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Conformational Studies by Dynamic NMR. 100.[1] Enantiomerization Process of Stereolabile Atropisomers in Pyridine-Substituted Adamantane Derivatives

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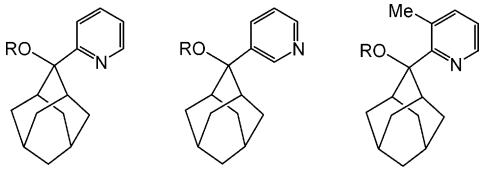
Abstract: The barriers for interconverting the conformational enantiomers (stereolabile atropisomers) of pyridine-substituted adamantane derivatives have been determined by dynamic ^{13}C NMR spectroscopy. The trend of these values parallels that anticipated by MM calculations. In at least one case, the computed structure was found to agree with that obtained by single-crystal X-ray diffraction. In addition, it has been possible to achieve a physical separation of a pair of these stereolabile atropisomers at −60 °C by means of the enantioselective cryogenic HPLC technique.

Restricted rotations of aryl groups bonded to bicyclic moieties (norbornanes[3,4] or bicyclononanes[5]) have been recently detected and the corresponding barriers measured by dynamic NMR spectroscopy. We report here the study of an analogous rotation process involving a pyridine ring bonded to the position 2 of an adamantane moiety, which also bears a OH or a OMe substituent at the same position. The search for an experimental determination of such a process was stimulated by MM calculations[6] on compounds **1**−**6** (Chart 1) that predicted how the corresponding rotation barriers (see Table 1) should cover a range of values accessible to NMR investigation.[7] As an example of these computations the energy surface, calculated as function of the rotation angles of the OH and pyridine groups bonded to adamantane, is displayed in Figure 1 for the case of compound **1**.

According to these calculations, the ground-state conformation has a structure where the plane of pyridine is nearly orthogonal to the local plane of symmetry of the adamantane moiety containing the oxygen atom, as shown, for instance, in Figure 2 for derivative **3**. Such an arrangement deprives compounds **1**−**6** of any element of symmetry (C_1 point group), thus entailing the existence of two conformational enantiomers (stereolabile atropisomers).

The helical chirality of these compounds is confirmed by X-ray diffraction: the crystal cell of **3**, for instance, contains eight molecules of the same enantiomer (see the Supporting Information). The absolute configuration,

CHART 1



1 R = H, **2** R = Me | **3** R = H, **4** R = Me | **5** R = H, **6** R = Me

TABLE 1. Experimental and Computed Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Enantiomerization Process of Compounds 1−6

compd	$\Delta G^{\ddagger}$ expt	$\Delta G^{\ddagger}$ comput	solvent	^{13}C NMR frequency (MHz)
1 (R = H)	6.3_5	5.9	$CHF_2Cl/CHFCl_2$	100.6
2 (R = Me)	9.9	7.5	CHF_2Cl	100.6
3 (R = H)	6.3	5.9	Me_2O	150.8
4 (R = Me)	11.9	13.6	CD_2Cl_2	100.6
5 (R = H)	7.9	7.2	CHF_2Cl	150.8
6 (R = Me)	16.6	21.2	C_2Cl_4	100.6

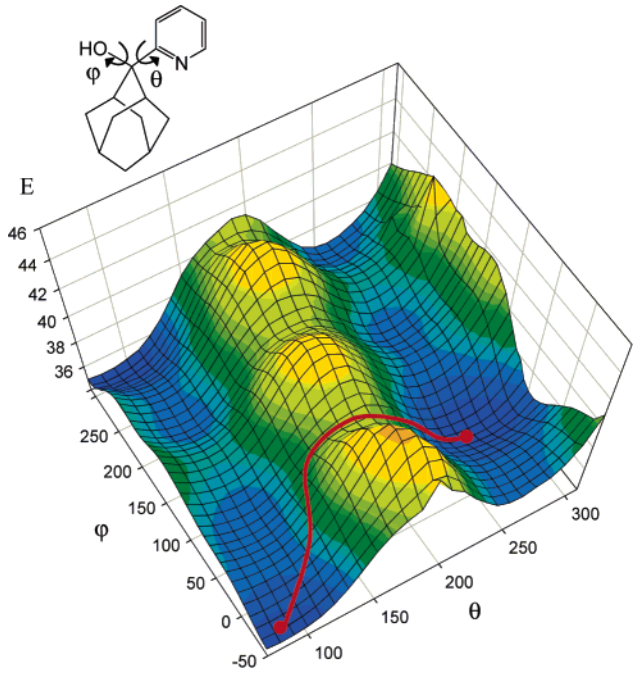


FIGURE 1. Energy surface of **1** computed as a function of the adamantane−OH and adamantane−(2-pyridinyl) dihedral angles (φ and θ, respectively, where θ is defined by the N−Cq−Cq−O atoms). The red line describes the rotation pathway of the pyridine ring.

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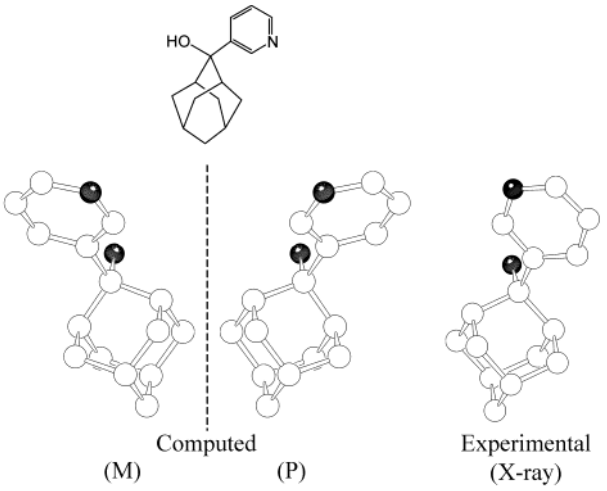

FIGURE 2. Left: computed structure of the enantiomers (M and P) of **3**, where the hydrogen atoms are omitted and the heteroatoms N and O are represented as black. Right: experimental structure by single-crystal X-ray diffraction (the absolute configuration reported is arbitrary).

however, could not be assigned, due to the absence of atoms heavy enough as to provide an anomalous dispersion to be confidently used. The experimental structure,[8] arbitrarily labeled as P (Figure 2, right), is very similar to that anticipated by calculations (see the Supporting Information), thus making reliable also the computed structures of the other derivatives of this series.

Since the calculations predict that the interconversion barriers (Table 1) are relatively low, a quite rapid rotation is expected to occur in a rather large temperature range, thus creating a dynamic plane of symmetry which renders equivalent (enantiotopic) the three pairs of carbons in positions 1 and 3, 4 and 9, and 8 and 10 of the adamantane ring. As a consequence, these carbon atoms usually display only three lines in the ^{13}C NMR spectra as shown, for instance, in Figure 3 (trace at −30 °C) for the case of derivative **1**. On further lowering the temperature, however, the rotation of the pyridine ring becomes slow in the NMR time scale and the lines broaden, eventually decoalescing into two signals with a 1:1 intensity ratio. Under these conditions, six lines for the six diastereotopic carbons are observed, as shown in the trace at −152 °C of Figure 3.

Computer line shape simulations[9] at intermediate temperatures (two selected examples are reported in Figure 3) provide the rate constants for the enantiomerization process brought about by the pyridinyl−adamantane bond rotation. From these data, the corresponding $\Delta G^{\ddagger}$ values can be obtained (see Table 1): as often observed[10] in conformational processes, the free energy of activation is independent of temperature, within the experimental errors (±0.15 kcal mol^{-1}).

The trend of the computed barriers is in fair agreement with the experimentally determined sequence: in particular, it is verified the prediction that substitution of the oxidryl hydrogen of the alcohols **1**, **3**, and **5** with a methyl group enhances the barrier of the resulting ethers (i.e., **2**, **4**, and **6**), owing to the increased steric hindrance. For the same reason the experimental and computed barrier of the 3-pyridinyl derivative **4** is higher[11] than

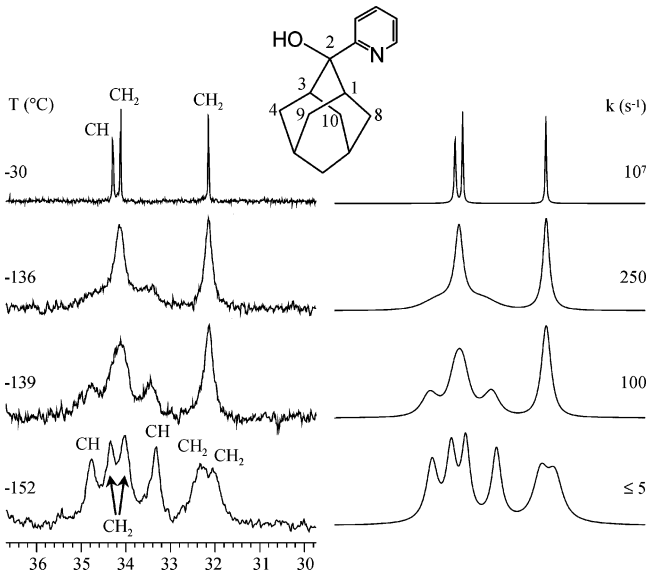

FIGURE 3. Left: temperature dependence of the ^{13}C NMR signals (100.6 MHz in $CHF_2Cl/CHFCl_2$) of CH carbons 1, 3 and of CH_2 carbons 4, 9 and 8, 10 of compound **1** (the signals of the three unlabeled CH, CH, and CH_2 carbons lay outside the reported scale). Right: computer simulation obtained with the rate constants indicated.

that of the corresponding 2-pyridinyl analogue **2** and, likewise, introduction of a methyl group in position 6 of the 2-pyridinyl compounds (derivatives **5** and **6**) enhances the barrier with respect to the corresponding compounds **1** and **2**.

In the case of **6** the enhancement is so large as to indicate the possibility of carrying out a physical separation of the two atropisomers. The NMR measured $\Delta G^{\ddagger}$ value of 16.6 kcal mol^{-1} corresponds, in fact, to a half-life time of a few hours at a temperature lower than −50 °C so that the use of the cryogenic enantioselective HPLC technique[12] should allow this separation to be achieved. Such an experiment was successfully performed as reported in Figure 4: the two conformational enantiomers of **6** display two peaks, with retention times differing by 0.4 min, when an enantioselective column,

(6) MMX force field as implemented in the computer package PC Model v 6, Serena Software, Bloomington, IN.

(7) The barriers for the OH and OMe rotations were computed to be so low (about 2 and 4 kcal mol^{-1}, respectively) as to prevent the possibility of an experimental observation by NMR.

(8) A compound similar to **3** was also found to have an analogous structure; see: Singelenberg, F. A.; van Eijck, B. P. *Acta Crystallogr. C: Cryst. Struct. Commun.* **1987**, *43*, 309.

(9) PC version of the QCPE program no. 633, Indiana University, Bloomington, IN.

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(11) As predicted by computations, the experimental barrier of **3** is equal to that of **1** (Table 1) despite the larger steric hindrance exerted by the 3- with respect to the 2-pyridinyl substituent. This could be a consequence of the stabilization of the ground state of **1** due to hydrogen bonding between OH and the nitrogen atom, an effect which cannot occur in **3**.

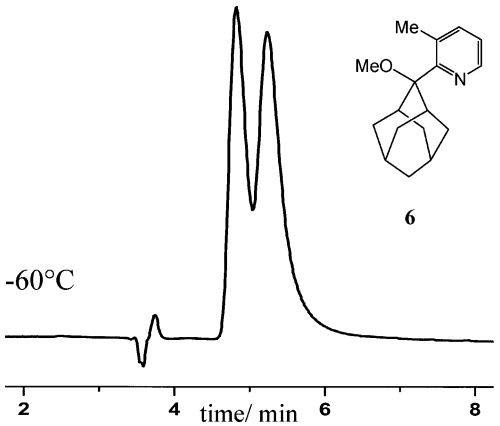

FIGURE 4. HPLC trace of **6** on an enantioselective column cooled at −60 °C showing the separation of the two conformational enantiomers.

cooled at −60 °C, is employed (see the Experimental Section).

Experimental Section

Materials. 2-(3-Pyridinyl) 2-adamantanol (3) was prepared according to the literature.[13]

2-(2-Pyridinyl)-2-adamantanol (1). 2-Bromopyridine (0.7 mmol in 2 mL of dry Et_2O) was added to *n*-BuLi at −70 °C (0.7 mmol, 0.45 mL, solution 1.6 M in hexane).[13] The solution was stirred for 30 min at −70 °C and then treated with 2-adamantanone (0.67 mmol in 2 mL of dry Et_2O). After being stirred for 3 h, the mixture was warmed to room temperature, treated with NH_4Cl, extracted with Et_2O (50 mL), and dried (Na_2SO_4) and the solvent removed. The crude product was purified by a silica gel chromatography column (petroleum ether/Et_2O 9/1) to give **1** (0.48 mmol, overall yield 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62−1.80 (9H, m), 1.9 (1H, m), 2.02 (1H, s), 2.38−2.46 (2H, m), 2.7 (2H, m), 7.15 (1H, m), 7.5 (1H, m), 7.7 (1H, m), 8.6 (1H, m); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 27.0, 27.4, 33.0, 34.5, 35.0, 38.0, 77.8, 120.2, 122.1, 136.6, 149.2, 162.8. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.51; H, 8.38; N, 6.14.

2-(2-Methoxy-2-adamantyl)pyridine (2). A solution of **1** (0.22 mmol in 5 mL of dry THF) was added to NaH (2.2 mmol, 10 equiv, in 5 mL of dry THF), treated with MeI (2.2 mmol, 10 equiv, neat), and refluxed for 5 h. To the cooled mixture was added H_2O dropwise, and the mixture was then extracted with Et_2O (30 mL) and dried with (Na_2SO_4) to obtain **2** (yield 99%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62−1.78 (9H, m), 1.9 (1H, m), 2.26−2.34 (2H, m), 2.7 (2H, m), 2.85 (3H, s), 7.19 (1H, m), 7.5 (1H, m), 7.7 (1H, m), 8.6 (1H, m); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 27.0, 27.7, 32.6, 32.9, 34.6, 37.7, 48.6, 82.0, 121.7, 121.9, 136.2, 148.2, 162.8. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.80; H, 8.67; N, 5.71.

3-(2-Methoxy-2-adamantyl)pyridine (4). A solution of **3** (0.17 mmol in 5 mL of dry THF) was added to a suspension of KH (10 equiv, in 5 mL of dry THF) at −30 °C, and after 30 min the solution was treated with MeI (1.7 mmol, 10 equiv, neat) and stirred for 15 min. To the mixture, kept at −30 °C, was added MeOH dropwise, and the solution was warmed to room temperature, extracted with Et_2O (30 mL), and dried (Na_2SO_4) to obtain **4** (yield 99%): ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 1.60−1.68 (2H, m), 1.68−1.72 (2H, m), 1.75 (2H, bs), 1.78−1.82 (3H, m), 1.91 (1H, m), 2.32−2.36 (2H, m), 2.65 (2H, bs) 7.34 (1H m), 7.80 (1H m), 8.52 (1H m), 8.73 (1H m); ^{13}C NMR (CD_2Cl_2, 150.8 MHz) δ 27.7, 28.6, 30.5, 33.3, 33.5, 35.1, 38.3, 48.6, 79.8, 123.8, 135.7, 149.1, 150.1, 160.0. Anal. Calcd for $C_{16}H_{21}NO$: C, 79.33; H, 9.01; N, 5.44; O, 6.22. Found: C, 79.38; H, 9.03; N, 5.40.

2-(3-Methyl-2-pyridinyl)-2-adamantanol (5). 2-Bromo-3-methylpyridine (1.01 mmol in 2 mL of dry THF) was first added[14] to *n*-BuLi at −55 °C (1.01 mmol, 0.63 mL, solution 1.6 M in hexane), and the solution was stirred for 30 min at −55 °C and then treated with 2-adamantanone (0.67 mmol in 2 mL of dry Et_2O). After being stirred for 3 h, the mixture was warmed to room temperature, treated with NH_4Cl, extracted with Et_2O (70 mL), and dried (Na_2SO_4) and the solvent removed. The crude product was purified by a silica gel chromatography column (petroleum ether/Et_2O 9/1) to give **5** (0.48 mmol, overall yield 50%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.64−1.80 (8H, m), 1.87 (1H, m), 1.90−1.98 (2H, m), 2.35−2.43 (2H, m), 2.57 (3H, s), 2.70-(2H, bs), 7.06 (1H m), 7.42 (1H m), 8.36 (1H m); ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ 21.3, 26.9, 27.2, 33.2, 35.1, 35.7, 37.9, 79.8, 121.9, 140.6, 144.8, 161.7. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.51; H, 8.32; N, 6.17.

2-(2-Methoxy-2-adamantyl)-3-methylpyridine (6). A solution of **5** (0.33 mmol in 5 mL of dry THF) was added to NaH (10 equiv, in 5 mL of dry THF), treated with MeI (3.3 mmol, 10 equiv, neat), and heated to reflux for 5 h. To the mixture, cooled to 0 °C, was added H_2O dropwise, and the mixture was warmed to room temperature, extracted with Et_2O (40 mL), dried (Na_2SO_4), and purified on a silica gel chromatography column (petroleum ether/Et_2O 1/1) to obtain **6**: ^{1}H NMR ($CDCl_3$, 600 MHz) 1.50−1.78 (7H, m), 1.80−1.89 (2H, m), 2.14−2.22 (1H, m), 2.43−2.51 (1H, m), 2.53 (3H, s), 2.64(1H, bs), 2.66−2.74(1H, m), 2.83(1H, bs), 2.86(3H, s) 7.09 (1H m), 7.42 (1H m), 8.47 (1H m); ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ 20.5, 27.0, 27.5, 30.8, 33.0, 33.4, 34.3, 35.0, 35.7, 38.0, 48.7, 84.2, 121.7, 133.3, 140.2, 144.6, 159.7. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.38; H, 9.04; N, 5.49.

NMR Measurements. The samples for the very low temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the compound and some deuterated solvent (C_6D_6 or acetone-d_6) for locking purposes and condensing therein the gaseous solvents (CHF_2Cl, $CHFCl_2$, Me_2O) by means of liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the spectrometer. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple.

HPLC Analysis. The separation of the enantiomers of **6** was obtained at −60 °C by using a Chiralcel-OD column (250 × 4.6 mm, LxID), with pentane/2-propanol (99.5/0.5) as eluent (α = 1.29). The flow rate was 1 mL/min, and a 254 nm UV detector was employed. The cooling system has been described elsewhere.[12]

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Note Added after ASAP Posting. The substituents were incorrect in entries 2, 4, and 6 of Table 1 in the version posted ASAP July 16, 2004; the corrected version was posted July 16, 2004.

Supporting Information Available: Crystal data for compound **3**, Molecular Mechanics parameters for compounds **1**−**6**, a table of torsion angles for **1**−**6**, and a table of rate constants for the simulated spectra of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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