# **Conformational Studies by Dynamic NMR. 84.<sup>1</sup> Structure,** Conformation, and Stereodynamics of the Atropisomers of **N-Aryl-tetrahydropyrimidines**

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The existence of stereolabile atropisomers for a number of N-aryl-tetrahydropyrimidines in solution has been deduced from the observation of the anisochronous NMR signals of prochiral methylene groups. The interconversion barriers for these atropisomers have been measured by line shape analysis of dynamic NMR spectra at various temperatures: a Molecular Mechanics modeling resulted in good agreement with these values. In an appropriate case, distinct NMR signals for the two enantiomeric forms could be observed at ambient temperature in a chiral environment. Evidence was also obtained for an exchange process occurring between two conformers experiencing a very biased equilibrium. Single-crystal X-ray diffraction of one such compound yielded a molecular structure in good agreement with the results obtained by ab initio calculations.

### Introduction

Diversely substituted tetrahydropyrimidines have interesting biological activity<sup>3-5</sup> and pharmacological properties, acting as anthelmintics,<sup>6</sup> antidepressants,<sup>7</sup> and fungicides,<sup>8</sup> among others. In this context a number of yet unknown N-aryl-substituted tetrahydropyrimidines have been prepared, and the related stereochemical properties investigated here.

In particular, hindered N-aryl-tetrahydropyrimidines such as 1-3 are expected to have the plane of the orthosubstituted phenyl ring significantly twisted with respect to the time-averaged dynamic plane of the six-membered pyrimidine ring. The existence of such an Ar-N stereogenic axis would originate, in principle, a pair of stereolabile enantiomeric forms (atropisomers) if the corresponding rotation rate is rendered sufficiently slow.



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## **Results and Discussion**

Ab initio calculations (RHF 3-21G\* method<sup>9</sup>) applied to the *o*-chloro derivative **1** indicate indeed that the  $C_{2'}$ - $C_{1'}-N_1-C_6$  dihedral angle has a value of 72°, thus entailing the existence of two enantiomeric forms: in Figure 1 the computed structures predicted for this pair of enantiomers are displayed. A single-crystal X-ray diffraction of 1 confirms the theoretical results, in that shows that two of the four molecules within the crystal cell are the antipodes of the other two. The geometrical parameters determined in the solid state are quite similar to those computed for the isolated molecule, in particular the mentioned dihedral angle has a very similar value (71.1°). The experimental X-ray structures of the antipodes of **1** are also displayed in Figure 1.

Whereas in the crystalline state the internal molecular motions are frozen, so that the mentioned atropisomers can be regarded as stable species, this is not the case in solution where the internal motions happen to be quite rapid. For this reason the existence of the atropisomers of 1 in solution can be inferred by investigating the NMR spectra at a temperature sufficiently low as to make the rate of the enantiomerization process, brought about by the rotation about the Ar–N stereogenic axis, negligible. Although the NMR spectra of a pair of enantiomers are indistinguishable, the presence of prochiral probes allows one to detect the asymmetry of the molecule.<sup>10</sup> In the present case the two hydrogens of each methylene moiety

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<sup>(9)</sup> Computer package Spartan Pro 1.1

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**Figure 1.** Ab initio computed structures of the atropisomers of **1** (top). Underneath are reported the experimental structures as obtained by X-ray diffraction.

are enantiotopic (and the corresponding NMR signals accordingly isochronous) when the enantiomerization process, responsible for the time averaged symmetry ( $C_s$ point group), is fast in the NMR time-scale. These hydrogens become, however, diastereotopic, and the corresponding signals consequently anisochronous, when this process becomes sufficiently slow: in these conditions the molecule appears in fact asymmetric ( $C_1$  point group), thus chiral. To simplify the pattern of the <sup>1</sup>H NMR spectrum in the methylene region, the signals of the CH<sub>2</sub> in position 5 of compound 1 were saturated, making the pairs of hydrogens within the CH<sub>2</sub> moieties in positions 4 and 6 to yield each a single line when enantiotopic (e.g., at +80 °C, as in Figure 2). On the other hand, when the spectrum is recorded at lower temperature (e.g., at -9°C as in Figure 2) these hydrogens appear diastereotopic, each pair yielding the typical four-line pattern of an ABtype system. At intermediate temperatures the lines are broadened by the enantiomerization process which exchanges the relative positions of the methylene hydrogens, the corresponding rates can be therefore obtained by computer simulation<sup>11</sup> (Figure 2, right).

From these data a free energy of activation of 15.0 kcal  $mol^{-1}$  is obtained for the interconversion of the stereolabile atropisomers of  $1.^{12}$  This value corresponds satisfactorily to the barrier of 13.5 kcal  $mol^{-1}$  computed by Molecular Mechanics<sup>13</sup> for the rotation process of the



**Figure 2.** 300 MHz <sup>1</sup>H experimental signals (left) of the CH<sub>2</sub> hydrogens of **1** in positions 4 and 6 monitored at various temperatures in toluene- $d_8$  whereas decoupling at the frequency of CH<sub>2</sub> in position 5. On the right are reported the traces simulated with the rate constants indicated.

o-chloro phenyl group in 1, thus confirming that this motion is responsible for the observed enantiomerization. In Figure 3 the three-dimensional energy surface, computed as a function of the rotation angles about the Ar-N and the Ph–C axes ( $\theta$  and  $\varphi$ , respectively), is displayed: the full line represents the pathway required for the interconversion of the stereolabile atropisomers. These calculations show how the saddle point corresponding to the rotation transition state of 13.5 kcal mol<sup>-1</sup> describes the situation where the chlorine atom crosses over the CH<sub>2</sub> moiety in position 6. The other possible transition state, where the chlorine atom crosses over the phenylbonded trigonal carbon in position 2, has an energy 2 kcal mol<sup>-1</sup> higher. Although this computed difference is not very large and might be due, at least in part, to the approximations of the theoretical model employed, it does not seem unreasonable to conclude that the enantiomerization of the atropisomers of 1 is more likely to occur through the former of these two pathways, due to the inferior energy of its saddle point.

Analogous results were obtained in the case of **2** (X = NO<sub>2</sub>) and **3** (X = Me), the measured enantiomerization barriers being lower for the nitro derivative **2** (14.2 kcal mol<sup>-1</sup>) and higher for the methyl derivative **3** (16.6 kcal mol<sup>-1</sup>). The experimental  $\Delta G^{\ddagger}$  values (Table 1) follow the same trend of the effective van der Waals radii of the substituents, i.e., 1.73, 1.61, and 1.80 Å for the chlorine, nitro, and methyl groups, respectively.<sup>14</sup> This suggests

<sup>(11)</sup> PC version of the DNMR 6 computer program QCPE 663, Indiana University, Bloomington, IN.

<sup>(12)</sup> As often observed in conformational processes, the  $\Delta G^{\ddagger}$  value is independent of temperature within the experimental errors, indicating a negligible value for  $\Delta S^{\ddagger}$ . See: Lunazzi, L.; Macciantelli, D.; Grossi, L. *Tetrahedron* **1983**, *39*, 305. Anderson, J. E.; Tocher, D. A.; Casarini, D., Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731. Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. J. Org. Chem. **1997**, *62*, 4924.

<sup>(13)</sup> Since an ab initio modeling of the energy surface for a relatively large molecule like **1** would be quite time-consuming and considerably expensive, the MMX force field (Computer package PC Model, Serena Software, Bloomington, IN) was employed for calculating the barriers corresponding to the interconversion pathways of Figure 3.

## Atropisomers of N-Aryl-tetrahydropyrimidines



**Figure 3.** Energy surface of derivative **1** computed (Molecular Mechanics) as a function of the rotation angles  $\theta$  and  $\varphi$ . The full line represents the pathway for interconverting the atropisomers, the dotted line the pathway for the topomerisation process (phenyl ring rotation). The scale of the energy values is in kcal mol<sup>-1</sup>.

Table 1. Experimental  $\Delta G^{\ddagger}$  Values (kcal mol<sup>-1</sup>) for the<br/>Dynamic Processes Occurring in Compounds 1–4

compd	enantiomerization	topomerization	ring inversion
1	15.0	6.9	7.0
2	14.2	7.6	7.3
3	16.6	6.8	6.7
4	16.6	-	6.0

that the interconversion rates of the atropisomers of 1-3 mainly depend on the steric hindrance of the *ortho* substituents.

In the case of **3** (X = Me) the enantiomerization barrier is high enough as to allow the direct detection of the two enantiomers at ambient temperature. As shown in Figure 4 the single line of the methyl group splits into a pair of singlets of equal intensity (each of them corresponding to one of the two enantiomers), when the <sup>1</sup>H NMR spectrum is recorded at ambient temperature in an environment which has been rendered chiral by addition of an appropriate amount of an enantiopure chiral solvating agent.<sup>15</sup>

As reported in Figure 3, the rotation of the unsubstituted phenyl group bonded to C-2 follows a pathway (dotted line) whose transition state has a computed energy 10 kcal mol<sup>-1</sup> higher than the ground state. This topomerisation process exchanges the positions of the *ortho* and *meta* carbons in **1**, and the value of the calculated barrier (10 kcal mol<sup>-1</sup>) suggests that such a motion should be accessible to an experimental NMR detection. Actually, the single <sup>13</sup>C NMR lines observed for the *ortho* and for the *meta* carbons broaden on cooling below -100 °C and eventually split into a pair of signals: this is because the restricted rotation about the Ph–C bond has rendered diastereotopic the two *ortho* as



**Figure 4.** The <sup>1</sup>H methyl signal (300 MHz at ambient temperature) of compound **3** (top) splits into two (bottom) in the presence of a chiral solvating agent (see text).



**Figure 5.** Left: experimental  ${}^{13}C$  signals (75.5 MHz in CHF<sub>2</sub>-Cl) of the *ortho* and *meta* carbons of the unsubstituted phenyl group of **1** as function of temperature. Right: computer simulation obtained with the rate constants indicated.

well as the two *meta* carbons. In Figure 5 three lines, with a 1:1:2 intensity distribution, are observed at -140 °C due to one of the two *ortho* being accidentally coincident with one of the two *meta* signals. Line shape simulation allowed a free energy of activation of 6.9  $\pm$  0.15 kcal mol<sup>-1</sup> to be determined, in reasonable agreement with the computed value.

The spectra of compounds **2** and **3** also display the effect of the topomerisation process: the corresponding barriers are reported in Table 1.

Two additional internal motions might also occur in these derivatives, namely inversion of the formally sp<sup>3</sup>-hybridized nitrogen atom and inversion of the sixmembered ring. Although it is impossible to discriminate between these two possibilities solely on experimental ground, a number of considerations can be nonetheless

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<sup>(15)</sup> Use was made of R-*l*-1-(9-anthryl)-2,2,2-trifluoroethanol as in: Pirkle, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 477.



taken into account to propose a reasonable hypothesis about the motion which is more likely to be observed by NMR spectroscopy.

Both the crystal and computed structures indicate that in 1 the pyramid of the aryl-bonded sp<sup>3</sup> nitrogen atom is quite flat, the degree of pyramidalization being 5.8° (Xray) or 8° (ab initio <sup>9</sup>), i.e., values that are much closer to the 0° of a planar sp<sup>2</sup>-hybridized nitrogen atom than to the 27° of the truly pyramidal sp<sup>3</sup> nitrogen of trimethylamine.<sup>16</sup> Owing to this situation, the N-inversion barrier of **1** is presumably too low to be amenable to NMR observation, and this is confirmed by our ab initio calculations<sup>9</sup> that predict an N-inversion barrier in 1 equal to 2.7 kcal mol<sup>-1</sup>. It has also to be stressed that N-inversion processes sufficiently high (i.e. >4 kcal mol<sup>-1</sup>) to be measurable by dynamic NMR spectroscopy have never been reported for arylamines.<sup>17</sup> On the other hand, ring inversion of six-membered heterocycles, comprising an endocyclic double bond, have barriers accessible to NMR detection, since a number of derivatives were found<sup>18</sup> to display free energies of activation in the range 7-11 kcal mol<sup>-1</sup>. The asymmetry resulting from the "frozen" inversion of the six-membered ring creates a second source of chirality, in addition to the mentioned Ar-N stereogenic axis. As a consequence two stereolabile diastereoisomers, each entailing a pair of enantiomers, are expected to occur in these derivatives. The ab initio computation<sup>9</sup> for compound **1** predict that, in addition to the conformation depicted in Figure 1, the restriction of the ring inversion process should lead to a second minimum of energy, corresponding to a minor conformer. The two conformers were labeled anti (1b), when the CH<sub>2</sub> moiety in position 5 is on the opposite side of the chlorine atom, and syn (1a) when on the same side (Scheme 1). The corresponding energy difference was computed<sup>9</sup> to be 1.5 kcal mol<sup>-1</sup>, thus indicating that the proportion of the less stable conformer syn-1a should be very small (about 1%) in the temperature range where the ring inversion becomes sufficiently slow for NMR observation. For this reason it is unlikely that the spectrum of the minor conformer is directly visible.

Actually, in the low temperature  $^{13}C$  spectrum of 1 the signals of the minor conformer were not detected, but its presence could be nonetheless established in an indirect manner. For it was observed that one CH<sub>2</sub> broadens at low temperature considerably more than the other two CH<sub>2</sub> lines, reaches a maximum width at -127 °C, and sharpens again on further cooling to -147 °C (Figure 6). This is the typical feature expected for an exchange



**Figure 6.** <sup>13</sup>C signals (75.5 MHz in CHF<sub>2</sub>Cl) of the three methylene carbons of **1** at different temperatures. At -127 °C the central line broadens more than the other two, but sharpens again at -147 °C, indicating the occurrence of an exchange process involving an invisible species (see text).

process between two species experiencing a very biased equilibrium.  $^{\rm 19}$ 

The relationship  $k = 2\pi\Delta\omega$ , where  $\Delta\omega$  represents the maximum incremental width <sup>20</sup> (in the case of  $\mathbf{1} \Delta\omega$  was found  $14 \pm 1$  Hz at 75.5 MHz), allows one to obtain the rate constant, hence the  $\Delta G^{\ddagger}$  value (7.0  $\pm$  0.2 kcal mol<sup>-1</sup>) for the ring inversion process. An estimate of the signal-to-noise ratio indicates that the amount of the minor conformer  $\mathbf{1a}$  is certainly lower than 10%, in agreement with the theoretical prediction. As shown in Table 1 similar results were obtained for  $\mathbf{2}$  and  $\mathbf{3}$ .

It should be also noticed that in 1-3 the topomerization and ring inversion barriers (Table 1) are equal within the experimental errors. This might be due to an accidental coincidence, even though the possibility that these equal values are the consequence of a correlated motion cannot be, in principle, excluded. If so, the measured  $\Delta G^{\ddagger}$  values would be the manifestation of an unique dynamic process. A definite evidence, however, is not available to support this hypothesis which remains, therefore, rather speculative.

With the purpose of achieving direct evidence for the presence of two conformers, we searched for a compound

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**Figure 7.** Above -150 °C the <sup>1</sup>H NMR spectrum of **4** (300 MHz in CHF<sub>2</sub>Cl) displays a single line for the hydrogens of the *tert*-butyl group (top). Below -150 °C (bottom) the restriction of a dynamic process (presumably ring inversion) makes visible the signals due to a major and a minor conformer (in about a 93:7 ratio)

bearing a substituent which would display a very intense NMR signal. In this way even a small amount of the minor conformer would yield a detectable signal, particularly if such a substituent is appropriately selected as to allow the use of the much more sensitive <sup>1</sup>H frequency. The *o*-nitro phenyl derivative having a *tert*-butyl group at position 2 of the tetrahydropyrimidine ring **(4)** turned out to be well suited for such a purpose.



As shown in Figure 7, at -154 °C the single <sup>1</sup>H NMR line of the nine *tert*-butyl hydrogens splits into a pair of signals separated by 0.125 ppm, their relative proportion being approximately 93:7.

A barrier of 6.0 kcal mol<sup>-1</sup> for the corresponding dynamic process was obtained by line-shape simulation (Table 1). If, as previously discussed, this motion is assigned to ring inversion, the lower  $\Delta G^{\ddagger}$  value measured in **4** with respect to the corresponding derivative **3** (6.0 vs 7.3 kcal mol<sup>-1</sup>) should be a consequence of the steric effect of the *tert*-butyl moiety. This group would enhance the ground-state energy of the pyrimidine ring more than that of the transition state.<sup>21</sup> On the contrary, the *tert*butyl group in **4** would increase the enantiomerization barrier with respect to that of the analogous phenyl derivative **3** (16.6 vs 14.2 kcal mol<sup>-1</sup>). In the latter process the steric hindrance acts evidently in the opposite sense, enhancing the energy of the rotation transition state more than that of the corresponding ground state.

## Conclusions

Three different dynamic processes have been detected, and the corresponding barriers measured, by dynamic NMR in some *N*-aryl-substituted tetrahydropyrimidines, namely enantiomerization of stereolabile atropisomers, topomerization about the Ph–C axis and, presumably, ring inversion of the six-membered ring. The X-ray determined structure of one such a derivative is in good agreement with that obtained by computation, thus making the conformation and the stereodynamic assignments carried out by theoretical methods reliable.

### **Experimental Section**

**Material**. 1-Aryl-2-substituted-1,4,5,6-tetrahydropyrimidines **1**–**4** were synthesized by ring closure of the corresponding *N*-acyl-*N*-aryltrimethylenediamines.<sup>22–24</sup> Yields and physical data of new compounds are reported as Supporting Information.

X-ray Diffraction. Crystal data for 1-(2-chlorophenyl)-2phenyl-1,4,5,6-tetrahydropyrimidine (1):  $C_{16}H_{15}ClN_2$  (270.75), monoclinic, Space group  $P2_1/c$ , Z = 4, a = 13.9710(9), b =9.3524(6), c = 11.1445(7) Å,  $\beta = 100.718(2)$ , V = 1430.76(16)Å <sup>3</sup>,  $D_{\rm c} = 1.257$  g cm<sup>-3</sup>, F(000) = 568,  $\mu_{\rm Mo} = 0.255$  cm<sup>-1</sup>, T =293 K. Data were collected using a graphite monochromated Mo–K $\alpha$  X-radiation ( $\lambda = 0.71073$  Å) in the range 1.48° <  $\theta$  < 30.17°. Of 18657 reflections measured, 4199 were found to be independent ( $R_{\rm int} = 0.0487$ ), 2177 of which were considered as observed [ $I > 2\sigma(I)$ ], and were used in the refinement of 172 parameters leading to a final  $R_1$  of 0.0443 and a  $R_{all}$  of 0.0861. The structure was solved by direct method and refined by full-matrix least squares on F<sup>2</sup>, using SHELXTL 97 program packages. In refinements were used weights according to the scheme  $w = [\sigma^2(F_0^2) + (0.0650P)^2 + 0.0000P]^{-1}$  where  $P = (F_0^2) + 2F_c^2)/3$ . The hydrogen atoms were located by geometrical calculations and refined using a "riding" method.  $wR_2$  was equal to 0.1207. The goodness of fit parameters S was 0.843. Largest difference density between peak and hole was 0.306 and -0.330 eÅ<sup>-3</sup>. Crystallographic data (excluding structure factors and including selected torsion angles) have been deposited with the Cambridge Crystallographic Data Center, CCDC 166141.

NMR Measurements. The assignment of the signals was obtained by means of DEPT, gHSQC, and gHMBC sequences carried out in a 400 MHz spectrometer. The samples for the low-temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the desired compounds dissolved in some C<sub>6</sub>D<sub>6</sub> or CD<sub>2</sub>Cl<sub>2</sub> for locking purpose and condensing therein the gaseous solvents by means of liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the 300 MHz spectrometer operating at 75.45 MHz for  $^{13}\mathrm{C}$  or 400 MHz operating at 100.6 MHz for <sup>13</sup>C. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Total line shape simulations were achieved by using a PC version of the DNMR-6 program.<sup>11</sup> Since at the low temperatures required to observe the exchange process the intrinsic line width of the compounds was significantly temperature dependent, the corresponding dependence of the solvent signal was measured. The appropriate ratio with the line width of the compound was

<sup>(21)</sup> The same trend also results from Molecular Mechanics calculations (MMX force field<sup>13</sup>) where the computed barrier for the ring inversion process in **2** was found lower than in **4** (8.8 and 11.1 kcal mol<sup>-1</sup>, respectively).

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then taken into account. We also checked that errors as large as 50% on this value affected the activation energy by less than 0.05 kcal mol<sup>-1</sup> in the temperature range investigated.<sup>25</sup>

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preparation of some intermediates. Financial support was received by MURST (national project "Stereoselection in Organic Synthesis") and by the University of Bologna (Funds for selected research topics 1999-2001).

**Supporting Information Available:** Characterization data for compounds **1–4** and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org. JO015743X