4-(decyloxy)pyridine hydrochloride, 136616-64-3; 3-chloropropionyl chloride, 625-36-5.

Supplementary Material Available: Selected ^1H NMR data of compounds **15**, **20**, and **22–28** (Table III); selected ^{13}C NMR spectroscopic data of compounds **9–13**, **19**, **31**, and **32** (Table IV); selected ^{13}C NMR spectroscopic data of compounds **15**, **20**, **22–24**, and **26–28** (Table V); elemental analyses of new compounds (Table VI) (4 pages). Ordering information is given on any current masthead page.

Conformational Study of (*R*)-(−)-2,2,2-Trifluoro-1-(9-anthryl)ethanol (Pirkle's Alcohol) by Dynamic NMR

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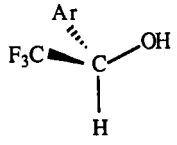
Observation of anisochronous ^1H and ^{13}C NMR signals in (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol at low temperature indicates that restricted rotation around the C(sp^2)–C(sp^3) bond occurs. From the coalescence temperature data and the corresponding chemical shift difference, the free energy of activation for rotation was evaluated to be 14.5 kcal mol^{-1} at 320 K in deuteriochloroform. These results, together with MM2 calculations, indicate that the ground-state conformation is that in which the trifluoromethyl group is almost orthogonal to the anthracene ring. The transition state will correspond then to the conformation in which the CF_3 group eclipses the aromatic nucleus. Complete ^1H and ^{13}C NMR assignments of the system at the frozen ground state (340 K) were made by homo- and heteronuclear COSY experiments and NOE difference spectroscopy.

Introduction

Enantiomerically pure (+)- and (−)-1-aryl-2,2,2-trifluoroethanols **1**, also known as Pirkle's alcohols, have been widely applied as optically active NMR reagents and as chiral stationary phases in chromatography.[1]



a, Ar = phenyl

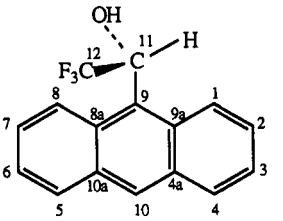
b, Ar = α-naphthyl

c, Ar = 9-anthryl

1

Even though **1a** and **1b** have been the most frequently used for the NMR determination of enantiomeric purity and absolute configuration, it has been proved that **1c**, despite its modest solubility, induces greater spectral nonequivalence between enantiomeric solutes than either **1a** or **1b**; it is not uncommon to observe nonequivalence magnitudes of 0.1 ppm.[2] Resolved (*R*)-(−)-fluoro alcohol **1c** was used throughout this study without other precaution than to protect it from light and oxygen.[3]

In spite of the general uses of **1c** in organic chemistry, a detailed description of its NMR properties has never been reported in the literature.[4] This situation prompted us to perform a systematic ^1H and ^{13}C NMR study of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol at several temperatures in order to facilitate its NMR applications as a chiral reagent. We report here evidence for restricted rotation involving an sp^2–sp^3 bond (C_9–C_{11}) connecting the trifluoroethanol group to the anthracene ring in Pirkle's alcohol **1c**, and also the application of molecular mechanics (MM2) calculations to this molecule.



R-(−)- **1c**

MM2 Theoretical Calculations

MM2 Theoretical Calculations

Although compound **1c** has a π electron system, it does not electronically interact with the substituent at C_9; therefore, MM2 calculations[5] treating the anthracene moiety mechanically have been undertaken. From them, it appears that **1c** assumes a ground-state conformation in which the trifluoromethyl group is almost orthogonal to the aryl group. The calculations have been performed considering the variety of intermediate conformations obtained by extensive drive of C_{9a}–C_9–C_{11}–OH and C_9–C_{11}–O–H bonds from 180 to −180° at 15° steps. According

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(3) Complete structural characterization of the isolated head-to-tail photodimer from **1c** by recrystallization in ethanol without protection from oxygen and light is now in progress.

(4) To our knowledge only Pirkle, W. H. *et al.* (Pirkle, W. H. et al. *J. Org. Chem.* **1977**, *42*, 384) describe the ^1H NMR of **1c** in carbon tetrachloride: δ (in ppm) = 3.42 (d, 1 H, exchangeable OH, J = 5.2 Hz), 6.28 (d of q, 1 H, J_d = 5.2 Hz, J_q = 8.0 Hz), 7.15–7.45 (m, 4 H), 7.62–7.85 (m, 2 H), 7.6–9.1 (m, very broad, 2 peri H), and 8.20 (s, 1 ArH at position 10).

(5) (a) Allinger, N. L. *QCPE* **1982**, *3*, 32. (b) Beckhaus, H. D. *Chem. Ber.* **1983**, *116*, 115.

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Table I. ^1H NMR and ^{13}C Chemical Shifts (δ in ppm versus TMS) and Coupling Constants (J in Hz) of Pirkle's Alcohol 1c in $CDCl_3$

protons	temperature 340 K[a]	temperature 245 K[b]	carbons	temperature 340 K	temperature 245 K
H_1	8.54 (d)	7.88 (d) (8.12)[c]	C_1	124.3	122.2
H_8	8.54 (d)	8.83 (d) (8.94)[c]	C_8	124.3	126.3
H_2	7.53 (ddd)	7.47 (dd)	C_2	126.7	125.9
H_7	7.53 (ddd)	7.50 (dd)	C_7	126.7	127.0
H_3	7.45 (ddd)	7.38 (dd)	C_3	124.9	124.7
H_6	7.45 (ddd)	7.48 (dd)	C_6	124.9	124.6
H_4	7.99 (dd)	7.80 (d) (8.04)[c]	C_4	129.4	128.8
H_5	7.99 (dd)	7.97 (d) (8.05)[c]	C_5	129.4	129.5
H_{10}	8.49 (s)	8.32 (s) (8.56)[c]	C_9	123.9	122.8
H_{11}	6.62 (dq)	6.35 (dq) (6.65)[c]	C_{10}	130.7	130.6
OH	3.68 (d)	3.64 (d) (3.15)[c]	C_{11}	70.0	70.0 ^2J (C,F) = 30.0 Hz
			CF_3	125.4	125.2 ^1J (C,F) = 285.0 Hz
			C_{4a}	130.8	130.0[d]
			C_{10a}	130.8	130.3[d]
			C_{8a}	131.5 (broad)	130.4[d]
			C_{9a}	131.5 (broad)	131.2[d]

[a] $J_{1,2} = J_{7,8} = 9.0$; $J_{1,3} = J_{6,8} = 1.0$; $J_{2,3} = J_{6,7} = 7.0$; $J_{3,4} = J_{5,6} = 8.4$; $J_{2,4} = J_{5,7} = 1.5$; $J(H_{11}, OH) = 4.2$; $J(H_{11}, CF_3) = 8.0$. [b] $J_{1,2} = 9.0$; $J_{2,3} = 8.1$; $J_{3,4} = 8.2$; $J_{5,6} = 8.0$; $J_{6,7} = 8.0$; $J_{7,8} = 9.1$; $J(H_{11}, OH) = 4.0$; $J(H_{11}, CF_3) = 8.0$. [c] Values at infinite dilution. [d] These signals can be reversed.

to MM2 calculations the two possible interconversion processes have almost the same relative energy (15.53 and 15.23 kcal mol^{-1}).

Transition-state conformations are of very similar geometry. The methine proton is almost perpendicular to the aryl plane, and nonbonded interactions $CF_3/H_{8(1)}$ and $OH/H_{1(8)}$ are present as deduced from bond angle values (H_1–C_1–$C_{9a} \approx 124°$ and H_8–C_8–$C_{8a} \approx 122°$).

Static and Dynamic NMR

The ^1H NMR (400 MHz) of (*R*)-(−)-1c in $CDCl_3$ (0.23 M) has been recorded as a function of the temperature. At high temperature (340 K) the molecule appears symmetrical due to rapid conformational equilibria involving rotation around the C(sp^2)–C(sp^3) bond (C_9–C_{11}). Only seven signals for protons H_1 (H_8), H_2 (H_7), H_3 (H_6), H_4 (H_5), H_{10}, H_{11}, and OH were observed. However at lower temperatures, 260 K, the internal rotation is frozen and the following pairs of protons become anisochronous: H_1 and H_8, H_2 and H_7, H_3 and H_6, H_4 and H_5.

The rotational barrier was measured by line-shape analysis[6] of anthracene protons H_1 and H_8 which split into a pair of lines below a coalescence temperature of 320 K with a maximum difference of 373 Hz at 245 K ($\Delta G^{\ddagger} = 14.5 \pm 0.2$ kcal mol^{-1}).

The rotational barrier was also estimated, although less precisely, from the ^{13}C DNMR spectra by monitoring the anisochronous C_1 and C_8 carbons of the anthracene ring ($\Delta G^{\ddagger}_{296} = 13.5 \pm 0.8$ kcal mol^{-1}).

Assignment of the proton resonances at high temperature (Table I) follows from inspection of integrals, chemical shifts, and coupling constants considering the values for anthracene derivatives[7] and leads to the following sequence:

$$\delta H_1 > \delta H_{10} > \delta H_4 > \delta H_2 > \delta H_3 > \delta H_{11}$$

At low temperature (Table I), assignments were made on the basis of nuclear Overhauser effect (NOE) difference spectroscopy. When the methine proton (H_{11}) at 6.53 ppm was irradiated at 245 K NOE enhancements of 23% for H_1, 8% for OH, 7% for H_8, and −2% for H_2 were observed. At 292 K irradiation of the same H_{11} proton gave similar NOE enhancements (12%) for H_8 and H_1 confirming that NOE effect for H_8 was due to the kinetic process[8,9] where H_1 and H_8 are interconverted during irradiation time. Moreover, if we irradiate H_1 at this temperature we observe, in addition of the saturation transfer[8,10] on H_8, the same NOE (17%) at H_{11} as if the decoupler frequency was on H_8.

At this temperature, the interchange rate is so fast ($k > T_1^{-1}$) that the enhancements are averaging like the corresponding relaxation rates and so slow on the chemical shift time scale ($k < \Delta\delta$) that we observe two signals without coalescence. Homonuclear COSY spectra at 340 and 245 K confirmed the proton assignments. We noted that ^1H chemical shifts in 1c were sensitive to the concentration.

Carbon assignments, given in Table I, were obtained from the ^{13}C NMR chemical shifts of anthracene[11] and 2D HETCOR spectra with optimized delays in the pulse sequence for large (160-Hz) one-bond couplings.

As expected, the larger effects are observed on signals, protons, and carbons belonging to positions 1 and 8. Those of position 8 appear deshielded about 400 Hz relative to those of position 1. The deshielding of H_8 and C_8 is partly due to the proximity of the OH group in the ground-state conformation (through-space anisotropic effects). However, the electronic distribution of the whole anthryl residue is affected, since far away signals, like H_4/H_5 and C_4/C_5, are also separated by about 70 Hz.

Conclusions

Although this study was carried out with the (*R*)-(−) enantiomer, the following conclusions should apply to both enantiomers:

(i) When the barrier separating enantiomers, for instance, helical ones,[2d] is quite low and Pirkle's alcohol 1c is to be used at temperatures lower than room temperature, care has to be taken when interpreting the change in appearance of the chiral reagent signals.

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(11) Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Wiley: New York, 1988.

(ii) The dynamic process present in compound 1c involves a rotation about the anthryl-C(sp^2)/substituent-C(sp^3) bond with a barrier of 14.5 kcal mol^{-1}.

(iii) Allinger's MM2 calculations provided an excellent estimation of the barrier, 15 kcal mol^{-1}; moreover, the origin of the barrier and the most stable conformation were ascertained.

(iv) The calculated most stable conformation, explains the NOE results at low temperature ($H_1 \leftarrow\!\!\sim\!\!\rightarrow H_{11}$).

Experimental Section

Materials. (*R*)-(−)-2,2,2-Trifluoro-1-(9-anthryl)ethanol was purchased from Aldrich and used without further purification.

NMR Measurements. The NMR spectra at variable temperatures were taken with a Bruker AM 400 WB spectrometer, in a 5-mm dual probe with $CDCl_3$ as solvent, operating at 400.13 MHz for ^1H and 100.62 MHz for ^{13}C.

The temperature of the probe was calibrated by the methanol standard method, and a delay of 600 s was used before registering the NMR spectra at each temperature. NOE difference spectra were obtained using a low decoupler setting (typically 40 L, 5 mW approximately) with a total presaturation time resulting from the three times irradiation during 1 s in each individual quartet signals of H_{11}, following a NOEMULT sequence. In the case of the irradiation of H_1 or H_8 a single frequency was used during 10 s. A 512 number of transients was acquired using 16K points and a sweep width of 5000 Hz in alternate groups of eight, irradiating on/off resonance. A 90° pulse was used during acquisition.

In the 2D experiments, the standard Bruker sequences were applied. The COSY experiment was carried out with 1024 and 512 points along *f*2 and *f*1, respectively. The *f*1 time domains were zero filled and both directions multiplied by a sine square bell function before Fourier transformation.[12] The $^1H/^{13}C$ correlation spectrum was obtained from 256 time increments, each of 2K points, and Fourier transformed after zero filling to 256 points along *f*1 and exponential multiplication in *f*2.

Computational Details. Calculations were performed on a VAX-8820 computer in the Computer Center of the Universitat Autònoma de Barcelona, using the MM2PRIME program.[13] Allinger's MM2 (77) force field together with all MM2 (85) parameters have been used throughout this work.[14]

Acknowledgment. This work was supported by CICYT of Spain (Project Number PB87-0094-CO2-00). Servei d'Espectroscopia RMN of UAB is greatly acknowledged for allocating spectrometer time.

Registry No. (*R*)-(−)-1c, 53531-34-3.

Supplementary Material Available: MM2 contour map of the torsional energy surface obtained by driving ω_1 (C_{9a}–C_9–C_{11}–OH) and ω_2 (C_9–C_{11}–O–H), ^1H NMR spectra between 260 and 340 K, NOE difference experiments at 245 and 292 K, plot of proton chemical shifts vs concentrations at 245 K, and heteronuclear ^1H–^{13}C correlation spectra at 245 and 340 K (6 pages). Ordering information is given on any current masthead page.

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Total Synthesis of 6-Deoxy-6-aminoheptopyranuronic Acid Derivatives[1]

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Two enantio couples of terminal *C*-glycopyranosyl α-amino acids, namely the aminopyranuronic acids L-**9**, D-**9** and L-**10**, D-**10**, have been synthesized from the serine-derived pair L-**2**, D-**2** by exploiting enantiomerically pure butenolide intermediates **3** and **4**. The key synthetic steps involved the sequential antiselective cis dihydroxylation of the butenolide double bond and the clean furanose-to-pyranose ring expansion to construct the sugar skeleton with the proper stereochemistry. In our best performance, homogeneous L-**9** was prepared from L-**2** in four steps and 10 reactions in 20% overall yield.

Glycopyranosyl α-amino acids, where the α-aminoacyl residue is appended at the nonanomeric terminal of a pyranose via a carbon–carbon link, are the core components of a quite rare subclass of nucleoside antibiotics including amipurimycin[2] and the miharamycins,[3] both displaying activity against the causative agent for rice blast disease *Pyricularia oryzae*.[4]

A totally synthetic approach to amipurimycin, recently reported by Garner,[5] utilizes L-serine-derived oxazolidine aldehyde L-**2** as the homochiral progenitor, according to the Danishefsky's diene–aldehyde cyclocondensation protocol, while a nonnatural pyranosyl representative, 6-acetamido-2,3,4-tri-*O*-allyl-6-deoxy-α-D-*gluco*-heptopyranosiduronic acid, was synthesized by Antonakis[6] by

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