Synthesis and Separation of Atropisomers of 9,10-Dipivaloylanthracene and 9,10-Bis(1-imino-2,2-dimethylpropyl)anthracene. Structural Study by NMR, Molecular Mechanics, and X-ray Diffraction

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Cisoid and transoid conformations of 9,10-dipivaloylanthracene and 9,10-bis(1-imino-2,2-dimethylpropyl)anthracene were separated and detected for the former and isolated for the latter at room temperature. The transformation between two atropisomers was studied by NMR and modeled by MM methods. X-ray diffraction was performed for the imino derivatives.

Introduction

Recently, the preparation of 9-anthryl-*tert*-butyl-carbinol[1] from its parent ketone 9-pivaloylanthracene (**1**) and of 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroan-thracene[2] from its parent imine 9-(1-imino-2,2-dimeth-ylpropyl)anthracene (**2**) have been reported. Both compounds showed a high rotational barrier around the C_9−C_{11} bond. Homochiral forms of **1** behaved as chiral solvating agents and could be useful in chiral induced cycloadditions[3] such as Diels−Alder reaction.

The conformational study of some substituted 9-an-thrylcarbinol derivatives had shown that the rotation barrier around C_9−C_{11} for the *tert*-butyl derivative is so high that the usual NMR methods are not applicable, and a method based in the NOE transfer[4] must be used instead. Similarly, it can be assumed that the energy corresponding to the rotation around the C_9−C_{11} bond in compounds **1** and **2** should be very high. It is not possible to determine the rotational barrier around the C_9−CO axis and the C_9−CNH axis in these two compounds using NMR methods due to their inherent symmetry. Nevertheless, barriers have been calculated by molecular mechanics (MM3* force field) to be of 24.8 kcal/mol for **1** and of 24.7 kcal/mol for **2**. MM calculations also showed a preferred conformation where the aromatic ring plane and that containing the carbonyl or the imino moiety were orthogonal (Figure 1).

Some changes in the molecular structure could be envisaged for allowing us to determine these rotational energies (derivation, formation of a complex, etc.). However, those changes could modify the conceptual value of the energy found or even could involve compounds that are of great synthetic difficulty.

Analogous 9,10-disubstituted anthracene derivatives, like 9,10-dipivaloylanthracene (**3**) and 9,10-bis(1-imino-2,2-dimethylpropyl)anthracene (**4**), would have the same structural properties as **1** and **2**. Assuming an orthogonal position of substituents on C_9 and on C_{10} in respect
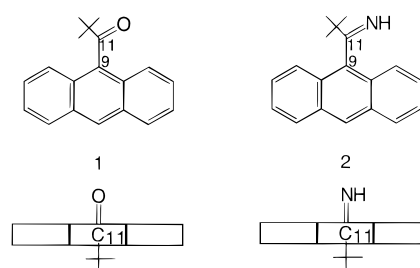

Figure 1. Compounds **1** and **2** and their conformational projection.
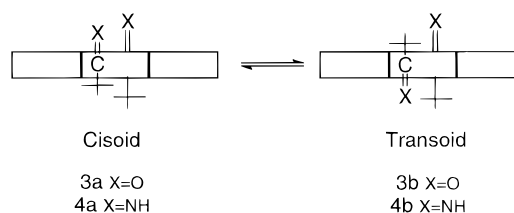

Figure 2. Equilibrium between atropisomers (**a** and **b**) of compounds **3** and **4**.

to the anthracene plane, **3** and **4** could adopt two conformations called cisoid and transoid (Figure 2) depending on their relative position (same or opposite side of the referenced plane, respectively). These two conformers should not be exchangeable at room temperature owing to the restricted rotation about the two conformational stereogenic axes (C_9−C=X and C_{10}−C=X with X = O in **3** and X = NH in **4**). Similarly, 1-naphthyl sulfoxides and 1,5-naphthyl disulfoxides, studied by Villani et al.,[5,6] present exchanging rotamers which were resolved by low temperature chiral HPLC.

In the present study, compounds **3** and **4** were prepared with the aim to use some of their derivatives as chiral shift reagents. Atropisomers of **3** were studied by HPLC and by the HPLC−NMR coupled technique. Corresponding isomers of **4** were isolated by flash chromatography and were studied by NMR spectroscopy and X-ray diffraction. Molecular mechanics calculations were of great help to assign their stereochemistry and to explain their structural behavior.

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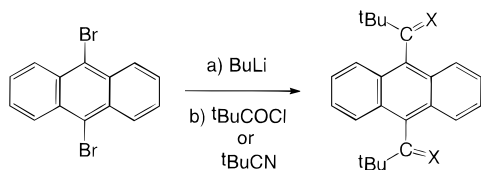
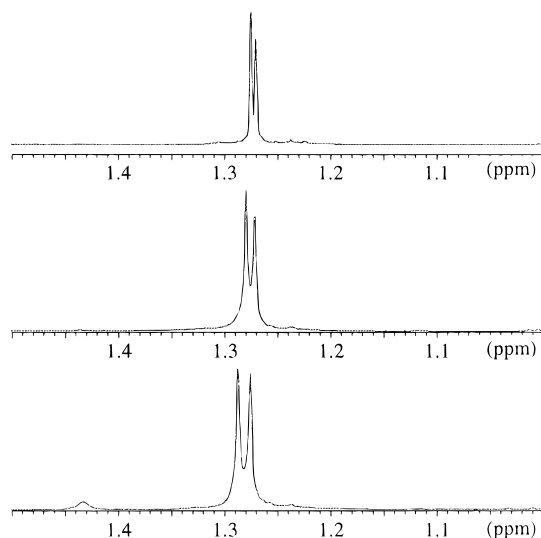**Figure 3.** Synthesis of compounds **3** (X = O) and **4** (X = NH).

Figure 4. Variation of population in diketones **3a** and **3b** with temperature. Upper spectrum: 285 K; medium: 310 K; lower: 340 K.

Results and Discussion

Compounds **3** and **4** were synthesized using the same published method as for monoderivatives **1** and **2**. Thus, the dilithium anthracene intermediate, prepared by reaction of 9,10-dibromoanthracene with butyllithium, reacted with pivaloyl chloride and pivalonitrile in ethyl ether, yielding **3** and **4**, respectively (Figure 3).

The aromatic and the double bond (C=O or C=NH) planes are perpendicular in **3** and **4**, as in compounds **1** and **2**. The two possible conformers for **3** and **4** (cisoid and transoid) could only be interconverted by surpassing a high free energy of activation (around 25 kcal/mol as calculated by MM3*; see below).

Diketones **3** were obtained at room temperature (298 K) as a mixture of both conformers in a 45:55 ratio (cisoid, **3a**:transoid, **3b**). Minor changes in the population ratio were observed by the NMR study of **3** at different temperatures (Figure 4). Similar population changes were observed on NMR spectra when different solvents were used.

The flash chromatography of the mixture on silica gel yielded several fractions enriched in one of the isomers which had been studied by NMR. Isomers were successfully separated by applying the new technique LC/NMR, and they were analyzed by NMR.

Calculations on diketones **3a** and **3b** have been carried out using the four force fields[7] implemented in Macromodel[8] (Table 1) either in vacuum or using the GB/SA solvation model.[9] Transoid and cisoid isomers have very similar populations as deduced from NMR data, but one of the isomers (that with $\delta_{CH_3} = 1.28$) is more stable than the other in chloroform as solvent. This experimental finding correlates well with the results obtained from all the force fields used, but in the case of AMBER* the opposite is found. However, calculated energy differences

involved in these equilibria are not large enough to consider these results as contradictory.

No parameters were available to imitate solvation by acetone in the version used of Macromodel.[8] Calculations were, thus, carried out in water (as a model for a polar solvent) and in chloroform. Computed steric energies on Table 1 allow us to deduce an increase in the cisoid isomer population when increasing the solvent polarity in all the force fields studied. Accordingly, the transoid isomer **3b** could be assigned to the first eluted compound ($\delta_{CH_3} = 1.28$) in the flash-chromatography (which is also the major isomer obtained experimentally) by comparison of these computed results with experimental NMR data at room temperature.

Diimines **4a** and **4b** were obtained in a 90:10 ratio (cisoid,**4a**:transoid,**4b**). Physical separation of atropisomers was achieved at room temperature by flash chromatography. The first eluted atropisomer was **4b,** thus displaying lower polarity than **4a**. MM calculations also predict **4b** to have smaller dipole moment than **4a** (Table 2).

Calculated steric energies for diimines **4a** and **4b** show slightly larger energy differences (0.5−0.7 kcal/mol) than those computed for diketones **3a** and **3b** (0.3−0.4 kcal/mol). Cisoid isomer **4a** is always computed as the most stable, in agreement with an experimentally more populated cisoid isomer in the diimine equilibrium.

Suitable monocrystals of **4a** and **4b** were obtained and subjected to X-ray analysis. Drawings[10] corresponding to **4a** (Figure 5) and **4b** (Figure 6) structures show the cisoid and transoid conformations as described above. There is a great difference in the crystalline structure of these two compounds. Intermolecular hydrogen bondings N−H···N are present in the cisoid compound **4a** [N−H, 0.94(3) Å; N···N, 3.357(4) Å; H···N, 2.45(3) Å; N−H···N, 163(3)°]. Centrosymmetric dimers containing two hydrogen bonds can be considered. Contrary, no hydrogen bonds are observed in the transoid isomer **4b**.

Moreover, the anthracene ring in **4a** is not planar. The dihedral angle between the two lateral benzenic rings is of 13.8°. This finding is also observed in other compounds with only one substituent, such as 9-*tert*-butylanthracene[11] and to a greater extent in those with two substituents, such as 9,10-bis(trimethylsilyl)anthracene.[12] In contrast, compound **4b** is centrosymmetric planar. Relevant crystallographic data are given in Table 3, and supplementary crystallographic material is available as Supporting Information.

When the most stable isomer **4a** was studied by NMR at 360 K, the signal corresponding to the less abundant atropisomer **4b** increased with time (Figure 7) until the equilibrium between the atropisomers (58:42) was reached (about 6 h). The kinetic process could thus be followed by monitoring the change on the relative intensities

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Table 1. Calculated Steric Energies (kcal/mol) and Dipole Moments (debyes) for Diketones 3a and 3b

| | MM3* | | | | MM2* | | | | AMBER* | | | | OPLS | | | |
| | cisoid **3a** | | transoid **3b** | | cisoid **3a** | | transoid **3b** | | cisoid **3a** | | transoid **3b** | | cisoid **3a** | | transoid **3b** | |
	E	μ	E	μ	E	μ	E	μ	E	μ	E	μ	E	μ	E	μ
vacuum	43.17	5.8	43.11	0.1	36.43	6.0	36.28	0.3	43.48	7.3	43.02	0.2	37.28	4.9	37.32	0.1
$CHCl_3$	30.04	5.9	30.15	0.1	23.50	6.1	23.58	0.3	29.52	7.4	29.44	0.2	24.28	4.9	24.43	0.1
H_2O	41.10	5.9	41.52	0.1	34.94	6.0	35.35	0.3	37.11	7.5	37.39	0.2	34.94	4.9	35.34	0.1

Table 2. Calculated Steric Energies (kcal/mol) and Dipole Moments (debyes) for Diimines 4a and 4b

| | MM3* | | | | MM2* | | | | AMBER* | | | | OPLS | | | |
| | cisoid **4a** | | transoid **4b** | | cisoid **4a** | | transoid **4b** | | cisoid **4a** | | transoid **4b** | | cisoid **4a** | | transoid **4b** | |
	E	μ	E	μ	E	μ	E	μ	E	μ	E	μ	E	μ	E	μ
vacuum.	46.19	2.2	46.32	0.0	39.15	1.1	39.42	0.1	34.48	0.3	35.29	0.0	37.43	1.6	37.95	0.0
$CHCl_3$	32.68	2.2	32.92	0.0	26.90	1.1	27.21	0.0	22.02	0.3	22.53	0.0	24.09	1.6	24.77	0.0
H_2O	42.78	2.2	43.29	0.0	40.65	1.1	41.09	0.1	33.65	0.3	34.12	0.0	34.28	1.7	34.92	0.0
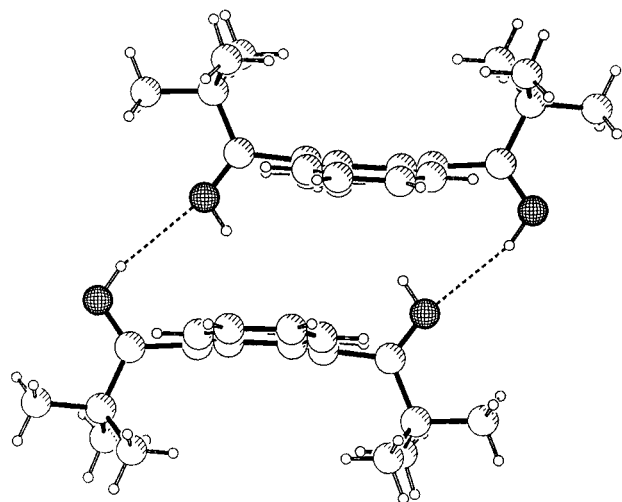
Figure 5. Drawing of compound **4a** showing hydrogen bondings (PLUTON).[10]
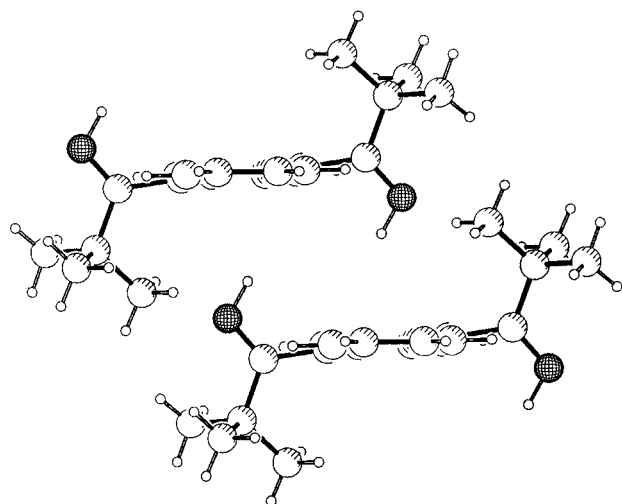
Figure 6. Drawing of compound **4b** (PLUTON).[10]

Table 3. Crystallographic Data for Compounds 4a and 4b

	4a (*cisoid*)	**4b** (*transoid*)
formula	$C_{24}H_{28}N_2$	$C_{24}H_{28}N_2$
color	yellow	colorless
fw	344.48	344.48
crystal shape	tabular	prismatic
crystal dimensions (mm)	$0.50 \times 0.50 \times 0.10$	$0.43 \times 0.32 \times 0.22$
crystal system	triclinic	triclinic
a (Å)	9.701(4)	5.802(3)
b (Å)	11.172(4)	9.360(2)
c (Å)	11.364(2)	9.398(2)
α (deg)	103.97(3)	89.46(2)
β (deg)	114.28(2)	85.30(3)
γ (deg)	106.17(3)	78.09(3)
space group	$P\text{-}1$	$P\text{-}1$
Z	2	1
V	985.1(6)	497.7(3)
d_{calc} (g cm^{-3})	1.161	1.149
T (K)	293	293
radiation λ (Å)	Mo Kα (0.71069)	Mo Kα (0.71069)
μ (mm^{-1})	0.068	0.067
no. of unique reflections	3466	1720
no. observed reflections ($I > 2\sigma(I)$)	1721	1219
no. parameters refined	249	125
$R(F)$ (for observed reflections)	0.051	0.047
$R_w(F^2)$ (all reflections)	0.134	0.139
GOF (all reflections)	0.83	1.04
max/min heights (e Å^{-3})	0.18/$-$0.19	0.16/$-$0.22

(obtained after deconvolution of the NMR signals). The rate constant obtained is $k = 0.0019$ s^{-1}, which corresponds to a $\Delta G^{\ddagger} = 25.68$ kcal/mol at 87 °C. MM3* calculations gave a value for the rotational barrier of 24.95 kcal/mol in good accordance with experimental results and with computed values for **1** and **2**, see above.

Experimental Section

Synthesis of 9,10-Dipivaloylanthracene (3) and 9,10-Bis(1-imino-2,2-dimethylpropyl)anthracene (4). A solu-

tion (1.6 M) of butyllithium (5.6 mL, 9 mmol) was slowly added to a diethyl ether (20 mL) solution of 9,10-dibromoanthracene (1 g, 3 mmol) kept under N_2 with continuous stirring. The reaction was completed after 3 h, and pivaloyl chloride (1.1 mL, 9 mmol) for **3** or pivalonitrile (1.1 mL, 9 mmol) for **4** was added dropwise at room temperature. After 2 h, the reaction was quenched, and the organic layer was separated, dried, and concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane 9/1 v/v) for **3** or (hexane/ethyl acetate 2/1 v/v) for **4**, yield 40%, white solid for **3** and yellow needles for **4**.

3a and 3b. Mp: 230−5 °C (d). IR (KBr) cm^{-1}: 2973 , 2983, 2875, 1679.7 (for **3b**), 1693.6 (for **3a**), 1461, 1398, 1363, 1229, 1180, 1075, 913, 779. EM *m/z* (%): 347 (M + 1, 4), 346 (M, 4), 289 (19), 263 (10), 262 (13), 261 (52), 209 (27), 205 (25), 189 (13), 178 (13), 177 (13), 176 (18), 152 (12), 85 (17), 57 (100), 41 (30). ¹H-NMR (CDCl₃) (ppm): 1.27 (s, tBu **3a**), 1.28 (s, tBu **3b**), 7.46 (4H, m), 7.72 (4H, m). ¹³C-NMR (CDCl₃) (ppm) **3b**: 28.19, 46.21, 126.08,126.67, 137.58, 217,31; **3a**: 28.09, 46.13, 126.01, 126.57, 137.33, 218.61. Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20%; H, 7.56%. Found: C, 83.06%; H, 7.26%.

4a. Mp: 162−8 °C (dec). IR (KBr) cm^{-1}: 3241, 3219, 2966, 1609, 1476, 1356, 1314, 1209, 1075, 871, 794. EM *m/z* (%): 344 (M,20), 287 (100), 231 (87), 230 (62), 229 (94), 204 (35), 203 (37), 57 (23), 41 (26). ¹H-NMR (CDCl₃) (ppm): 1.26 (s,
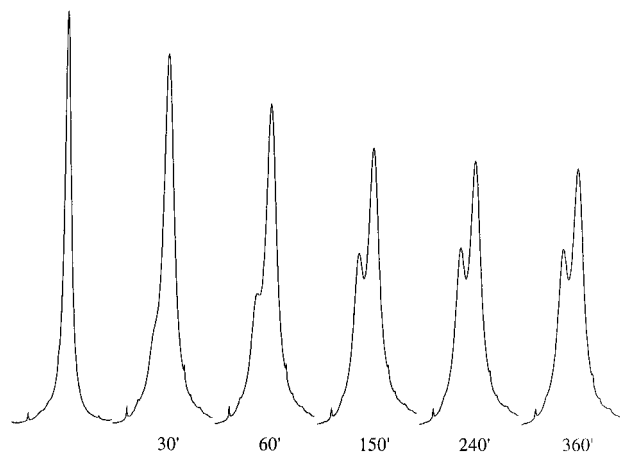
Figure 7. Changes observed on the **4a** and **4b** methyl signals as a function of time at 360 K starting from pure *cisoid* **4a**.

tBu), 7.45 (4H, m), 7.87 (4H, m). ^{13}C-NMR (CDCl$_3$) (ppm): 29.82, 41.36, 125.66, 126.73, 127.20, 190.39. Anal. Calcd for C$_{24}$H$_{28}$N$_2$: C, 83.80%; H, 8.20%; N, 8.14%. Found: C, 83.63%; H, 8.20%; N, 8.15%.

4b. Mp: 165−8 °C (dec). IR (KBr) cm^{-1}: 3248, 2973, 2952, 2910, 2868, 1616, 1469, 1363, 1300, 1202, 1047, 892, 773. ^{1}H-NMR (CDCl$_3$) (ppm): 1.27 (s, tBu), 7.45 (4H, m), 7.88 (4H, m). ^{13}C-NMR (CDCl$_3$) (ppm): 29.97, 41.40, 125.56, 126.88, 127.34, 191.03. Anal. Calcd for C$_{24}$H$_{28}$N$_2$: C, 83.80%; H, 8.20%; N, 8.14%. Found: C, 83.58%; H, 8.19%; N, 8.09%.

Chromatographic Separations. The mixture of diketones **3a** and **3b** was chromatographed on Baker silica gel of 30−60 μm using hexane:dichloromethane (8:1) as eluent.

For HPLC−NMR separations at 35 °C, a β-cyclodextrin column (Cyclobond ISN-250 × 4.6 mm) was used using mixtures of D$_2$O/CH$_3$CN as eluent changing from 70% to 90% in 25 min. A 3 μL volume of a solution (24 mg/mL) of the mixture of diketones was injected under a flow of 1 mL/min.

X-ray Diffraction.[15] Suitable monocrystals of **4a** and **4b** were obtained by vapor diffusion using methylene chloride and pentane. All the measurements were made on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo Kα radiation. The cell dimensions were obtained from least-square refinement on diffractometer angles for 25 centered reflections. The data were collected using the $\omega/2\theta$ scan method to a maximum of 2θ value of 50°. One intense reflection was monitored every hour to check stability. No decay was observed in either case. The data were corrected for Lorentz and polarization effects. No absorption correction was made. The structures were solved by direct methods using the SHELXS-86.[13] All non hydrogen atoms were found in this step. The refinement was performed by full matrix least-squares methods on F^2 for all reflections using SHELXL-93.[14] The H atoms were introduced in calculated positions with isotropic temperature factors fixed at 1.5 (methyl hydrogens) or 1.2 (the rest) U_{eq} of the corresponding carbon atoms.

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(15) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.