Conformational Studies by Dynamic NMR. 54.[1] Trigonal Nitrogen Inversion and Enantiomerization Processes in the Stereolabile Chiral Isomers of *N*-Naphthylimines[†]

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Imines bearing the 1-naphthyl substituent bonded to the C=N nitrogen atom were found to have the planes containing the naphthyl and the imino moieties significantly twisted. Even for the less hindered derivative investigated (**1a**, *E*-isomer), the corresponding dihedral angle in solution has been estimated (NOE experiment) to be approximately equal to 65 ± 6°. This feature allows for the existence of conformational enantiomers (atropisomers) due to restricted rotation about the nitrogen–naphthyl bond. This form of chirality was observed below −90 °C by means of dynamic NMR spectroscopy (^{1}H or ^{13}C) either by taking advantage of the presence of prochiral substituents (e.g., isopropyl groups) or by making use of chiral solvating agents (Pirkle's alcohols). Computer line shape simulation of the appropriate NMR signals yielded the free energies of activation for the *R,S* interconversion process (enantiomerization). The atropisomers were usually observed only in one of the two possible stereolabile *E,Z* isomers, except in one case (**1c**) where both of them displayed evidence of atropisomerism, with two different barriers for the related enantiomerization processes (8.4 and 9.9 kcal mol^{-1} for the *E*- and *Z*-isomer, respectively). Also, the free energies of activation for the *E* to *Z* interconversion were measured and found to cover a range of values much higher (15.8–19 kcal mol^{-1}) than the values for the enantiomerization processes (8.4–10.8 kcal mol^{-1}), except in the crowded imine **2**, which has two *tert*-butyl groups bonded to the C=N carbon atom. In this case, it was possible to demonstrate that both the exchange of the *E,Z* positions and the *R,S* interconversion occur *via* the same pathway, which must be consequently identified as an inversion of the trigonal nitrogen atom (lateral shift).

Introduction

Alkyl- or aryl-substituted aldimines ($R^1CH{=}NR^2$) and ketimines ($R^1R^2C{=}NR^3$) are known to exist as stereolabile *E,Z* isomers that interconvert with a free energy of activation covering the range of 12–29 kcal mol^{-1}, depending on the nature of the substituents.[2] This process might be due, in principle, either to the rotation about the C=N double bond or to the inversion of the trigonal nitrogen atom (lateral shift).[2] Additional possibilities have been also considered such as tautomerization to enamines (followed by C–N rotation) and acid-catalyzed mechanisms.[2] Tautomerization to enamines should be accessible only to imines having a C-alkyl substituent with at least one α-hydrogen atom, and an acid-catalyzed process would obviously require traces of H^+ in the solvent or in the compound. Accordingly, imines lacking such types of substituents (e.g., aryl or *tert*-butyl derivatives) cannot undergo tautomerization, and an acid-catalyzed mechanism can be excluded if any trace of acid is carefully removed. This leaves rotation and sp^2 N-inversion as the only possible pathways for the *E,Z* interconversion when the conditions for the previously mentioned alternative mechanisms do not apply. Although many observations seem to favor the N-inversion process,[2,3] an unambiguous choice could not be, so far, obtained for imines solely on an experimental ground. Theoretical calculations indicate, however, that the C=N rotation would require an activation energy twice as large as that expected for the inversion of trigonal nitrogen.[2,4] Furthermore, the barriers computed for the latter process match reasonably well the experimental values.[5]

In *N*-arylimines, such as substituted benzylideneanilines, the N-bonded phenyl group adopts a conformation in which its plane is twisted with respect to that of the N=CH moiety. The corresponding dihedral angles were found to cover the range 40–55° in the solid state (X-ray), depending on the nature of the substituents on the phenyl group.[7] The similar value (52°) found for benzylideneaniline itself (Ph-N=CHPh) in the gaseous phase (electron diffraction)[8] indicates that the twisting of this angle is not due to the effects of the crystal packing but is an inherent molecular property. This feature suggests that a N-bonded aromatic group would wobble

[†] This work is dedicated to the beloved memory of Anna Franceschi Lunazzi, 1940–1994.

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(5) As an example, the barriers computed with various theoretical approaches[2] for N-inversion in $CH_2{=}NH$ are in the range 26–31 kcal mol^{-1}, to be compared with the experimental $\Delta G^{\ddagger}$ value of 28.8, measured[6] by dynamic NMR for the *E* to *Z* isomerization of ArCH=NMe, Ar being 9-anthryl.

(6) Boyd, D. B.; Watson, C. E.; Jennings, W. B.; Jerina, D. M. *J. Chem. Soc., Chem. Commun.* **1972**, 183. See also: Jennings, W. B.; Al-Showiman, S.; Boyd, D. R.; Campbell, R. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1501.

(7) (a) Bürgi, H. B.; Dunitz, J. D. *J. Chem. Soc., Chem. Commun.* **1969**, 472. (b) Bürgi, H. B.; Dunitz, J. D. *Helv. Chim. Acta* **1970**, *53*, 1747.

(8) Traetteberg, M.; Hilmo, I.; Abraham, R. J.; Ljunggren, S. *J. Mol. Struct.* **1978**, *48*, 395.

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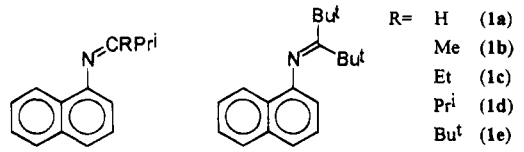
around a plane twisted with respect to that of the N=C moiety, and in the absence of a local C_2 symmetry axis about the Ar–N bond, it would deprive the whole molecule of any plane of symmetry. As a consequence, such an imine would become a compound with a chiral structure by virtue of a stereogenic axis (atropisomer), similar to what is observed in imines with a bulky aromatic substituent at the C=N carbon atom.[9,10]

To make the identification of such a chirality possible, it is obviously required that the Ar–N rotational barrier is not extremely low, to avoid a too rapid interconversion of the two conformational enantiomers. In benzylideneaniline itself, the Ph–N rotational barrier has been calculated to be quite low (about 7 kcal mol^{-1}) for the more stable *E*-isomer[11a] but it is expected to be higher for the more hindered *Z*-isomer, which, however, was not observed in any appreciable amount.[11b] In order to prove that chirality due to restricted Ar–N rotation can indeed be detected in arylimines we prepared a number of N-substituted 1-naphthylimines and investigated them by low-temperature NMR spectroscopy. The 1-naphthyl substituent, in fact, not only is lacking the local C_2 symmetry axis about the naphthyl–nitrogen bond but it is also sufficiently bulky to make the naphthyl–nitrogen rotational barrier high enough to become NMR detectable at accessible temperatures (−120 °C or higher).

Results and Discussion

The following compounds were, accordingly, synthesized:



1 2

In the case of **1a** (R = H), the ^{1}H NMR spectrum at room temperature (in $CDCl_3$) indicates that only one of the two possible *E*,*Z* isomers is present: the shift of the isopropyl being 1.28 ppm (two enantiotopic methyl groups) and 2.75 ppm (methine hydrogen). In order to unambiguously assign the *E* or *Z* structure to the only visible isomer of **1a**, a difference NOE experiment was performed whereby the signal of the hydrogen in position 2 of the naphthalene ring (H-2) was saturated. As shown in Figure 1, an enhancement (4.8% ± 0.4) of the N=CH signal, similar to that (8.2% ± 0.6) displayed by the hydrogen in position 3 of naphthalene (H-3), was detected. This means that the distances between H-2 and the two hydrogens displaying NOE effects are quite similar, thus indicating that the structure *E* has to be assigned to **1a** (in the *Z* structure the distance between H-2 and N=CH is much larger than that between H-2 and H-3, suggesting a negligible NOE effect for N=CH, contrary to the experimental finding). In addition to the structural determination, it has been also possible to evaluate the conformational preference of **1a** by using the NOE result in conjunction with the T_1 values. In a number of papers,[12] it has been reported that the ratio of the NOE's, divided by the corresponding T_1 values, can be used to derive an approximated estimate of the ratio between the reciprocal interproton distances elevated to the sixth power (a more rigorous treatment would require[13] the time-consuming determination of the cross-relaxation parameters σ, but this is beyond the aim of the present investigation). The T_1 values, measured in the very same sample used for the NOE experiment, were found to be 7.2 ± 0.5 and 8.3 ± 0.4 s for H-3 and N=CH, respectively; thus, the ratio of the interproton distances H-2, H-3 (r_1) and H-2, N=CH (r_2) becomes $r_1/r_2 = 0.89 \pm 0.04$, as it follows from the relationship:

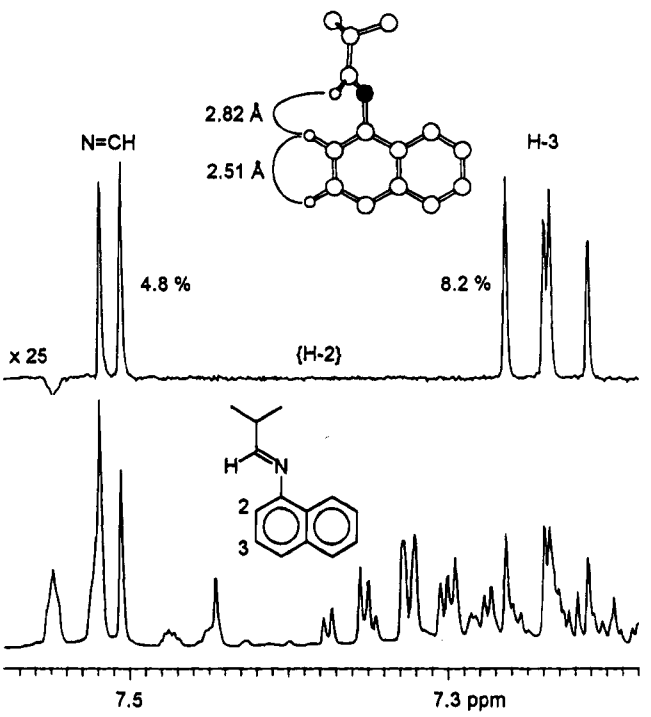


Figure 1. Partial aromatic region of the 300 MHz spectrum of **1a** in C_6D_6 (bottom). On the top is displayed the difference NOE spectrum (vertically amplified 25 times) obtained by irradiating the H-2 naphthalene signals (not displayed). The enhancements of the NCH and H-3 signals (4.8% and 8.2%, respectively) are indicated. The interproton distances shown in the picture (2.82 and 2.51 Å for NCH, H-2 and H-2, H-3, respectively) correspond to those of a structure having the planes of the naphthalene and imino moieties twisted by 65° (see text).

$$(r_1/r_2)^6 = (4.8/8.3):(8.2/7.2) = 0.51$$

Whereas r_1 is a fixed value (about 2.51 Å) the value of r_2 depends, in the isomer *E*, upon the torsion angle ϑ between the planes of naphthalene and of the N=CH moieties. The corresponding interproton distances were

(9) (a) Boyd, D. R.; Al-Showiman, S.; Jennings, W. B. *J. Org. Chem.* **1978**, *43*, 3335. (b) Hamor, T. A.; Jennings, W. B.; Proctor, L. D.; Tolley, M. S.; Boyd, D. R.; Mullan, T. *J. Chem. Soc., Perkin Trans. 2* **1990**, 25.

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(13) (a) Bruch, M. D.; Noggle, J. H.; Gierasch, L. M. *J. Am. Chem. Soc.* **1985**, *107*, 1400. (b) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH Publishers, Inc.: New York, 1989.

evaluated by molecular mechanics calculations,[14] which show how the r_1/r_2 ratio varies from 1.15 (planar structure with $\vartheta = 0$) to 0.73 (orthogonal structure with $\vartheta = 90°$), the experimental value (i.e., 0.89 ± 0.04) being reproduced by a torsion angle ϑ equal to 65 ± 6° (of course, the quoted error cannot account for the additional uncertainty due to the approximations intrinsic to the formula employed). The value, however, is quite reasonable as this angle is indeed expected to be larger in **1a** than those (40−55°) reported in the literature,[7,8] since the 1-naphthyl is bulkier than the phenyl moiety of the benzylideneanilines investigated by X-ray[7] and electron diffraction[8] (the 1-naphthyl group can be regarded as an *ortho*-substituted phenyl moiety). On the contrary, the *Z* structure of **1a** has the r_1/r_2 ratio essentially independent of the torsion angle ϑ, its value always being 0.60. Clearly, the isomer *Z* of **1a** cannot match the experimental value ($r_1/r_2 = 0.89 \pm 0.04$), whichever conformation is considered, thus proving that the assignment of the *E* structure to **1a** is indeed correct. It is also worth mentioning that the MM calculations[14] predict the same assignment (*E*-isomer) to the more stable of the two isomers of **1a**, as experimentally observed.

In **1d** (R = Pr^i) two equally intense NMR signals were obviously observed for the isopropyl groups, and in all cases (**1a**−**1e**), the shifts of the isopropyl methyl hydrogens in $CDCl_3$ never exceed the ranges 1.32 ± 0.04 or 0.95 ± 0.02 ppm, respectively, for the positions *anti* or *syn* to the naphthalene ring.[15] The shift to higher field for the *syn* position (as assessed by the NOE experiment in **1a**) is a consequence of the ring current effects[16] exerted by the π-electrons upon the protons directly facing an aromatic ring, as expected for a situation *syn* of this type. Since the ^{1}H shifts of the isopropyl methyl groups are essentially independent of the other substituents in the molecule (i.e., always equal either to 1.32 or to 0.95 ppm, as mentioned above) they can be safely used to distinguish the *E* from the *Z* isomer. In **1b** (R = Me) the isomer ratio is 88/12 (in $CDCl_3$ at room temperature), and from the mentioned chemical shift values (see Experimental Section) the assignment of the *E* structure to the more stable isomer is straightforward. In **1c** (R = Et) the ratio is 65/35 in favor of the *E* form whereas in **1e** (R = Bu^t) only a single isomer (*E*) was observed.

By warming the sample above room temperature the two *syn, anti* aliphatic signals of **1b**−**1d** broaden and eventually coalesce in a reversible manner. A typical example is offered by the ^{1}H isopropyl methyl signals of **1d**, reported in Figure 2 with the corresponding computer line shape simulation (the spectrum was decoupled at the frequency of the methine proton to eliminate the splitting due to the coupling between CH an CH_3). The computed rate constants (k in s^{-1}) allowed the determination of the $\Delta G^{\ddagger}$ values at various temperatures. In **1d** it was also found that the activation entropy was not significantly different from zero ($\Delta S^{\ddagger} = -5 \pm 5$ eu); thus, the average of the $\Delta G^{\ddagger}$ values was taken as a reliable measurement of the barrier (the same situation was assumed to hold also in **1c** and **1b**). The free energy of activation measured in this way is that required to thermally convert the more stable into the less stable isomer (in **1d** of course we are dealing with a degenerate isomerization, often called topomerization[17]). Mechanisms other than direct thermal interconversion were excluded on the basis of the following experiments carried out on **1d** as a test sample:

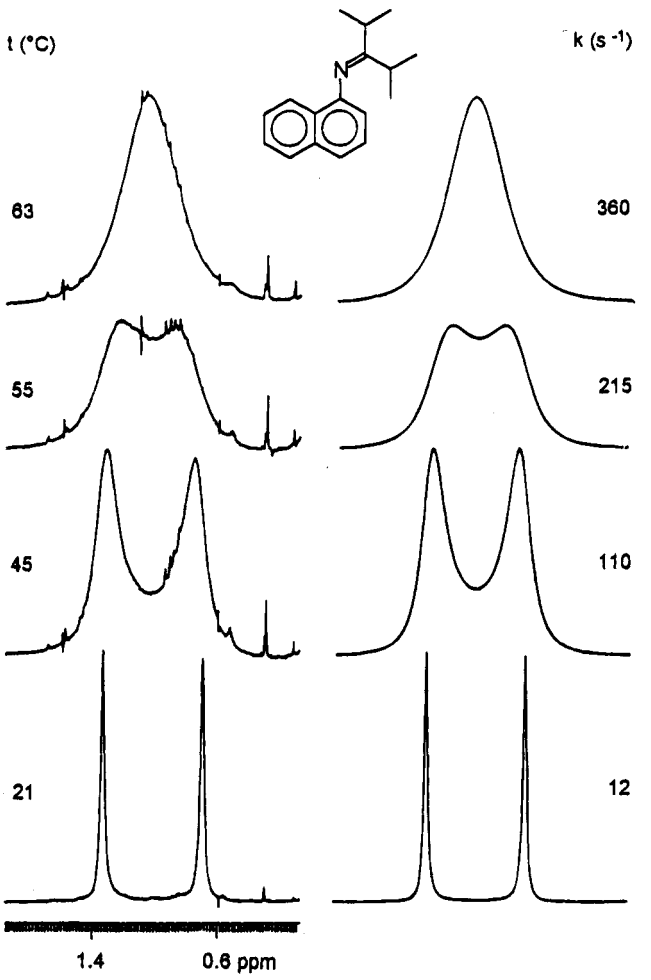

Figure 2. Temperature dependence (left) of the 200 MHz signals of the isopropyl methyl groups of **1d** (decoupled at the frequency of the corresponding methine protons) in C_6D_6. On the right is displayed the computer simulation obtained with the rate constants (k, s^{-1}) corresponding to the E,Z topomerisation process.

(i) The rates of the exchange were found independent of the concentration.

(ii) Use of NMR tubes sealed *in vacuo* and containing BaO to eliminate possible traces of acid[18] did not affect the rate of the process.

(iii) Addition of catalytic amounts of acetic acid did not result in any appreciable effect.[19]

(iv) Warming the sample in CD_3OD as solvent did not reveal any H/D exchange, thus ruling out the possibility

(14) The MMX force field as implemented in the program PC Model, Serena Software, Bloomington, IN, was employed. See also: Gajewski, J. J.; Gilbert, K. K.; Mc Kelvey, J. In *Advances in Molecular Modelling*; JAI Press: Greenwich, 1990; Vol. 2.

(15) The separation of these signals (62−86 Hz in $CDCl_3$ at 200 MHz, see Experimental Section) becomes much larger in C_6D_6 (Table 1), a feature which allowed the *E,Z* exchange to be follwed in a wider temperature range in this solvent.

(16) (16) Haigh, C. W.; Mallion, R. B. *Progr. Nucl. Magn. Reson. Spectrosc.* **1980**, *13*, 303.

(17) Eliel, E. E.; Wilen S. H. *Stereochemistry of Organic Compounds*; J. Wiley and Sons: New York, 1994; p 1210.

(18) (a) Lunazzi, L.; Panciera, G.; Guerra, M. *J. Chem. Soc., Perkin Trans. 2* **1980**, 52. (b) Lunazzi, L.; Parisi, F.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1025. (c) Anet, F. A. L.; Ji, X. *Tetrahedron Lett.* **1984**, *25*, 1419.

(19) Acid-catalyzed interconversion was, on the contrary, observed in *N*-alkylimines such as 4-$NO_2C_6H_4$-(Ph)C=NMe (Jennings, W. B.; Al-Showiman,S.; Tolley, M. S.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1535.).

Table 1. *E/Z* Isomer Ratios and Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Interconversion of the *E*- into the *Z*-Isomer in 1b−1d and 2

compd	*E/Z* ratio	$\Delta G^{\ddagger}$	monitored signal	solvent	$\Delta\nu^a$ (Hz)	temp (°C)
1b	92:8	19.0	MeC=N (^{1}H)	C_2Cl_4	107	25
1c	65:35	16.8	Me_2 (^{1}H)	C_6D_6	120	22
1d	50:50	15.8[b]	Me_2 (^{1}H)	C_6D_6	128	20
		15.8[b]	Me_2 (^{13}C)	C_2Cl_4	156	20
2	50:50	9.5[b]	Me_3 (^{1}H)	CD_2Cl_2	91[c]	−95
		9.7[b]	Me_3 (^{1}H)	toluene-d_8	138[c]	−95

[a] Chemical shift differences measured at the temperatures indicated for **1b-1d** at 200 or 50 MHz for ^{1}H and ^{13}C respectively. [b] Degenerate isomerization (topomerization). [c] At 300 MHz.

of a mechanism involving tautomerization to enamines.[2,20]

Therefore, either a C=N rotation or a sp^2 N-inversion are left as the only possible ways to achieve *E,Z* interconversion. The barriers reported in Table 1 decrease significantly with the increasing dimension of the substituent R in **1b−1d**, the $\Delta G^{\ddagger}$ values being 19.0, 16.8, and 15.8 kcal mol^{-1} for R = Me, Et, and Pr^i, respectively. In the very hindered imine **2**, where both substituents to N=C carbon are *tert*-butyl groups, the value becomes so low (9.5 kcal mol^{-1} in CD_2Cl_2) as to be observable only at very low temperatures (between −95° and −70°): such a steric acceleration is not unexpected for a N-inversion process.[2,21]

Having established, by the mentioned NOE experiment, that even the less hindered (**1a**, *E*-isomer) of these naphthylimines is not planar, we should be able to detect also a second dynamic process due to the restricted rotation about the N−C1 single bond joining the naphthyl and the imino moieties. For, when the motion becomes slow the molecule loses its dynamic plane of symmetry yielding, as a consequence, a pair of enantiomeric conformers (atropisomers). The methyl groups of the prochiral isopropyl substituent will thus become diastereotopic, and their NMR signals can be used to determine the barrier to the enantiomerization. Not even at −140 °C was such an effect observed in **1a** (R = H), since the rotational barrier of its *E* structure (the isomer *Z* was not observed) is too low for NMR detection, owing to small steric effects. On the other hand, the *Z* isomer of **1b** (R = Me) displayed a pair of NMR signals for the isopropyl methyl protons at −100 °C. The rate constant (line shape simulation) yielded a $\Delta G^{\ddagger}$ value (10.0 kcal mol^{-1}) much lower than that (19.0 kcal mol^{-1}) for the interconversion of *E* into *Z*. As observed in **1a**, the less hindered *E*-isomer of **1b** (contrary to its corresponding *Z*-isomer) also does not display diastereotopic signals, whereas both isomers of **1c** (R = Et) yield, at −120 °C, a pair of ^{13}C lines for the isopropyl methyl groups (Figure 3). The corresponding enantiomerization barrier for **1c-*Z*** is higher (9.9 kcal mol^{-1}) than that (8.4 kcal mol^{-1}) of **1c-*E***. This agrees well with the structural assignment in that the enantiomerization is expected to be faster for the isomer *E*, which has the naphthyl *syn* to the ethyl group (and *anti* to the bulkier isopropyl group), than for isomer *Z* where the bulkier isopropyl group occupies the

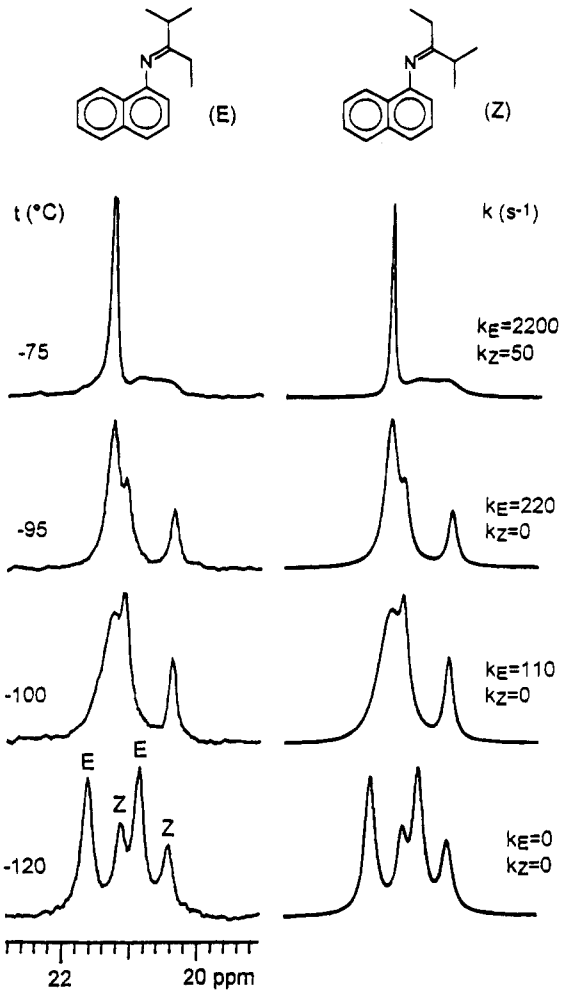

Figure 3. On the left are shown the ^{13}C signals (50.3 MHz) of the isopropyl methyl groups of **1c** in CHF_2Cl as function of temperature. The two signals with lower intensity are those of the *Z*-isomer, those with higher intensity are those of the *E*-isomer. On the right are shown the computer simulations obtained with the rate constants (in s^{-1}) corresponding to the enantiomerisation process (k_Z for the isomer *Z*, k_E for the isomer *E*).

Table 2. Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Enantiomerization Process Obtained by Monitoring the Diastereotopic Isopropyl Methyl Signals of 1b−1e

compd	$\Delta G^{\ddagger}$	$\Delta\nu^a$ (Hz)	temp (°C)
1b, *Z*	10.0	40 (^{1}H)	−100
1c, *E*	8.4	37 (^{13}C)	−120
1c, *Z*	9.9	35 (^{13}C)	−120
1d	10.4	13 (^{13}C);[b] 35 (^{13}C)[c]	−110
	10.5	50 (^{1}H)[c,d]	−100
1e, *E*	10.8	148 (^{1}H); 192 (^{13}C)	−70
2	9.8	50 (^{1}H)[d,e]	−95

[a] Chemical shift differences measured at the temperatures indicated in CHF_2Cl (**1b−1d**) or in CD_2Cl_2 (**1e**) at 200 or 50 MHz for ^{1}H and ^{13}C, respectively. [b] Downfield isopropyl group. [c] Upfield isopropyl group. [d] At 300 MHz. [e] Separation (in CD_2Cl_2) of the signals due to the *R,S* enantiomers of the *tert*-butyl methyl groups in position *syn* to the naphthalene moiety in the presence of a 80:1 molar excess of a Pirkle's alcohol (see text).

position *syn*. Barriers similar to those of **1b-*Z*** and **1c-*Z*** were found also for **1d** and **1e** (the latter only exists as the *E*-isomer). These values cover a quite narrow range (9.9−10.8 kcal mol^{-1}), and their similarity (Table 2) is a consequence of the isopropyl group being *syn* to the naphthalene moiety in all the four compounds, so that

(20) In the same conditions H/D substitution was, on the contrary, observed in *N*-alkyl imines such as 1-naphthyl-C(Me)=NR (*Z*-isomer), R being Me or Pr^i (Jennings, W. B.; Boyd, D. R. *J. Am. Chem. Soc.* **1972**, *94*, 7188).

(21) It should be stressed, however, that, in principle, a rotational process might also entail a steric acceleration effect, due to ground state destabilization.[2]

analogous steric effects for the naphthyl–nitrogen rotation are experienced in each case.

In the much hindered imine **2**, as mentioned, the exchange between the *E* and *Z* positions (topomerization) has a $\Delta G^{\ddagger}$ value (9.5 kcal mol^{-1}) which is the lowest ever reported[2] for an imine with a =N–C single bond and it is as low as that for the imine having a =N–Ge bond (9.2 kcal mol^{-1}).[22] Such a circumstance affords the opportunity of carrying on an experimental test, which would allow a discrimination between the N-inversion and N=C rotation pathways. For, if the enantiomerization occurred in **2** *via* a naphthyl–nitrogen rotation, as in **1b–1e**, the corresponding barrier should be much higher than that (10.8 kcal mol^{-1}) measured for **1e** (*E*-isomer) since the *tert*-butyl group *syn* to the naphthalene moiety would restrict the rotation much more than the isopropyl group in the same position. Of course, in **2** such a process cannot be monitored in achiral solvents, contrary to the cases of **1b–1e,** due to the absence of prochiral probes. However, the use of a chiral solvating agent (CSA) would provide distinguishable NMR signals for the *R* and *S* conformational enantiomers. Thus, whereas at −95 °C (in CD_2Cl_2) the ^{1}H spectrum of **2** displays only a pair of signals for the *syn* and *anti tert*-butyl groups, addition of an enantiomerically pure Pirkle's alcohol[23] further splits into two the upfield *tert*-butyl signal (the analogous splitting expected for the downfield signal was not observed either because of an accidental degeneracy within the relatively broad line width at such a low temperature or because of a negligible effect of the CSA upon this line). The signal additionally split in the presence of the CSA corresponds to that of the *tert*-butyl *syn* to the naphthalene moiety which is shifted upfield,[24] with respect to its *anti* companion, by the mentioned ring current effects.[16] If the three spectral lines with a 2:1:1 relative intensities are labeled *a*, *b*, *c* (the corresponding shifts at −95 °C being 1.44, 1.09, and 0.92 ppm, respectively, as shown in Figure 4) the line shape simulation in the exchange region (see, for instance, the spectrum at −75 °C in Figure 4) could only be obtained with rate constants $k_{bc} = 0$ and $k_{ab} = k_{ac}$. Any attempt to use k_{bc} values different from zero resulted into unacceptable simulations. This proves that the *syn tert*-butyl of the enantiomer *R* does not exchange directly with the *syn tert*-butyl group of the enantiomer *S* and *vice versa*: this exchange occurs *solely* through the intermediacy of the *tert*-butyl in position *anti*. In other words, the direct enantiomerization, which in **1b–1e** was achieved by virtue of naphthyl–nitrogen rotation, does not occur anymore in **2**, as now a different enantiomerization pathway with a *lower* activation energy has become available to the molecule.[25] This pathway is the same by which the topomerization occurs, in that the line *a* exchanges with the lines *b* and *c* essentially with the same activation energy as that of the two unsplit lines in the *syn* and *anti tert*-butyl groups of **2** in the absence

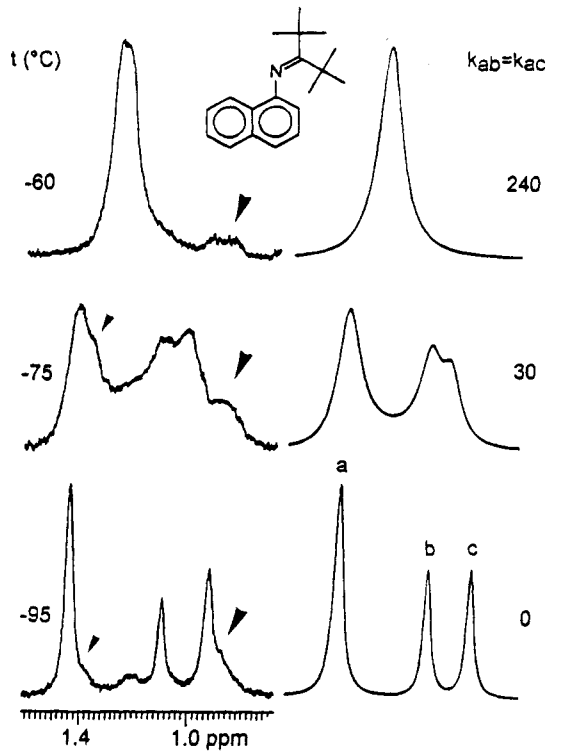

Figure 4. Experimental (left) ^{1}H signals (300 MHz) of the *tert*-butyl methyl groups of **2** in CD_2Cl_2 at various temperatures in the presence of a 80:1 molar excess of a chiral solvating agent. At −95 °C the upfield signal of the *tert*-butyl *syn* to naphthalene is split into two lines (*b* and *c*) due to the *R* and *S* enantiomers. The simulation (right) indicates that the lines *b* and *c* do not exchange directly (k_{bc} is *always* 0) but only through the intermediacy of line *a* ($k_{ab} = k_{ac}$, s^{-1}, see text). The signals indicated by the arrows are due to impurities.

of the chiral solvating agent.[26] Of the two possible pathways (C=N rotation and N-inversion) only N-inversion allows us to achieve, *simultaneously*, both the exchange of the conformational enantiomers and of the positions *syn*,*anti* of the *tert*-butyl groups (topomerization). On the contrary, rotation about the C=N double bond cannot interconvert (as can N-inversion) the *R* and *S* conformational enantiomers. As a consequence, they should still be detectable above −70 °C,[25] even in the presence of a fast topomerization process: a result in obvious contrast with the experimental observation. In Figure 5, the enantiomerization pathway occurring *via* naphthyl–nitrogen rotation for **1d** (top) and *via* trigonal N-inversion for **2** (bottom) is illustrated (these molecules are drawn in Figure 5 with a 85° twisting angle in their ground state, as a result of MM calculations:[14] these

(22) Cook, R. J.; Mislow, K. *J. Am. Chem. Soc.* **1971**, *93*, 6703. Such a low $\Delta G^{\ddagger}$ value is indicative of a N-inversion process, although Cook and Mislow pointed out that an alternative mechanism (C=N rotation) could not be rigorously excluded on the basis of that finding.

(23) A molar excess (~80:1) of (*S*)-*d*-2,2,2-trifluoro-1-(9-anthryl)-ethanol was employed (Pirkle, V. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837).

(24) This assignment was confirmed by a NOE experiment carried out on **2** at −95 °C in CD_2Cl_2 at 300 MHz. Irradiation of the upfield line of the *tert*-butyl methyl groups (*syn* to naphthalene) enhanced the H-2 and H-8 naphthalene signals (3.8% and 2.5%, respectively), whereas irradiation of the downfield line of the *tert*-butyl methyl groups (*anti* to naphthalene) *did not* enhance any signals of the naphthalene moiety.

(25) It should be recalled once more that the naphthyl–nitrogen rotation in **2** should have had an activation energy much higher than the value of 10.8 kcal mol^{-1} found in **1e** for the *E*-isomer (which at −70 °C displays two sharp doublets for the two diastereotopic isopropyl methyl groups): a *tert*-butyl is in fact a much bulkier substituent than an isopropyl group.

(26) The fact that the $\Delta G^{\ddagger}$ in the presence of CSA (which was computed with a $k = k_{ab} + k_{ac}$ to account for the mutual exchange of both enantiomers) is slightly higher than in its absence (i.e., 9.8 vs 9.5 kcal mol^{-1} in CD_2Cl_2) is due to the effects of the Pirkle's alcohol. The presence of an alcohol is known, in fact, to *enhance* the barriers involving N-inversion processes.[27] Indeed, the $\Delta G^{\ddagger}$ value for **2** measured in CD_2Cl_2 but in the presence of the *racemic* version of the same Pirkle's alcohol (which does not discriminate the *R*,*S* atropisomers, thus yielding only two *tert*-butyl signals at low temperature) becomes essentially the same (i.e., 9.7 kcal mol^{-1}).

(27) (a) Drakenberg, T.; Lehn, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 532. (b) Casarini, D.; Davalli, S.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1989**, *54*, 4616.

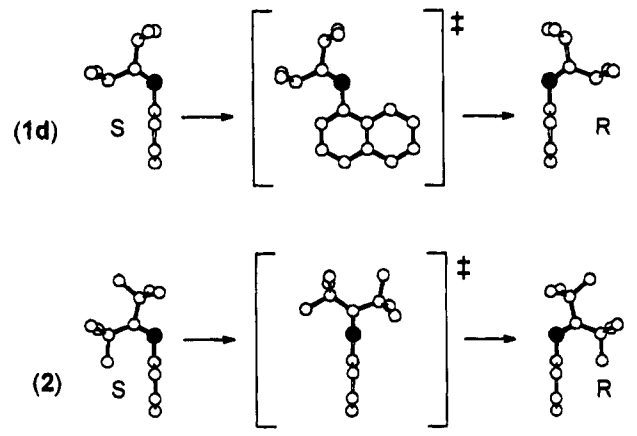

Figure 5. Top: schematic representation of the mechanism for the direct *S,R* enantiomerization of **1d**, which occurs *via* rotation about the naphthyl–nitrogen bond. Bottom: schematic representation of the mechanism for the *S,R* interconversion of **2** which occurs *via* a concomitant exchange of the *E* and *Z* positions of the *tert*-butyl groups (inversion of the trigonal nitrogen).

computed values seem quite reasonable since these imines are much more hindered than the *E*-isomer of **1a**, where a 65 ± 6° dihedral angle was estimated on the basis of a NOE experiment).

The present interpretation of the motion of **2** is essentially analogous to that discussed by Kessler and co-workers[28] for a guanidine derivative, although in that case it was not necessary, as in the present one, to resort to a chiral environment.

Conclusions

The prediction of possible conformational enantiomers due to the presence of a stereogenic naphthyl–nitrogen chiral axis has been verified in a number of *N*-naphthylimines and the related enantiomerization barriers measured by taking advantage of the diastereotopic methyl groups of a prochiral probe (isopropyl group). In only one case (compound **1c**) were these enantiomers observed in both *E*- and *Z*-isomers, and the two corresponding enantiomerization barriers were found to differ by about 1.5 kcal mol^{-1}. The analysis of the *R,S* enantiomerization and of the *E,Z* interconversion processes in a quite hindered imine (**2**) allowed us to reach the conclusion that the *E,Z* exchange must occur *via* inversion of the trigonal N-atom (lateral shift). This experiment, which was achieved by simulating the line shape of the low-temperature NMR spectra of **2** in the presence of a chiral solvating agent, provides a further proof of the occurrence of the N-inversion process in imines.

Experimental Section

Materials. Compounds **1a**–**1e** and **2** were prepared according to the general procedure of the literature,[29] using the method employing titanium tetrachloride. The analytical data are as follows:

Isobutylidenenaphthalen-1-ylamine (1a): ^{1}H NMR ($CDCl_3$) d 1.28 (d, 6H, J = 7.0 Hz, $(CH_3)_2CH$), 2.75 (two sept, 1H, J = 7.0, 4.5 Hz, $CH(CH_3)_2$), 6.83 (dd, 1H, J = 1.2, 7.2 Hz, H-2), 7.38 (dd, 1H, J = 7.2, 8.3 Hz, H-3), 7.83 (d, 1H, J = 4.5 Hz, N=C*H*), 7.1–8.2 (5H Ar); ^{13}C NMR ($CDCl_3$) d 19.25 ($(CH_3)_2$-CH), 34.98 ($(CH_3)_2CH$), 171.32 (*C*=N); mass spectrum *m/e* calcd for $C_{14}H_{15}N$ 197.1204, found 197.1201. Anal. Calcd for $C_{14}H_{15}N$: H, 7.66; C, 85.24; N, 7.10. Found: H, 7.72; C, 85.45; N, 7.01.

(1,2-Dimethylpropylidene)naphthalen-1-ylamine (1b): ^{1}H NMR ($CDCl_3$) isomer *E* 1.32 (d, 6H, J = 6.9 Hz, $(CH_3)_2CH$), 1.71 (s, 3H, CH_3), 2.78 (sept, 1H, J = 6.9 Hz, $(CH_3)_2CH$), 6.69 (dd, 1H, J = 1.2 Hz and 7.2 Hz, H-2), 7.26–7.85 (6H, Ar); isomer *Z* δ 0.98 (d, 6H, J = 6.9 Hz, $(CH_3)_2CH$), 2.24 (s, 3H, CH_3), 2.56 (sept, 1H, J = 6.9 Hz, $(CH_3)_2CH$), 6.76 (dd, 1H, J = 2.4 Hz and 6.1 Hz, H-2), 7.26–7.85 (6H, Ar); ^{13}C NMR ($CDCl_3$) isomer *E* 18.11 (CH_3), 20.62 ($(CH_3)_2CH$), 39.78 ($(CH_3)_2CH$), 114.02, 123.33, 123.62, 125.73, 126.41, 126.45, 128.45 (*C*H Ar), 134.65, 148.39 (*C* quat Ar), 178.08 (*C*=N); isomer Z δ 21.14 (CH_3), 33.04 ($(CH_3)_2CH$)); mass spectrum *m/e* calcd for $C_{15}H_{17}N$ 211.1361; found 211.1365. Anal. Calcd for $C_{15}H_{17}N$: H, 8.11; C, 85.26; N, 6.63. Found: H, 7.98; C, 85.33; N, 6.75.

(1-Ethyl-2-methylpropylidene)naphthalen-1-ylamine (1c): ^{1}H NMR ($CDCl_3$) isomer *E* 0.89 (t, 3H, J = 7.7 Hz, CH_3CH_2), 1.33 (d, 6H, J = 6.9 Hz, $(CH_3)_2CH$), 2.10 (q, 2H, J = 7.7 Hz, CH_2CH_3), 2.82 (sept, 1H, J = 6.9 Hz, $CH(CH_3)_2$), 6.66 (1H, H-2), 7.29–7.83 (6H, Ar); isomer *Z* δ 0.95 (d, 6H, J = 6.9 Hz, $(CH_3)_2CH$), 1.34 (t, 3H, J = 7.3 Hz, CH_3 CH_2), 2.51 (q, 2H, J = 7.3 Hz, CH_2 CH_3), 2.62 (m, 1H, J = 6.9 Hz, $CH(CH_3)_2$), 6.66 (1H, H-2), 7.29–7.83 (6H, Ar); ^{13}C NMR ($CDCl_3$) isomer *E* δ 12.47 (CH_3CH_2), 21.36 ($(CH_3)_2CH$), 26.38 (CH_3CH_2), 36.32 ($(CH_3)_2CH$), 113.80, 123.19, 123.84, 125.75, 128.48 (*C*H Ar), 134.74, 148.35 (*C* quat Ar), 182.19 (*C*=N); isomer *Z* δ 11.61 (CH_3CH_2), 20.71 ($(CH_3)_2CH$), 26.05 (CH_3CH_2), 33.20 ($(CH_3)_2CH$), 113.69, 123.08, 123.96 (*C*H Ar), 181.32 (*C*=N); mass spectrum *m/e* calcd for $C_{16}H_{19}N$ 225.1517, found 225.1512. Anal. Calcd for $C_{16}H_{19}N$: H, 8.50; C, 85.29; N, 6.22. Found: H, 8.59; C, 85.41; N, 6.12.

(1-Isopropyl-2-methylpropylidene)naphthalen-1-ylamine (1d): ^{1}H NMR ($CDCl_3$) δ 0.99 (d, 6H, J = 6.7 Hz, $(CH_3)_2CH$ *syn*), 1.36 (d, 6H, J = 6.7 Hz, $(CH_3)_2CH$ *anti*), 2.63 (m, 1H, J = 6.7 Hz, $(CH_3)_2CH$ *syn*), 2.91 (m, 1H, J = 6.7 Hz, $(CH_3)_2CH$ *anti*), 6.62 (dd, 1H, J = 1.2 Hz and 7.2 Hz, H-2), 7.32–7.82 (6H, Ar); ^{13}C NMR ($CDCl_3$) d 19.82, 22.78 ($(CH_3)_2$-CH), 30.43, 33.17 ($(CH_3)_2CH$, 112.94, 122.54, 123.37, 125.22, 125.93, 126.03, 127.94 (*C*H Ar), 126.06, 134.21, 147.75 (*C* quat Ar), 185.11 (*C*=N); mass spectrum *m/e* calcd for $C_{17}H_{21}N$ 239.1674, found 239.1670. Anal. Calcd for $C_{17}H_{21}N$: H, 8.84; C, 85.31; N, 5.85. Found: H, 8.72; C, 85.20; N, 5.71.

(1-*tert*-Butyl-2-methylpropylidene)naphthalen-1-ylamine (1e): ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6H, J = 7.2 Hz, $(CH_3)_2CH$), 1.35 (s, 9H, $(CH_3)_3C$), 3.03 (sept, 1H, J = 7.2 Hz, $(CH_3)_2CH$), 6.69 (dd, 1H, J = 1.2 Hz and 7.1 Hz, H-2), 7.25–7.81 (6H, Ar); ^{13}C NMR ($CDCl_3$) d 21.97 ($(CH_3)_2CH$), 29.02 ($(CH_3)_3C$), 33.34 ($(CH_3)_2CH$), 42.98 ($(CH_3)_3C$), 112.87, 122.04, 124.33, 125.37, 125.97, 126.26, 128.26 (*C*H Ar), 125.75, 134.41, 148.08 (*C* quat. Ar), 183.15 (*C*=N); mass spectrum *m/e* calcd for $C_{18}H_{23}N$ 253.1830, found 253.1828. Anal. Calcd for $C_{18}H_{23}N$: H, 9.15; C, 85.32; N, 5.53. Found: H, 9.03; C, 85.44; N, 5.65.

(1-*tert*-Butyl-2,2-dimethylpropylidene)naphthalen-1-ylamine (2): ^{1}H NMR ($CDCl_3$) d 1.30 (s, 18H, $(CH_3)_3C$), 6.50 (dd, 1H, J = 2.3 Hz and 6.1 Hz, H-2), 7.30–7.78 (6H, Ar); ^{13}C NMR ($CDCl_3$) d 31.20 ($(CH_3)_3C$), 44.09 ($(CH_3)_3C$), 108.78, 119.77, 123.97, 124.65, 125.77, 125.87, 127.76 (*C*H Ar), 123.68, 134.08, 148.28 (*C* quat. Ar), 179.64 (*C*=N); mass spectrum *m/e* calcd for $C_{19}H_{25}N$ 267.1987, found 267.1982. Anal. Calcd for $C_{19}H_{25}N$: H, 9.42; C, 85.34; N, 5.24. Found: H, 9.55; C, 85.25; N, 5.37.

NMR Measurements. The variable temperature NMR spectra in solution were recorded either at 200 or 300 MHz for ^{1}H and at 50.3 or 75.5 MHz for ^{13}C: the temperature within the probe was calibrated as described in ref 30. The computer simulations of the line shape was performed with a two sites

(28) By taking advantage of the presence of prochiral isopropyl groups in the ortho positions of the *N*-phenyl moiety, Kessler and co-workers showed that in an appropriately symmetric guanidine the enantiotopomerization rate is the same as the *syn-anti* topomerization rate and thus concluded that the sp^2 nitrogen atom of that molecule undergoes a N-inversion process (lateral shift): Kessler, H.; Leibfritiz, D. *Tetrahedron Lett.* **1970**, *17*, 1423; *Chem. Ber.* **1971**, *104*, 2143. See also: Kalinowski, H.-O.; Kessler, H. *Top. Stereochem.* **1973**, *7*, 295.

(29) Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246.

exchange program[30] based on the Bloch equations, and the best fit was visually judged by superimposing the plotted and the experimental traces. When using CHF_2Cl as a solvent the samples were prepared by connecting the NMR tubes, containing a C_6D_6 solution of the compounds, to a vacuum line and condensing the gaseous CHF_2Cl with liquid nitrogen. The tubes were then sealed *in vacuo* and introduced in the precooled probe of the spectrometer.

The difference NOE measurements of **1a** were carried out in C_6D_6 solutions (previously purged from dissolved oxygen with a flux of nitrogen) by presaturating the signals for about 30 s and acquiring the spectra with the decoupler turned off. The irradiated lines were saturated by cycling the irradiation frequencies about 50 times. A program that accumulates the difference between the two FID's (that being irradiated and that acquired with the irradiation frequency kept away from any signal) was employed. Usually, 256 scans were accumulated at constant temperature (24 °C); the control spectrum was subsequently acquired with half the number of scans.

(30) (a) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839. (b) Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1986**, *51*, 517.

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