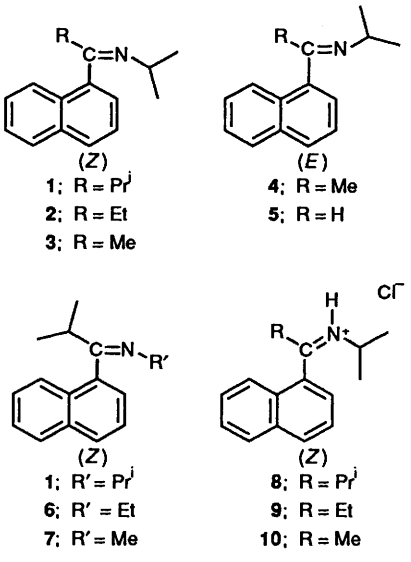
Conformational Studies by Dynamic NMR. Part 48.[1] Conformational Preferences and Stereomutational Processes of the Rotational Enantiomers of Hindered Naphthylimines and Imonium Salts

Daniele Casarini,[a] Lodovico Lunazzi *,[a] and Dante Macciantelli[b]
[a] *Department of Organic Chemistry 'A. Mangini', The University, Risorgimento 4, Bologna 40136, Italy*
[b] *I.Co.C.E.A., C.N.R., Via della Chimica, Ozzano Emilia, Bologna, Italy*

A number of 1-naphthylimines (and some of the corresponding imonium chlorides), having the isopropyl group as a prochiral probe, have been synthesized and their configurations assigned by the combined use of NOE experiments and molecular mechanics calculations. This method also provides reliable information about the conformations adopted in solution. The existence of diastereotopic methyl groups in the isopropyl moiety indicates the presence of conformational enantiomers, due to the rotation about the naphthyl–imino bond in nonplanar conformers. The barriers for the stereomutation of such enantiomeric forms have been determined by line-shape analysis of the temperature-dependent ^1H or ^{13}C signals of the prochiral probe. Molecular mechanics calculations have also helped in suggesting which is the preferred stereomutation pathway and in predicting the existence of a derivative having configurationally stable enantiomers. Such a compound has been synthesized and is found to display the predicted property (atropisomerism), in that the two enantiomers can be separated.

Recently we reported the detection of conformational enantiomers in hindered naphthyl derivatives and measured the corresponding barriers to stereomutation by dynamic NMR spectroscopy.[1–3] Amines[2] and ketones[1,3] containing the 1-naphthalene moiety were investigated: the analogous imines are also known to display this kind of behaviour.[4] The presence of such enantiomeric forms in imines has also been detected by observing the mutarotation of chiral imines prepared from optically pure amines.[5,6] The situation for the imines is complicated by the fact that they can exist, in principle, in the *E*- or *Z*-configuration. The enantiomerism, however, has been only observed in the *Z*-isomers[4,6] and not in the corresponding *E*-isomers. This was attributed to the lower steric requirements for the aryl–imino bond rotation in the *E*-configuration.[7]

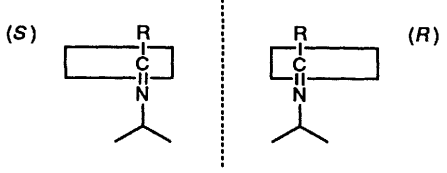
In order to investigate in detail the conformational enantiomerism expected for these compounds we have synthesized a number of 1-naphthylimines containing, as a prochiral probe,[8] an isopropyl group. These imines are likely to adopt, in the *Z*-configuration, a twisted conformation which creates a molecular chiral centre: a pair of conformational enantiomers can thus be generated owing to the restricted rotation about the naphthyl–imino bond. As a consequence, the methyl groups of the isopropyl moiety are diastereotopic, and potentially anisochronous, when the dynamic process is slow. On raising the temperature, and thus the rate of the process, they become homotopic (and isochronous), allowing the enantiomerization barrier to be determined for the *Z*-isomers.



Results and Discussion

The 1-naphthylimines **1–7** and imonium hydrochlorides **8–10** (derived from imines **1–3**) were obtained.

Compounds **1–3** and **6–10** were isolated in the *Z*-configuration. As reported by Jennings *et al.*,[9] when R = Me (**3**), NMR evidence for the presence of the less stable *E*-configuration **4** was obtained, owing to a *Z*–*E* equilibrium in solution.[9] A similar equilibrium also occurs for the corresponding imonium salts (*i.e.* between **10** and **11** having, respectively, the *Z*- and *E*-configuration). Imines **1–3**, **6** and **7** display, even at room temperature, anisochronous ^1H and ^{13}C NMR signals for the geminal methyl groups of the isopropyl substituent. This is due, as mentioned above, to a slow rotation about the Ar–CN bond in a nonplanar conformation.[4,7] The resulting conformational enantiomers are represented in Scheme 1.



Scheme 1 Top view of the 1-naphthylimino derivatives showing the two possible conformational enantiomers

In contrast, in the case of **4** (*E*, R = Me) and **5** (*E*, R = H) the isopropyl methyl signals were found to be isochronous even at very low temperatures (−130 °C in

Table 1 NOE values for **1** (expressed as a percentage of the original signals) observed for a given proton, on irradiation of the hydrogen indicated. CH and NCH indicate the methine protons of the isopropyl groups bonded, respectively, to the carbon and to the nitrogen atoms of the imino moiety; 2-H and 8-H refer to the corresponding positions in the naphthalene ring

Observed	Irradiated	NOE
8-H	CH	1.30
	NCH	1.20
2-H	NCH	1.25
	CH	1.00
CH	8-H	1.85
	2-H	1.10
NCH	2-H	1.10
	8-H	1.15

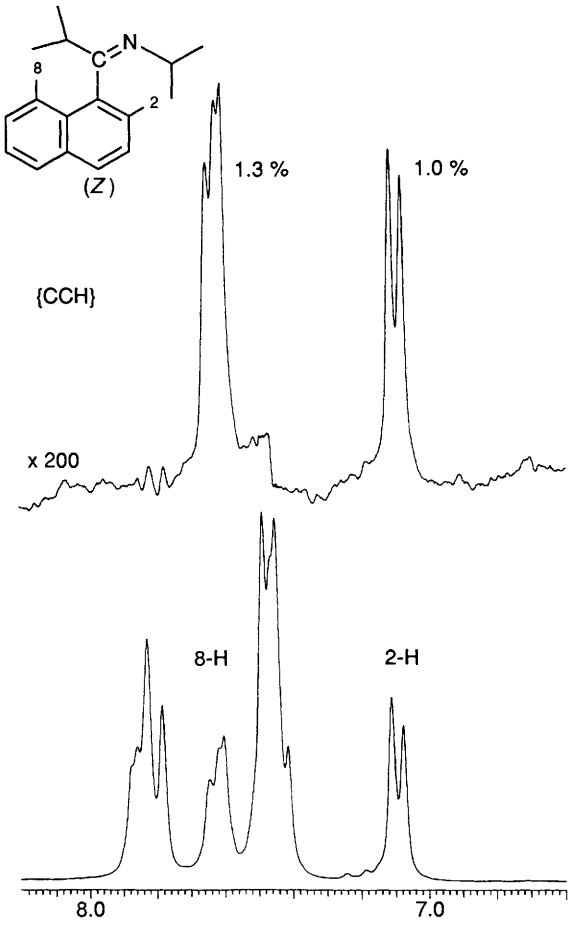


Fig. 1 Aromatic region of the 200 MHz differential NOE spectrum (vertically amplified 200 times with respect to the control spectrum shown underneath) obtained on irradiation of the CCH multiplet of compound **1**. The signals of the hydrogens in positions 8 and 2 of naphthalene display enhancements of 1.30 and 1.0%, respectively.

CHF_2Cl). This indicates either that the enantiomerization barrier cannot be detected for technical reasons (accidentally degenerate lines or $\Delta G^{\ddagger}$ values lower than 5 kcal mol^{-1})* or that these molecules, being less hindered, adopt a planar conformation, where the NMR signals in question can be isochronous even in the case of a slow Ar–CN rotation. This second hypothesis could however be eliminated on the basis of the NOE experiments described in the following section.

* 1 cal = 4.18 J.

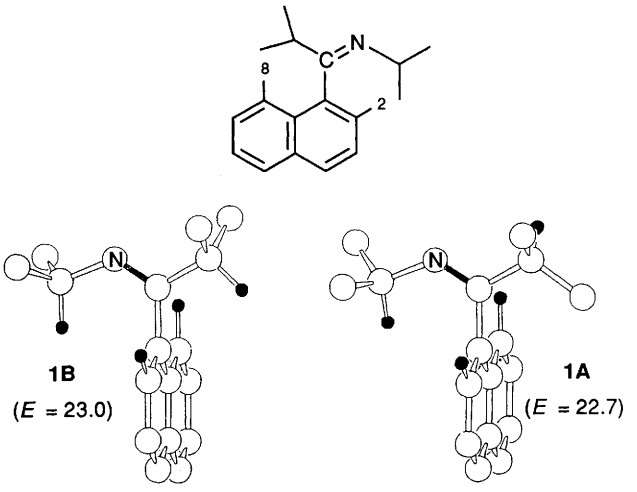


Fig. 2 Representation of two possible conformers of **1** (*Z*-configuration) as obtained from molecular mechanics calculations: the computed energies (*E*, in kcal mol^{-1}) are also reported. The hydrogens involved in the NOE experiments are represented by full dots.

Structural and Conformational Analysis.—The configurations of imines **1–7** were ascertained by combining[10] the results of NOE experiments with the geometry obtained from MM2 calculations. In addition to the structural assignment, this approach also provided reliable information about the conformation adopted by these molecules.

Compound **1** yields the NOE values reported in Table 1, a typical differential NOE spectrum being illustrated in Fig. 1. In order to assign the two closely spaced methine multiplets of the two isopropyl groups (*i.e.* NCH and CCH at 3.12 and 2.8 ppm, respectively) a 2D heterocorrelated experiment (HETCOR) was carried out. The ^{13}C shift of the NCH group of **1** is undoubtedly that at 52.9 ppm (as indicated by the very similar values for **2** and **3**, reported in the experimental section) and the HETCOR related it to the ^{1}H multiplet at 3.12 ppm: the NOE values of Table 1 were thus attributed accordingly.

Molecular mechanics (MM) calculations[11] suggest two possible conformational situations for the *Z*-configuration of **1**: both have the planes of the naphthalene ring and of the imino moiety orthogonal to each other (the twisting angles are 85°, in agreement with the X-ray diffraction value of 87°, obtained in a closely related derivative[7]). One possible conformation (indicated as **1B** in Fig. 2) has the two methine hydrogens lying in the same plane defined by the C–N=C–C moiety and directed toward the naphthalene ring. The other possible conformation (**1A**, Fig. 2) has the two methine hydrogens tilted away from the C–N=C–C plane and pointing in opposite directions (the NCH toward the naphthalene and the CCH away from it). This conformer also has a degenerate companion (**1A′**) in which the dihedral angles H–C–N=C and N=C–C–H have opposite signs with respect to those of **1A** (*i.e.* the CCH and NCH hydrogens are closer to 8-H than to 2-H in **1A** whereas the opposite occurs in **1A′**). The difference between the energy of **1B** (23.0 kcal mol^{-1}) and that of the pair **1A**, **1A′** (22.7 kcal mol^{-1}) is too small to allow one to choose between the two possibilities. On the other hand the corresponding interproton distances are quite different and are thus expected to affect the NOE values. Also the barrier to interconversion of the two degenerate forms **1A** and **1A′** is conceivably very low so that a rapid equilibrium between these two forms has to be considered as an alternative possibility to the single conformer **1B**. As the ratio of the NOE values (raised to the power $-1/6$) is approximately equal to the corresponding ratio of the proton distances,[12] it is possible to check whether **1** assumes the *Z*-configuration and, in addition, whether the degenerate pair **1A**, **1A′** or **1B** is the preferred conformation. The *E*-configuration should yield a quite large

Table 2 Ratios of the distances of selected pairs of hydrogens computed (MM2) for compound **1**. **1A** (and its nearly degenerate form **1A'**, see text) and **1B** refer to conformers of Fig. 1. The ratios of the experimental NOEs of Table 1 (raised to the power $-1/6$) are also reported: the first hydrogen is the one being observed, the second one that irradiated (see text)

	Distance ratio		$\left(\frac{NOE}{ratio}\right)^{-1/6}$
	1B	Equilibrium (**1A**, **1A'**)	
8-H/CH / 8-H/NCH	1.06	1.12	0.99
2-H/NCH / 2-H/CH	1.07	0.86	0.96
CH/8-H / CH/2-H	1.08	0.95	0.92
NCH/2-H / NCH/8-H	1.05	1.01	1.01

Table 3 Ratios of the average distances for the conformers **2A** and **2A'** and for their rapid equilibrium (see Scheme 2). The ratios (raised to the power $-1/6$) of the experimental NOE values (divided by the number of irradiated protons) are also reported

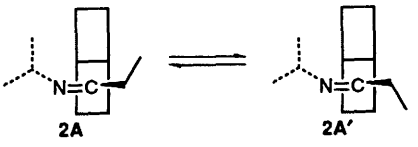
	Distance ratio			$\left(\frac{NOE}{ratio}\right)^{-1/6}$
	2A	**2A'**	Equilibrium (**2A**, **2A'**)	
8-H/Me / 8-H/Me_2	0.73	1.03	0.94	1.02
8-H/NCH / 8-H/CH_2	0.82	1.04	0.89	0.99
2-H/NCH / 2-H/CH_2	1.08	0.86	0.93	0.96
2-H/Me / 2-H/Me_2	0.99	0.76	0.92	1.02
CH_2/8-H / CH_2/2-H	1.23	0.78	0.98	0.92
NCH/2-H / NCH/8-H	1.08	1.05	1.06	1.02

NOE effect between the CCH and NCH hydrogens, since they are close to each other (2.35 Å, in the most stable conformer of the *E*-configuration, according to the MM calculations); however, no such effect was observed experimentally, thus ruling out the *E* structure for **1**. On the contrary, in both the conformers **1A** and **1B** of the *Z*-configuration this distance is quite large (4.49 and 4.69 Å, respectively) thus explaining the absence of observable NOE effects (in these derivatives NOEs were observed only when protons were separated by less than 3.5–4.0 Å).

In Table 2 the ratios of the NOEs (raised to the power $-1/6$) are compared with the appropriate distance ratios (as an example, the first entry corresponds to the ratio between the NOEs experienced by 8-H when irradiating, respectively, the CCH and NCH hydrogens). The deviation of the computed from the experimental ratios should not exceed 10–15%: this deviation allows for the various approximations involved (mainly the use of the observed NOEs rather than the cross relaxation rates)[12,13] as well as for the experimental uncertainty in measuring such small NOEs. From Table 2 it appears that the equilibrium between the degenerate forms of lower energy (**1A**, **1A'**) fits the experimental data better than the single conformer **1B** of slightly higher energy. The choice between these two models, however, can hardly be considered unambiguous, thus we looked for an independent, additional support to the proposed conformation by means of a lanthanide induced shift (LIS) experiment.[14]

A 'shift reagent' such as Yb(fod)$_3$* is expected to interact essentially with the nitrogen atom at a distance of *ca.* 3–4 Å, approximately along the direction of the lone pair.[15] Inspection of the geometry of conformer **1B** (Fig. 2) indicates that the Yb atom will be closer to the NCH than to the CCH hydrogen: on the contrary in conformers **1A** and **1A'** it will be much closer to the CCH hydrogen. The LIS effect was indeed found to be larger for the upfield (CCH) than for the downfield (NCH) methine signal: addition of increasing amounts of Yb(fod)$_3$ caused the two multiplets eventually to overlap. Therefore this experiment further supports the conclusion that the conformation of **1** is the equilibrium between **1A** and **1A'**, rather than conformation **1B**.

In regard to derivative **2** (R = Et), the MM calculations indicate that here too there is a pair of almost degenerate conformers, corresponding to the absolute minimum of energy: they only differ for the position of the CH_3 group of the ethyl moiety, as shown in Scheme 2. The barrier for conversion of



Scheme 2

one conformer into the other (*i.e.* **2A** into **2A'**) is conceivably negligible, thus suggesting again that there is a fast equilibrium between these pairs of conformers.

It should be mentioned that for **2** the NOEs were obtained by irradiating groups of equivalent protons (*e.g.* the three hydrogens of a methyl group); as a consequence, the values used in Table 3 are the observed NOEs divided by the number of protons being irradiated.[15] The correctness of this procedure in similar types of derivatives has been recently tested experimentally.[10]

Neither of the individual conformers **2A** or **2A'** of Scheme 2 fits the experimental NOEs satisfactorily (Table 3): however, if the above-mentioned fast equilibrium between the two forms is assumed, the agreement becomes quite good.

Finally it is worth mentioning that in **2** irradiation of the CH_2 signal does not yield a NOE for the NCH hydrogen as the corresponding distances in the proposed conformers (4.65 Å in both **2A** and **2B**) are larger than the distances (3.5–4 Å) yielding observable NOEs.

As mentioned, in the case of R = Me only one isomer (**3**) could be isolated. The other isomer (**4**) was only observed (but not isolated) in the NMR spectra of samples at equilibrium.[9] The assignment of the *Z*-configuration to **3** (and hence of the *E*-configuration to **4**)[9] is confirmed by the NOE values in Table 4, where it is also obvious that the *E*-configuration is not appropriate for **3**.

In the case of R = H (**5**) only one isomer was isolated: no spectroscopic evidence was obtained for the presence of the other isomer. Contrary to the previous cases, the *E*-configuration must be assigned to **5**, as was also found in the case of other aldimines.[16] This clearly derives from the observation of a very large NOE (13%) experienced by the imino hydrogen (HC=N) on irradiation of the methine hydrogen of the isopropyl group. Likewise a NOE is also detectable (2.3%) when observing the methine hydrogen on irradiation of the HC=N signal. In addition, the *E*-configuration also explains the

* Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)-ytterbium.

Table 4 Ratios of the interproton distances (computed for the *E*- and *Z*-configuration) of derivatives **3** and **7**. The ratios (raised to the power −1/6) of the experimental NOEs (divided by the number of irradiated protons) are also given. Me represents the methyl group bonded to the carbon (in **3**) or to the nitrogen atom (in **7**) of the imino moiety; conversely CH represents the methine group bonded to the nitrogen (in **3**) or to the carbon atom (in **7**)

	Compound **3**			Compound **7**		
	Distance ratio		$\left(\frac{NOE}{ratio}\right)^{-1/6}$ [a]	Distance ratio		$\left(\frac{NOE}{ratio}\right)^{-1/6}$
	E	*Z*		*E*	*Z*	
8-H/CH / 8-H/Me	1.16	0.88	0.95	0.75	0.91	0.91
2-H/CH / 2-H/Me	1.15	0.91	0.92	0.88	0.77	0.79
CH/2-H / CH/8-H	1.05	1.06	1.04	1.35	0.93	0.96

[a] The NOE experiments confirm the assignment (ref. 9) of the *Z*-configuration to **3**.

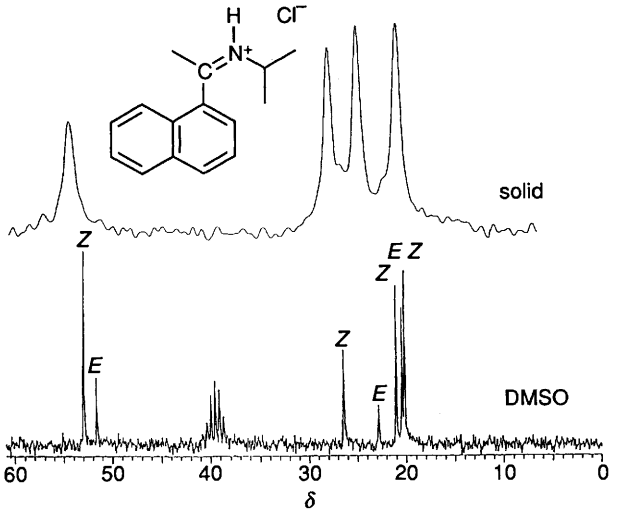


Fig. 3 Top: CP MAS solid state ^{13}C NMR spectrum of the imonium hydrochloride **10**, showing the existence of only one configuration (*Z*). Bottom: the solution spectrum in [$^2H_6$]dimethyl sulfoxide displays the signals of the *Z*- and *E*-configurations (**10** and **11**, respectively) in a 2.5:1 ratio.

existence of a relatively large coupling constant ($^4J_{HH}$ = 1 Hz) between the imino and the methine hydrogens: the *E*-configuration allows these hydrogens to be in an *anti* relationship, which enhances the corresponding *J* coupling.

The reversal of the configuration of the more stable isomer in **5** (R = H), with respect to **3**, **2**, **1** (R = Me, Et, Pr^i, respectively), is probably due to the diminished steric effect. When R is an alkyl group, the more favourable steric situation is to have R *anti* and naphthalene *syn* to the *N*-isopropyl moiety (*Z*-configuration); on the contrary for R = H the reverse situation (*i.e.* hydrogen *syn* and naphthalene *anti* to the *N*-isopropyl group) is preferred. Owing to the smaller steric effects it might even be considered that **5** adopts a planar, rather than a twisted conformation: this might also explain why the two isopropyl methyl groups are homotopic even at very low temperature (−130 °C). However, the NOE experiments contradict this hypothesis and indicate that **5** still has an orthogonal conformation: in fact the HC=N hydrogen experiences the *same* NOE (0.6%) on irradiation of both the 8-H and 2-H signals of the naphthalene ring. Also the NOEs observed for the 8-H and 2-H on irradiation of the HC=N signal are very similar (1.6 and 1.8%. respectively). This implies that the corresponding distances must also be very similar, a situation impossible for a coplanar arrangement. The calculations support this conclusion in that the energy minimum for **5** corresponds to a conformation with a twisting angle of 92° and the distances separating HC=N from 8-H and 2-H are very similar, *i.e.* 2.91 and 3.22 Å, respectively.

Compounds **6** and **7** (R′ = Et and Me respectively) have, like **1** (R′ = Pr^i), an isopropyl group bonded to the carbon atom of the imino moiety: they too have the *Z*-configuration, as shown in Table 4 for the case R′ = Me (**7**).

The imonium hydrochlorides **8**–**10** were also isolated as solid precipitates by passing gaseous HCl into ethereal solutions of **1**–**3**. The imonium salts **8** and **9** (derived from imines **1** and **2**) are present solely in the *Z*-configuration, as observed for the parent imines. The imonium hydrochloride **10** (derived from the imine **3**), however, yields, in solution, an equilibrium with its *E*-configuration **11**, as observed for the corresponding amine. The *Z*:*E* ratio of these imonium salts (*i.e.* the ratio **10**:**11**) is not the same, however, as the ratio of parent imines **3**:**4**. For instance, the ratio **10**:**11** is 2.5:1 in dimethyl sulfoxide (DMSO), to be compared with a 10:1 ratio for the parent imines (**3**:**4**) under the same conditions. In the solid state, on the other hand, the imonium chloride is present solely in one of the two possible configurations (conceivably the *Z*-configuration **10**), as shown in the CP MAS solid state NMR spectrum of Fig. 3. It can thus be concluded that the imonium hydrochlorides **10** and **11** reach their own *Z*:*E* equilibrium in solution in an independent manner with respect to that of the parent imines **3** and **4**.

Dynamic Stereomutation.—The proton NMR signals of the methyl groups of both the isopropyl moieties of **1** display two sets of four lines, owing to the diastereotopicity of these groups within each isopropyl substituent. Upon irradiation of the *downfield* methine multiplet (NCH) the four *upfield* methyl signals are decoupled into two lines. This pair of lines broaden and eventually coalesce at 177 °C (Fig. 4) in a reversible manner, allowing the free energy of activation (Table 5) for the interconversion of the rotational enantiomers *R* and *S* to be determined.

When R = Et (**2**), in addition to diastereotopic methyl, diastereotopic methylene hydrogens are observed. In this case the dynamic process could be better investigated by monitoring the ^{13}C signals of the methyl groups which have a larger chemical shift difference (Table 5).

The enantiomerization barrier could be obtained, in the case of R = Me, only for the *Z*-configuration (**3**): the corresponding signals for **4** (*E*-configuration) could not be made anisochronous even at −130 °C (both at the ^1H and ^{13}C frequencies). The same negative result was observed in the case of R = H (**5**, *E*-configuration). Indeed the changes in the steric requirements for the stereomutation might be large enough in **4** and **5** to

Table 5 Free energies of activation ($\Delta G^{\ddagger}$, kcal mol^{-1}), measured in the temperature range (°C) indicated, for the enantiomerization of imines **1–3, 6, 7** and **12** and for the imonium hydrochlorides **8–10**. The shift difference ($\Delta\nu$/Hz) is that of the methyl groups of the isopropyl moiety at the temperatures given in parentheses. In the last column the frequencies (MHz) of the spectrometers employed are reported

Compound	$\Delta G^{\ddagger}$/kcal mol^{-1}	Temperature range/°C	Solvent	$\Delta\nu$/Hz	Frequency/MHz
1	24.6	160–177	DMSO	7.6 (130 °C)	200 (^{1}H)
2	22.3	130–147	DMSO/ODCB[a]	10.7 (90 °C)	50.3 (^{13}C)
3	20.5[b]	100–110	Toluene	11.4 (40 °C)	50.3 (^{13}C)
6	23.1	145–165	DMSO	13.2 (100 °C)[c]	200 (^{1}H)
7	22.7	140–155	ODCB[a]	10.1 (110 °C)	50.3 (^{13}C)
8	23.4	145	DMSO	6.0 (120 °C)	200 (^{1}H)
9	20.3	55–75	DMSO	4.9 (45 °C)	300 (^{1}H)
10	17.8	70–85	DMSO	43.5 (30 °C)	50.3 (^{13}C)
12	>27	180	DMSO	12.0 (180 °C)[c]	200 (^{1}H)

[a] *ortho*-Dichlorobenzene. [b] 20.4 kcal mol^{-1} in ref. 4. [c] Methylene signals (AB system) of the N–Et moiety (J_{AB} = −12.5 Hz), obtained by decoupling the corresponding methyl triplet.

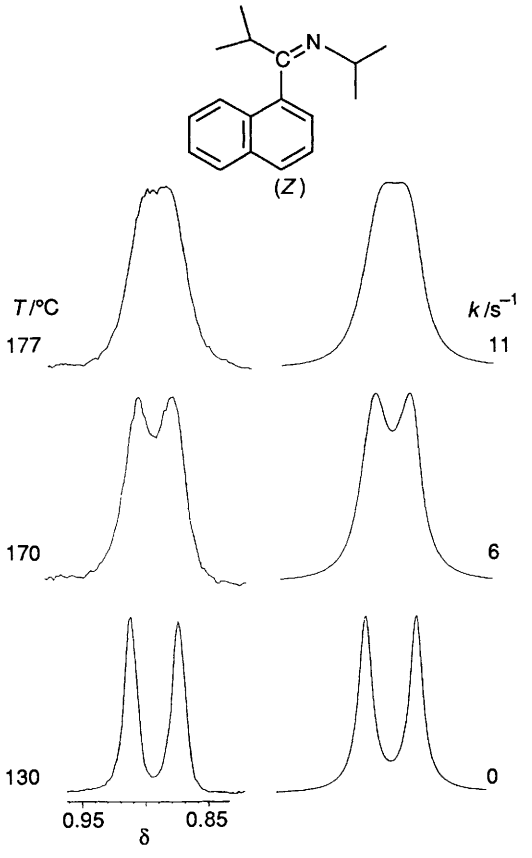


Fig. 4 Experimental (left hand side) 200 MHz ^{1}H methyl signals (CH decoupled) of the carbon-bonded isopropyl group of derivative **1**, recorded as a function of temperature. On the right hand side the corresponding computer simulations (with pertinent rate constants k, in s^{-1}), are displayed.

make the corresponding $\Delta G^{\ddagger}$ values so low (*i.e.* less than 5 kcal mol^{-1}) as to become undetectable by NMR techniques.

In order to clarify these points and to gain a better understanding of the enantiomerization pathway, the MM calculations were extended to the transition states. It is expected that these calculations account for the trends of the experimental $\Delta G^{\ddagger}$ values where the barriers increase with the increasing bulkiness of the substituent R in the *N*-isopropyl derivatives (**3** < **2** < **1**) and of the substituent R′ in the *C*-isopropyl derivatives (**7** < **6** < **1**).

In principle, two possible enantiomerization pathways are available to 1-naphthylimines *i.e.* either a passage through the planar transition state where the nitrogen atom crosses over C-2 of the naphthalene, or a passage where the crossing occurs over

Table 6 Computed energy differences (kcal mol^{-1}), for imines **1–7** and **12**, between the orthogonal ground state and the two possible planar transition states (*i.e.* those corresponding to the N-atom crossing over either C-2 or C-8 of naphthalene). The corresponding experimental $\Delta G^{\ddagger}$ values (also in kcal mol^{-1}) are reported for comparison

		Computed	
Compound	Experimental	N over C-2	N over C-8
1 (*Z*)	24.6	25.1	28.9
2 (*Z*)	22.3	24.5	29.2
3 (*Z*)	20.5	22.8	27.6
4 (*E*)	—	13.6	12.3
5 (*E*)	—	3.0	5.4
6 (*Z*)	23.1	23.7	27.0
7 (*Z*)	22.7	23.5	26.9
12 (*Z*)	>27	37.3	34.8

C-8. Computation of the energies for these two possible planar situations would yield, as a difference from the twisted ground state, the two corresponding theoretical barriers. The pathway having the lower of the two barriers would be that followed by the molecule. As shown in Table 6, the *Z* isomers of the homologous series **1–3** (isopropyl group bonded to nitrogen) and **1**, **6**, **7** (isopropyl group bonded to carbon) are predicted to have lower barriers when the nitrogen atom crosses over C-2 rather than C-8. Furthermore, the lower barriers agree with the experimental values much better than the higher ones. Since the observed trend is also reproduced, little doubt is left that the enantiomerization pathway for the *Z* isomers occurs through this type of transition state.

The same calculations also suggest that the barrier for imine **4** (*E*-configuration) should be 13.6 or 12.3 kcal mol^{-1}, depending on whether the nitrogen atom crosses C-2 or C-8, respectively. In both cases the value is expected to be *ca.* 10 kcal mol^{-1} lower than that for the corresponding *Z*-configuration **3** and should therefore be amenable, in principle, to NMR observation. The failure to observe anisochronous signals for **4** even at −130 °C seems therefore to indicate that an accidental degeneracy of the signals has occurred, at least at 200 MHz. In contrast, the computed barrier for R = H (**5**) is predicted to be so low, for both possible pathways (the computed values of Table 3 are 3.0 and 5.4 kcal mol^{-1}, respectively), as to account for the inability to achieve an experimental determination by NMR.

Also the imonium hydrochlorides in the *Z*-configuration (**8–10**) exhibit anisochronous signals for the methyl groups of the prochiral isopropyl moieties, allowing the corresponding enantiomerization barriers to be obtained (Table 5). The free energies of activation for **8–10** turn out to be lower than those determined for the parent imines **1–3**. This effect indicates that the steric requirements involved in the process are smaller for

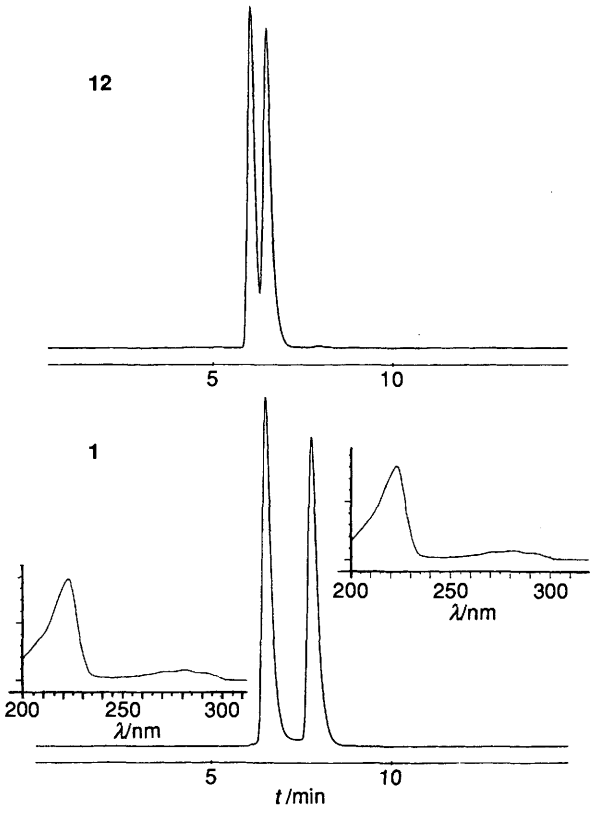
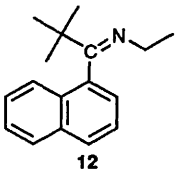


Fig. 5 Chromatographic peaks due to the enantiomers of **12** (top) obtained using a chiral column. An analogous separation is shown below for the case of **1** (the UV spectra of the enantiomers of the latter compound are also shown).

the protonated than for the unprotonated forms. This might be due to a widening of the C=N–C angle in the imonium with respect to the imine derivatives which would facilitate the passage through the planar transition state. Indeed MM calculations predict a C=N–C angle of *ca.* 125° for the imines and *ca.* 130° for the corresponding imonium salts.

Chiral Separation.—Finally, the calculations predict that replacement of the *C*-isopropyl group of these 1-naphthylimines by the bulkier *tert*-butyl moiety, would produce two enantiomers separated by a computed barrier of *ca.* 35 kcal mol^{-1} (Table 6): *tert*-butyl derivatives should thus exist as a racemic mixture of two *configurationally* stable enantiomers (atropisomers). One such compound was actually prepared



12

(**12**, *Z*-configuration), with an ethyl group serving as a chirality probe. The two anisochronous methylene signals (which by decoupling the methyl group appear as an AB system) do not broaden (within an accuracy of 0.3 Hz) even at 180 °C. Accordingly, the enantiomerization rate must be slower than 1 s^{-1} and the free energy of activation higher than 27 kcal mol^{-1} (Table 5), in agreement with the theoretical predictions. As $\Delta G^{\ddagger}$ values larger than 26 kcal mol^{-1} entail enantiomers with racemization lifetimes ($t_{0.5}$) of a few days at room temperature,[17] compound **12** must be considered a racemic mixture of two *configurational* (rather than conformational) enantiomers. As a consequence, it should be possible to achieve the physical separation of the *R* and *S* optical isomers (atropisomers) of **12**. The separation of these enantiomers was attempted on a chiral chromatographic column, monitoring the eluate by UV absorption at 280 nm. Two peaks of equal intensity were indeed observed (Fig. 5, top), each having, as expected, identical UV spectra: the predicted configurational atropisomerism is thus clearly established for imine **12**. Furthermore, since the whole procedure for the chiral separation can be performed in less than 10 min, the conformational enantiomers of **1** should also be amenable to a physical separation. The NMR measurement of the enantiomerization barrier for **1** (24.6 kcal mol^{-1}) entails, in fact, a lifetime of a few hours at room temperature. In Fig. 5 (bottom) the two HPLC peaks corresponding to the enantiomers of **1** are clearly visible, each of them displaying identical UV spectra. The chiral separation of both configurational and conformational enantiomers has thus been achieved in the case of hindered imines.

Conclusions

NOE experiments and dynamic NMR measurements were used to ascertain the configuration and conformation of a number of hindered naphthylimines, which were shown to exist as a pair of conformational enantiomers owing to the restricted Ar–CN rotation. The NMR determination of the enantiomerization rates allowed us to set up the conditions for achieving the separation (by chiral HPLC) of a pair of configurational (atropisomers) and of a pair of conformational enantiomers for two appropriate derivatives.

Experimental

Materials.—Imines **1–6** were prepared by reacting the appropriate carbonyl compounds with selected amines, a typical example being reported for the case of **1** (*Z*-isomer).

N-[1-(1-*Naphthyl*)-2-*methylpropylidene*]-1-*methylethylamine* (**1**). A benzene (50 cm^3) solution of isopropyl 1-naphthyl ketone (7.2 g, 30 mmol) and isopropylamine (10 g, 180 mmol), containing a few crystals of 4-toluenesulfonic acid was introduced into an autoclave and kept at 170 °C overnight. After evaporation of the solvent, the residue was distilled (0.2 mmHg). The first fraction (b.p. 100 °C) contained the major product **1** (*Z*-configuration) which crystallized from light petroleum (m.p. 66–68 °C). A second fraction (b.p. 101–105 °C) contained, in addition to **1**, the unchanged ketone: crystallization from light petroleum yielded an additional quantity of **1** (5 g, 57% overall yield); δ_H(200 MHz; $CDCl_3$) 0.95–1.2 (12 H, 4 d, CH_3), 2.8 (1 H, m, CCH), 3.12 (1 H, m, NCH), 7.1–7.9 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 20.4 (CH_3), 20.6 (CH_3), 23.7 (CH_3), 23.9 (CH_3), 39.5 (CH), 52.9 (NCH), 124.3 (CH), 125.35 (CH), 126.2 (CH), 126.5 (CH), 126.6 (CH), 128.29 (CH), 128.9 (CH), 130.7 (C), 133.8 (C), 137.6 (C), 173.1 (CN) (Found: M^+, 239.167 11. Calc. for $C_{17}H_{21}N$: *M*, 239.167 40) (Found: C, 85.6; H, 8.7; N, 6.0. $C_{17}H_{21}N$ requires C, 85.30; H, 8.84; N, 5.85%). The other compounds were identified as follows.

N-[1-(1-*Naphthyl*)*propylidene*]-1-*methylethylamine* (**2**) (m.p. 64–66 °C); δ_H(200 MHz; $CDCl_3$) 2.60 (2 H, m, CH_2), 3.18 (1 H, m, NCH), 7.1–7.9 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 11.3 (CH_3), 23.7 (CH_3), 23.9 (CH_3), 35.5 (CH_2), 53.0 (NCH), 123.9 (CH), 125.5 (CH), 125.6 (CH), 126.6 (CH), 126.8 (CH), 128.3 (CH), 128.9 (CH), 130.1 (C), 133.8 (C), 137.9 (C), 170.4 (CN) (Found: M^+, 225.151 83. Calc. for $C_{16}H_{19}N$: *M*, 225.151 75) (Found: C, 85.3; H, 8.6; N, 6.1. $C_{16}H_{19}N$ requires C, 85.28; H, 8.50; N, 6.22%).

N-[1-(1-*Naphthyl*)*ethylidene*]-1-*methylethylamine* (**3**, **4** *Z*- and *E*-configurations, respectively). **3** (m.p. 77–78 °C, lit.,[9] 78 °C); δ_H(200 MHz; $CDCl_3$) 1.04 (3 H, d, CH_3), 1.05 (3 H, d,

CH_3), 2.38 (6 H, s, CH_3), 3.15 (1 H, m, NCH), 7.15–7.9 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 23.7 (CH_3), 23.9 (CH_3), 29.5 (CH_3), 53.2 (NCH), 123.2 (CH), 125.2 (CH), 125.7 (CH), 126.6 (CH), 126.9 (CH), 128.3 (CH), 128.9 (CH), 129.6 (C), 133.9 (C), 138.9 (C), 166.1 (CN). **4** (not isolated);[9] δ_H(200 MHz; $CDCl_3$) 1.32 (6 H, d, CH_3), 2.32 (3 H, s, CH_3), 4.00 (1 H, m, NCH), the aromatic signals are obscured by those of **3**; δ_C(50.3 MHz; $CDCl_3$, obtained as a difference spectrum between that of the mixture of **3** and **4** at equilibrium and that of pure **3**) 19.6 (CH_3), 23.6 (2 CH_3), 51.7 (NCH), 124.7 (CH), 126.4 (CH), 126.8 (CH), 128.4 (CH), 128.8 (CH), 129.0 (CH), 130.6 (C), 133.4 (CH), 134.5 (C), 135.9 (C), 165.5 (CN).

N-[1-(1-*Naphthyl*)*methylidene*]-1-*methylethylamine* (**5**, *E*-configuration). B.p. 95 °C at 0.18 mmHg; δ_H(200 MHz; $CDCl_3$) 1.30 (6 H, d, CH_3), 3.6 (1 H, m, NCH), 7.4–8.8 (7 H, m, Ar), 9.00 (1 H, d, =CH); δ_C(50.3 MHz; $CDCl_3$) 24.4 (2 CH_3), 62.8 (NCH), 124.6 (CH), 125.6 (CH), 126.3 (CH), 127.3 (CH), 128.6 (CH), 128.92 (CH), 130.9 (CH), 131.7 (C), 132.4 (C), 134.2 (C), 158.0 (CN) (Found: C, 84.6; H, 7.9; N, 6.8. $C_{14}H_{15}N$ requires C, 85.24; H, 7.66; N, 7.10%).

N-[1-(1-*Naphthyl*)-2-*methylpropylidene*]*ethylamine* (**6**, *Z*-configuration). Oil purified by chromatography (light petroleum–ether* 3:1); δ_H(200 MHz; $CDCl_3$) 1.15 (9 H, m, CH_3), 2.8 (1 H, m, CH), 3.05 (2 H, m, NCH_2), 7.1–7.85 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 15.65 (CH_3), 19.8 (2 CH_3), 39.0 (CH), 47.3 (NCH_2), 123.7 (CH), 124.9 (CH), 125.3 (CH), 125.95 (CH), 126.3 (CH), 127.8 (CH), 128.4 (CH), 129.9 (C), 133.25 (C), 136.9 (C), 174.9 (CN) (Found: C, 85.1; H, 8.4; N, 6.4. $C_{16}H_{19}N$ requires C, 85.28; H, 2.59; N, 6.22%).

Compounds **7** and **12** were prepared by reacting 1-bromonaphthalene with the appropriate nitriles and iodides.

N-[1-(1-*Naphthyl*)-2-*methylpropylidene*]*methylamine* (**7**, *Z*-configuration). To a cooled solution (−50 °C) of 1-bromonaphthalene (6 g, 30 mmol) in anhydrous ether (125 cm^3), butyllithium (2.5 mol dm^{-3}; 13 cm^3, 33 mmol) was slowly added. After 0.5 h the reaction was complete and 2-methylpropionitrile (2.3 g, 33 mmol) was added and allowed to react for 1 h. Methyl iodide (4.65 g, 33 mmol) was then introduced and the reaction left to proceed at room temperature for *ca.* 2 h. After quenching with water, the organic layer was extracted with ether, dried and evaporated. The residue was distilled (b.p. 89–90 °C at 1.5 mm Hg) to yield 5.3 g of **7**; δ_H(200 MHz; $CDCl_3$) 1.15 (6 H, 2 d, CH_3), 2.8 (1 H, m, CH), 2.9 (3 H, d, NCH_3), 7.2–7.9 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 20.1 (CH_3), 20.2 (CH_3), 39.6 (CH), 40.9 (NCH_3), 124.2 (CH), 125.5 (CH), 125.8 (CH), 126.5 (CH), 126.9 (CH), 128.4 (CH), 129.0 (CH), 130.3 (C), 133.8 (C), 137.4 (C), 177.5 (CN) (Found: C, 85.2; H, 8.0; N, 6.7. $C_{15}H_{17}N$ requires C, 85.25; H, 8.11; N, 6.63%).

N-[1-(1-*Naphthyl*)-2,2-*dimethylpropylidene*]*ethylamine* (**12**, *Z*-configuration). The reaction, between 1-bromonaphthalene and 2,2-dimethylpropionitrile, was carried out as above, but the intermediate, 1-(1-*Naphthyl*)-2,2-*dimethylpropylidenamine*, was isolated (b.p. 106–105 °C at 0.01 mmHg). This product (2 g, 9.5 mmol) was dissolved in toluene (30 cm^3) and reacted with 50% sodium hydride (0.45 g, 9.5 mmol). After 1 h at room temperature, ethyl iodide (1.48 g, 9.5 mmol) was added and the temperature raised to 85 °C for 100 h; distillation yielded **12** (b.p. 69–70 °C at 0.02 mmHg); δ_H(200 MHz; $CDCl_3$) 1.05 (3 H, t, CH_3) 1.29 (9 H, s, CH_3), 3.0 (2 H, m, NCH_2), 7.1–7.9 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 16.1 (CH_3), 29.1 (3 CH_3), 40.4 (C), 48.0 (NCH_2), 124.4 (CH), 125.2 (CH), 126.3 (CH), 126.5 (2 CH), 128.0 (CH), 128.8 (CH), 130.9 (C), 133.7 (C), 147.0 (C), 177.3 (CN) (Found: C, 85.1; H, 8.6; N, 5.7. $C_{17}H_{21}N$ requires C, 85.30; H, 8.84; N, 5.85%).

The imonium hydrochlorides **8**–**10** were obtained by passing gaseous HCl into ethereal solutions of **1**–**3** respectively. They were characterized as follows.

8 m.p. 179–182 °C; δ_H(200 MHz; $CDCl_3$) 1.11 (3 H, d, CH_3), 1.4–1.55 (9 H, 3d, CH_3), 3.50 (1 H, m, NCH), 4.38 (1 H, m, CCH), 7.25–8.15 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 19.4 (CH_3) 20.6 (CH_3), 21.1 (CH_3), 21.9 (CH_3), 37.5 (CH), 54.3 (NCH), 123.9 (CH), 124.0 (CH), 125.2 (CH), 128.1 (CH), 128.9 (CH), 128.9 (C), 129.9 (CH), 132.05 (CH), 133.85 (C), 192.5 (CN).

9 m.p. 208–210 °C; δ_H(200 MHz; $CDCl_3$) 1.2 (3 H, t, CH_3), 1.5 (6 H, 2 d, CH_3), 3.55 (3 H, m, NCH and CH_2), 7.3–8.15 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 10.7 (CH_3), 20.5 (CH_3), 21.6 (CH_3), 32.4 (CH_2), 53.7 (NCH), 123.0 (CH), 123.5 (CH), 125.0 (CH), 127.8 (CH), 127.9 (C), 128.2 (C), 128.7 (C), 129.5 (CH), 131.9 (CH), 133.4 (C), 188.9 (CN).

10 (*Z*-configuration) m.p. 216–219 °C: δ_H(200 MHz; $CDCl_3$) 1.4 (6 H, 2d, CH_3), 3.05 (3 H, s, CH_3), 3.6 (1 H, m, NCH), 7.2–8.1 (7 H, m, Ar); δ_C(50.3 MHz; $CDCl_3$) 20.7 (CH_3), 21.7 (CH_3), 26.6 (CH_3), 53.9 (CH), 122.75 (CH_3), 122.95 (CH), 125.3 (CH), 127.5 (C), 127.9 (CH), 128.9 (CH), 129.55 (CH), 129.6 (C), 131.9 (CH), 133.6 (C), 184.7 (CN). **11** (*E*-configuration, not isolated, in equilibrium with **10** in DMSO): δ_H(DMSO) 1.5 (6 H, d, CH_3), 3.0 (3 H, s, CH_3), 4.6 (1 H, m, NCH). The aromatic region is obscured by the signals of **10**. δ_C(DMSO) 20.4 (CH_3), 22.8 (CH_3), 51.5 (NCH), the aromatic signals are obscured by those of **10**.

Spectral Measurements.—The differential NOE experiments were carried out in nitrogen-saturated $CDCl_3$ (or C_6D_6) solutions at 200 MHz. The signals were presaturated for 10 s before acquiring the spectrum with the decoupler turned off. To obtain a good selectivity, the irradiation was carried out with a low irradiation power, by setting the decoupler at the individual frequencies of the multiplets to be saturated and cycling it over these lines. A program that accumulates the difference between the FIDs (the one corresponding to the irradiated spectrum and the one where irradiation is kept away from any signal) was employed. Usually 256 scans (or more if required by the signal-to-noise ratio) were accumulated after two dummy scans, with the probe temperature maintained at 23 ± 0.1 °C. The resulting FID, acquired with 16 K (sweep width 3000 Hz), was transformed with 32 K (zero filling) using a line broadening of 3–4 Hz. A control spectrum was subsequently obtained and the NOE values determined by comparing the line intensities of the two spectra.

In order to obtain the average distances when the equilibrium between the single conformers **A** and **A′** was assumed (for compounds **1** and **2**), the MM-computed distances were averaged according to the following relationship, where $\bar{r}_i$ is the average distance between a pair of hydrogens and r_i^A and $r_i^{A'}$ are the distances between the same pair of hydrogens in conformer **A**

$$\bar{r}_i = [0.5(r_i^A)^6 + 0.5(r_i^{A'})^6]^{1/6}$$

and **A′** respectively. Since the calculations indicate that the two conformers are nearly degenerate, they were considered as equally populated (coefficient 0.5).

The temperatures for the dynamic NMR spectra were calibrated using the temperature dependence of the proton shift difference of ethylene glycol. Line-shape simulations were produced by means of a computer program based upon the modified Bloch equations.[18] The samples for the low temperature studies were prepared by connecting the NMR tube, containing the desired compound, to a vacuum line and condensing the gaseous solvent (CHF_2Cl) with liquid nitrogen. The tube, sealed *in vacuo*, was allowed to reach room temperature and was subsequently introduced into the probe, cooled below the boiling point of the solvent.

The ^{13}C solid-state NMR spectrum of **10** was obtained in the

* Ether refers to diethyl ether throughout.

usual Cross Polarisation (CP) Magic Angle Spinning (MAS) mode at 75.5 MHz, using a double bearing probe with a 7 mm Zr_2O rotor spinning at 3.6 kHz: the recycle time was 2 s, the contact time 1.5 ms and the number of accumulations 2000.

HPLC Chiral Separation.—The separation of the enantiomers of **1** and **12** was carried out on a chiral column (stationary phase CHIRALCEL OD 250 × 4.6 mm) using hexane as a mobile phase: the flow rate was 1.0 cm^3 min^{-1} and the eluate was monitored by means of a UV detector at 280 nm.

Calculations.—Molecular mechanics calculations were carried out using the MMX force field as implemented[11b] in the package PC Model, Serena software. The π-atom formalism was employed for the naphthalene ring and the C=N moiety. Whereas no restrictions were assumed when computing the energies of the ground states (which 'spontaneously' adopted a twisted structure), the energies corresponding to the two possible rotational transition states were obtained by forcing the C=N moiety to stay coplanar to the naphthalene ring, by constraining the C(2)–C(1)–C=N dihedral angle (which was 90° in the ground state) to be 0° (N over C-2) or 180° (N over C-8): within this constraint the structures were allowed to reach their own energy minimum.

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