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Preparation of Enantiomers of 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroanthracene. Conformational Study and their Behaviour as Chiral Solvating Agents.

Adriana Port, Albert Virgili* and Carlos Jaime.

Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain.

Abstract: Homochiral forms of 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroanthracene were prepared by hydrolysis of crystallised diastereomeric salts of mandelic acid. The activity as chiral solvating agent was tested in the presence of several alcohols and acids. A boat conformation of the central ring was demonstrated by NMR studies and MM3 calculations.

INTRODUCTION

Nuclear Magnetic Resonance (NMR) analysis has been used extensively in organic chemistry to determine the enantiomeric purity of a chiral molecule using a named chiral auxiliary which is added, in its homochiral form to the solution of the deuterated solvent. The association with each enantiomer gives us two diastereomeric forms that are magnetically non equivalent. There are three kinds of chiral auxiliary that convert the mixture of enantiomers into a diastereoisomeric mixture: Chiral Derivatizing Agents (CDA), Chiral Lanthanide Shift Reagents (CLSR) and Chiral Solvating Agents (CSA). A wide range of CSA has been studied: amines, alcohols, sulfoxides, cyclodextrines. Among them aryltrifluoromethylcarbinols and 1-arylethylamines have been applied extensively[1]. Recently, we have carried out the synthesis and structural study of new alcohols[2] with anthracenic structure which may behave as chiral solvating agents. Reagents of this type are now in the NMR test phase, and they have also been studied as chiral auxiliares in asymetric Diels-Alder reactions[3].

The use of optically active amines as chiral solvating agents in the NMR determination of enantiomeric excess (e.e., %) of chiral carboxylic acids has recently grown up[4]. Anisotropic groups (e.g. phenyl rings) in the homochiral compound have given rise to chemical shift non-equivalence in the diastereomeric complexes formed between amine and acid compounds. Amines such as (1*R*,2*R*)-1,2-diphenyl-1,2-diaminoethane[4a] and (-)-9-(1-aminoethyl)anthracene[4b] have been used as CSA with a wide range of chiral carboxylic acids.

Here we report the preparation of a new amine, 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroanthracene **1**, in its homochiral forms, and a complete conformational study by NMR techniques and molecular mechanics methods. The enantiomeric resolution has been carried out by fractional crystallisation using optically active mandelic acid as resolving

agent[5]. The capacity of chiral induction (as a CSA) was tested in the presence of several racemic and non racemic mixtures of enantiomeric alcohols and carboxylic acids.

RESULTS AND DISCUSSION

Synthesis and resolution

Racemic 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroanthracene **1** was obtained by reducing 9-(1-imino-2,2-dimethylpropyl)anthracene[6] which was prepared by a new process[7] based on the reaction of the lithium derivative of 9-bromoanthracene with pivalonitrile, in a yield of 80% (Figure 1).

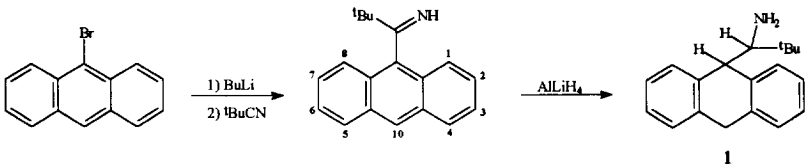


Figure 1

The intermediate product, 9-(1-imino-2,2-dimethylpropyl)anthracene, was also studied by NMR in order to assign the ^{1}H and ^{13}C-NMR signals which were not included in the original paper.[6]

Racemic 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroanthracene, **1**, was resolved efficiently by fractional crystallisation of its diastereomeric salts with homochiral mandelic acid, **2**, of which both enantiomers are commercially available. Treatment of racemic **1** with an equimolar amount of (R)-(-)-mandelic acid gave a pair of diastereomeric salts **3a** (+)-**1**-(R)-(-)-**2** and **4a** (-)-**1**-(R)-(-)-**2**. Their solubility in ethanol was different and they were resolved by simply fractional crystallisation obtaining **3a** (Figure 2). The remaining solution, enriched in compound **4a**, was hydrolysed and the isolated amine (enriched with (-)-**1**) was treated with an equimolar amount of (S)-(+)-**2** in ethanol, which gave the other pair of diastereomeric salts **3b** (-)-1-(S)-(+)-2 and **4b** (+)-**1**-(S)-(+)-**2**. In this case, the fractional crystallisation yielded **3b** (Figure 2) while its diastereomeric salt **4b** remained in solution. The yield of each fractional crystallisation was 58%. An almost quantitative yield was obtained by repetitive cyclic recrystallisation.

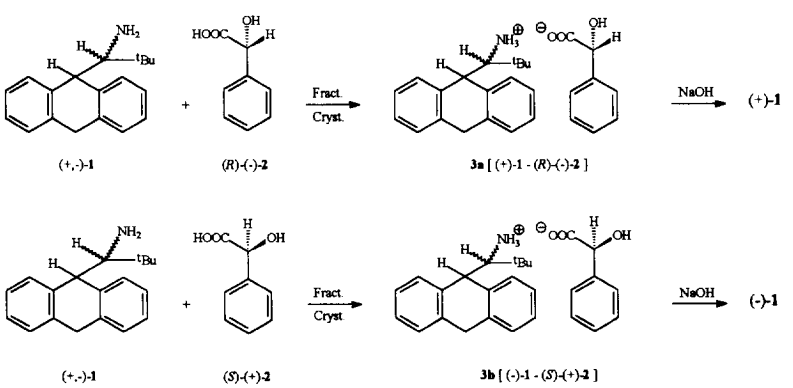


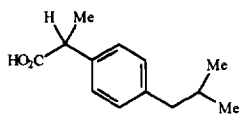
Figure 2

The two homochiral amines, (+)-**1** ($[\alpha]_D^{20}$ = +16.0; c=2.75, methanol) and (-)-**1** ($[\alpha]_D^{20}$ = -16.3; c=1.10, methanol), were obtained by hydrolysis of each enantiomeric salt with aqueous sodium hydroxide (95% yield).

The ^{1}H-NMR spectrum of (+)-**1** or (-)-**1** prepared as before in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol[8] (Pirkle's alcohol) showed its enantiomeric purity by comparison with a similar mixture using racemic (±)-**1**.

Chiral induction activity

A mixture of a chiral acid (ibuprofen **5**, methoxy mandelic **6**, 3-phenylbutyric **7** and 2-bromopropionic **8**) or an alcohol (1-phenyl-1,2-ethanediol **9** and 2,2,2-trifluoro-1-(9-anthryl)-ethanol **10**) with one or two equivalents of (-)-**1** in $CDCl_3$ or C_6D_6 (depending on the solubility) gave diastereomeric complexes in which ^{1}H-NMR chemical shift non-equivalence was observed. Integration of the separate anisochronous resonances allowed measurement of enantiomeric purity. Results are shown in Table 1.



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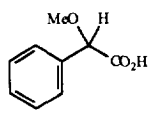

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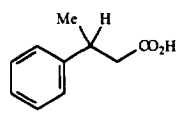

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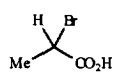

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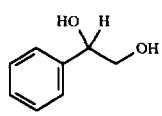

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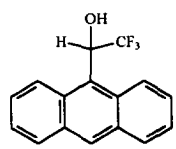

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entry	substrate	observed resonance	Δδ H (Hz) Stoichiometry* 1:2	1:1	solvent
1	**5**	H_c	0.005	0.005	$CDCl_3$
2		2-CH_3	0.005	0.004	$CDCl_3$
3		H_d	0.004	0.005	$CDCl_3$
4	**6**	2-H	0.011	0.014	$CDCl_3$
5		OCH_3	0.043	0.080	$CDCl_3$
6	**7**	3-H	—	<0.002	$CDCl_3$
7			—	<0.002	C_6D_6
8	**8**	CH_3	0.009	0.017	$CDCl_3$
9			—	0.009	C_6D_6
10		2-H	0.011	0.034	$CDCl_3$
11			—	0.017	$CDCl_3$
12	**9**	1-H	0.014[1]	0.020[2]	$CDCl_3$
13		2-CH_2	0.003[1]	0.005[2]	$CDCl_3$
14	**10**	1-H	—	0.030[2]	$CDCl_3$

Table 1. Measurement of the Enantiomeric Purity of Chiral Acids. *Stoichiometry of amine (**1**):chiral acid or alcohol; 295K. [1]Stoichiometry (1:1). [2]Stoichiometry (1:1.5).

Figure 3 shows the spectra obtained for the complexion of (±) **6** with the amine (-) **1**. NMR signal separation of (±)-methoxy mandelic acid was examined with 0.5 and 1.5 equivalents of (-)-**1** in $CDCl_3$. The observed non-equivalence of the methyl and the methine signals increased at higher concentrations of the amine (-)-**1**.

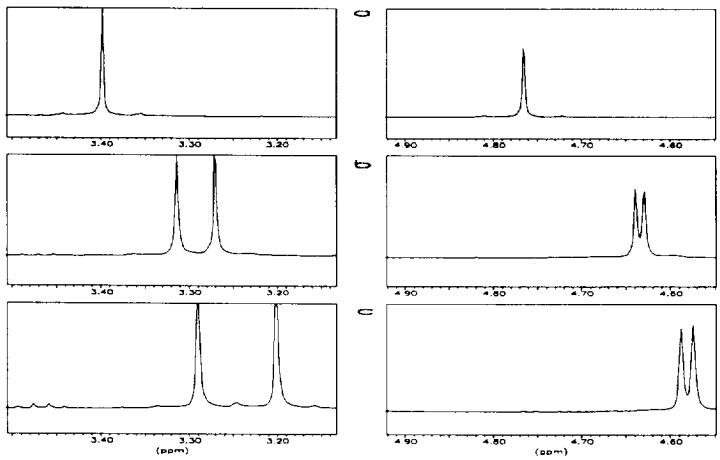

Figure 3: Evolution of $\Delta\delta_H$ for racemic methoxy mandelic acid, **6**, in the presence of (-)-**1** (measured at 400MHz in $CDCl_3$ and at 295 K). **a:** ^{1}H-NMR spectrum of **6**; **b:** ^{1}H-NMR spectrum of **6** with 0.5 equivalents of (-)-**1**; **c:** with 1.5 equivalents of (-)-**1**.

CONFORMATIONAL ANALYSIS OF 1

The stereochemistry of achiral 9,10-dihydroanthracene derivatives has been studied in depth by P.W.Rabideau[9]. The aromatic rings of 9-monosubstituted-9,10-dihydroanthracene are non planar and the central ring shows a boat conformation where, in the solid state, the R substituent is in a pseudoaxial position. In solution there could be an equilibrium between the two boat conformations, in which R can flip from pseudoaxial to pseudoequatorial position (Figure 4):

R-pseudoaxial (Rax) **R-pseudoequatorial (Req)**

Figure 4

The conformational study of amine 1 was carried out by combining MM3 calculations[10] and NMR experiments based on the nOe effect. The torsion energy surface representing the interconversion between the two possible boat conformations (R-ax and R-eq) was computed by driving the 10a-8a-9-9a dihedral angle from +120° to -120° at steps of 10°. The resulting plot contained only two conformers, one for each of the boat conformations. The presence in the molecule of two other rotatable bonds giving rise to energetically different conformers (i.e., the 9-11, and the 11-NH_2)

forced us to accomplish the full conformational study by covering all the possible rotamers within each boat conformation. A total of 9 rotamers were obtained for the R-ax boat conformation, while only 5 energetically different rotamers were obtained for the R-eq boat. The lower number of rotamers for the R-eq boat is due to large repulsions between the substituent and the peri hydrogens which produced either a change of the rotamer or a change of the boat conformation. The difference between the lowest energy minimum of the two boat conformation is 8.77 kcal/mol, favouring the R-ax boat conformation (Figure 5).

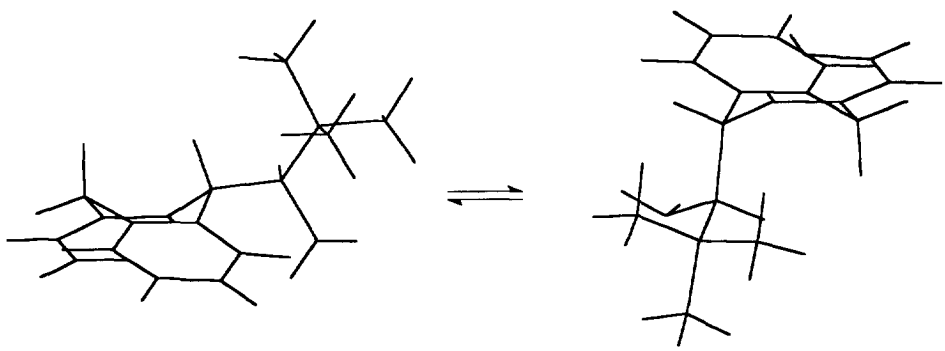

Figure 5: The lowest energy minimum for the R-eq and R-ax boat conformation of **1** as obtained by MM3 calculations.

The conformation of **1** was studied experimentally by NMR methods. Measuring the nuclear Overhauser effect on irradiation of H_{11} caused a small but significant increase in the integrated intensity of H_{10} (≈2.1%) as well as the absence of nOe on the aromatic protons. This effect may occur only when the bulky substituent in the C_9 occupies the pseudoaxial position but not when it occupies the pseudoequatorial position.

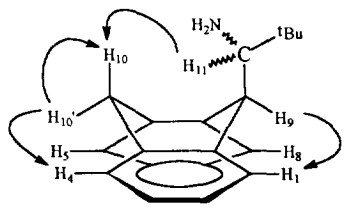

Figure 6: Representation of the nOe effect when H_{11}, H_9 and $H_{10'}$ have been irradiated in **1**.

The nuclear Overhauser effect was also been observed on $H_{1,8}$ and $H_{4,5}$ when H_9 and $H_{10'}$ were irradiated respectively. These experimental results agree with the conformation proposed (R-ax). Table 2 shows the results obtained when the different protons were irradiated.

	nOe effect				
H irradiated	**H_{10}**	**Harom.**	**H_{11}**	**^tBu**	**H_9**
H_{11}	2.01	1.9	—	6.8	2.9
H_9	—	14.6	1.77	—	—
$H_{10'}$	29	15.4	—	—	—

Table 2: Measurement of nOe effects when H_{11}, H_9 and $H_{10'}$ of **1** were irradiated.

Once the conformation of **1** was established, we were able to assign all ^{1}H-NMR (Figure 7) and ^{13}C-NMR signals. The latter was possible after some 2D-NMR experiments such as ^{1}H-^{13}C correlation, HMQC or HMBC.

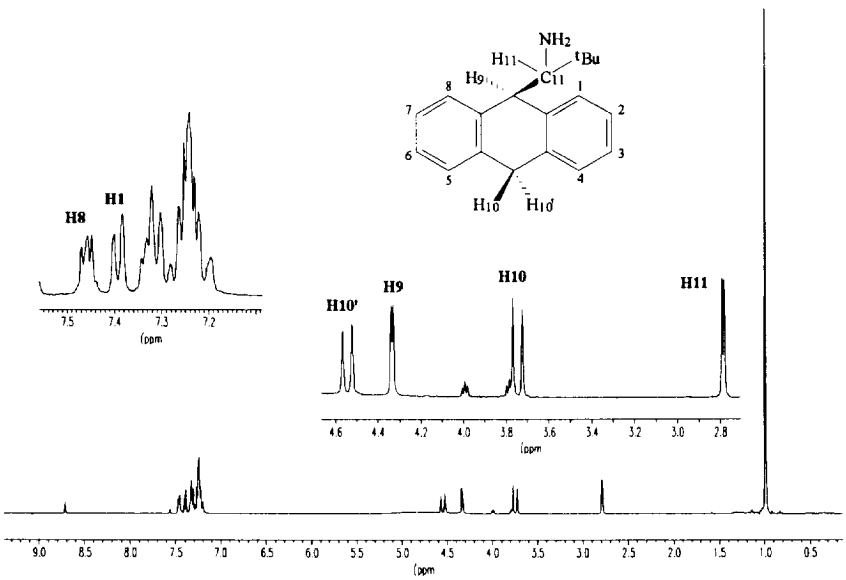

Figure 7: ^{1}H-NMR for amine **1** in pyridine-d_5

EXPERIMENTAL

Synthesis: 9-(1-imino-2,2-dimethylpropyl)anthracene: A solution (1.6M) of butyllithium (10.7 ml, 17.14 mmol) was slowly added to a diethyl oxide (70 ml) solution of 9-bromoanthracene (4 g, 15.58 mmol) kept under N_2 with continuous stirring. The reaction was completed after 30 minutes and pivalonitrile (1.9 ml, 17.14 mmol) was added dropwise at room temperature. After 1h, 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/ethyl acetate 90/10 v/v): yellow needles, m.p:113-114°C; IR (KBr) cm^{-1} 3240,3050,2959,2868,1609 (C=N), 1455,1314,895,737. ^{1}H-NMR ($CDCl_3$) (ppm): 1.29 (s, ^{t}Bu), 7.45 (m, H_2/H_3/H_6/H_7), 7.87 (m, H_1/H_8), 7.98 (m, H_4/H_5), 8.39 (s, H_{10}), 9.8 (broad, H_{NH}).

^{13}C-NMR ($CDCl_3$) (ppm): 29.8, 42.3, 125.2, 125.6, 126.4, 126.8, 128.5, 127.7, 131.1, 137.2, 190.7. EM m/z (%): 261 (11), 205 (17), 204 (100), 203 (26), 177 (16), 176 (16), 57 (28), 41 (37).

9-(1-amino-2,2-dimethylpropyl)anthracene 1: A diethyl oxide solution (10 ml) of 9-(1-imino-2,2-dimethylpropyl)anthracene (395 mg, 1.51 mmol) was slowly added to a diethyl oxide (20 ml) solution of $AlLiH_4$ (400 mg, 10.6 mmol) kept under N_2 with continuous stirring and the temperature kept at 310°K. After 25h, reduction was completed. The reaction was quenched and the organic layer was separated, dried and concentrated.

Optical resolution of (±)-1: Powdered (S)-(+)-mandelic acid **2** (379 mg, 2.49 mmol) was added to a solution of **(±)-1** (660 mg, 2.49 mmol) in ethanol (20 ml). The mixture was then stirred to give a clear solution and heated to about 40°C. After cooling to 20 °C, the precipitated salt **3b** was collected by vacuum filtration (310 mg, 0.74 mmol, 58% yield, 99% de). The salt was recrystallised from ethanol to give diastereomerically pure **3b**.

Enantiomerically pure **(-)-1** was obtained from the salt as follows: a suspension of the salt (300 mg) in water (10 ml) was stirred with 4 mol dm^{-3} aqueous sodium hydroxide and the oil released was extracted with diethyl oxide (20 ml). The organic layer was dried and concentrated. Recrystallisation from hexane give enantiomerically pure **(-)-1**.

The antipode, **(+)-1**, was obtained in a similar manner: (+) enriched **1** recovered from the mother liquor was treated with **(R)-(-)-2** to give diastereomerically pure **3a** salt. Treatment of the salt with aqueous sodium hydroxide gave enantiomerically pure **(+)-1**: white needles, **(+)-1** ($[\alpha]_D^{20}$ = +16.0; c=2.75, methanol) and **(-)-1** ($[\alpha]_D^{20}$ = -16.3; c=1.10, methanol), m.p: 74-75°C (from hexane); IR (KBr) cm^{-1}: 3395, 3325, 3065, 3023, 2959, 2868, 1722, 1652, 1609, 1476, 1455, 1363, 1124, 963, 745. ^{1}H-NMR (C_5D_5N) (ppm): 0.99 (s, ^{t}Bu), 2.78 (d, H_{11}, J_{AB}=4.0 Hz), 3.74 (d, H_{10}, J_{AB}=17.9 Hz), 4.33 (d, H_9, J_{AB}=3.9 Hz), 4.54 (d, $H_{10'}$, J_{AB}=17.9 Hz), 7.15-7.35 (m, 6H, aromatic H), 7.39 (d, H_1), 7.45 (m, H_8). ^{13}C-NMR ($CDCl_3$) (ppm): 27.4 (Me_{tBu}), 35.9 (Cq_{tBu}), 37.0 (C_{10}), 50.3 (C_9), 66.6 (C_{11}), 127.7-128.0 (C_4/C_5), 128.3-129.8 (C_1/C_8), 137.6-138.9 (C_{4a}/C_{10a}), 138.6-142.2 (C_{9a}/C_{8a}), 125.6-126.2 ($C_2/C_3/C_6/C_7$). EM m/z (%): 208 (M-57, (^{t}Bu), 2), 178 (14), 86 (^{t}BuCHNH$_2$, 100), 69 (21), 41 (14). $C_{19}H_{23}N$, calc: C, 86.12%; H, 8.75%; N, 5.29%; found: C, 86.01%; H, 8.82%; N, 5.24%.

3a and 3b: White needles; m.p: 161-163°C (from ethanol). **3a:** $[\alpha]_D^{20}$=+13.0; c=1.00; methanol; **3b:** $[\alpha]_D^{20}$ = -11.0; c=1.02; methanol. IR (KBr) cm^{-1}: 3346, 3262, 2959, 2910, 2474, 1637, 1553, 1518, 1476, 1427, 1075, 773, 695. ^{1}H-NMR (CD_3COCD_3) (ppm): 0.78 (s, ^{t}Bu), 3.65 (d, 1H, J_{AB}= 9.2 Hz), 3.85 (d, 1H, J_{AB}= 17.7 Hz), 4.28 (d, 1H, J_{AB}= 17.7 Hz), 4.57 (d, 1H, J_{AB}= 9.2 Hz), 4.98 (s, 1H), 7.05-7..35 (10H, aromatic H), 7.46 (m, 1H), 7.55 (d, 2H). ^{13}C-NMR (CD_3COCD_3) (ppm): 27.51, 35.87, 36.71, 50.08, 70.74, 74.21, 126.10, 126.776, 127.03, 127.43, 127.69, 128.17, 128.50, 128.54, 130.40, 130.61, 139.17, 139.50, 139.93, 140.73, 143.13, 176.26. $C_{27}H_{31}NO_3$, calc: C, 77.77%; H, 7.49%; N, 3.36%; found: C, 77.71%; H, 7.50%; N, 3.37%.

NMR experiments: NMR experiments were conducted on a Bruker ARX400 spectrometers with a 5mm QNP probe using C_5D_5N, CD_3COCD_3 and $CDCl_3$ as solvents. The operating frequency was 400.16 MHz for ^{1}H. All the steady-state nOe experiments were obtained using 8 s of low-power (typically 50L) presaturation; two dummy scans were used.

MM calculations: Calculations were carried out on a VAX-6640 computer at the Computing Center of the UAB. Allinger's MM3(92) force field was used throughout[10]. Phenyl rings were treated as a delocalised system using the standard MM3procedures. All computations were carried out assuming a vacuum.

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