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Preparation of (*R*)- and (*S*)-1-adamantyl-9-anthrylmethanol. Conformational study and their behaviour as chiral solvating agents

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Abstract

Enantiopure forms of 1-adamantyl-9-anthrylmethanol were prepared and a conformational study was carried out by MM and NOE transfer methodologies. The absolute configuration was determined by combining dynamic NMR and theoretical calculations of the carbamate derivatives. The activity as a chiral solvating agent was tested in the presence of oxygenated functional groups.

1. Introduction

Nuclear magnetic resonance (NMR) analysis has been used extensively in organic chemistry to determine the enantiomeric purity[1] of chiral molecules using particular chiral auxiliaries which are added, in enantiopure form, to the solution in deuterated solvent. The association with each enantiomer gives us two diastereomeric forms that are magnetically non-equivalent.

Recently, we have carried out the synthesis and structural study of new alcohols[2] and amines[3] with an anthracenic structure, which may behave as chiral solvating agents. We have demonstrated[4] that *tert*-butyl-9-anthrylmethanol, whose benzylic protons are less acidic than those of the Pirkle's alcohol, also forms chiral associations with several classes of compound; the strong conformational rigidity of this molecule allows us to observe intermolecular nuclear Overhauser effects[4] in these complexes.

Here, we report the preparation of 1-adamantyl-9-anthrylmethanol **1**, in its enantiomeric forms, and a complete conformational and dynamic study by NMR techniques and molecular mechanics methods. The capacity for chiral recognition (as a CSA) was tested in the presence of several racemic and non-racemic oxygenated compounds.

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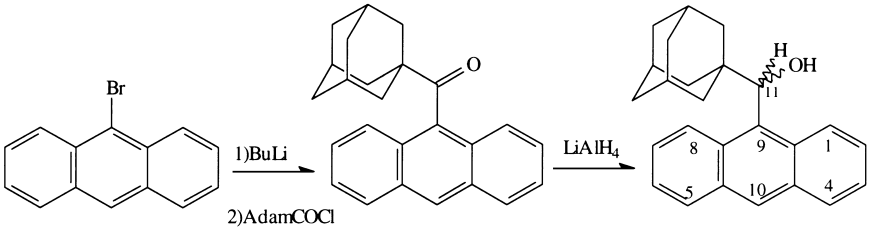
2. Results and discussion

2.1. Synthesis, resolution and structural study

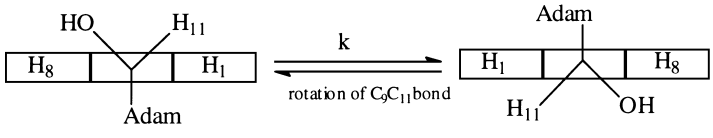
Racemic 1-adamantyl-9-anthrylmethanol **1** was obtained by reducing 1-adamantyl-9-anthrylketone which was prepared by condensation of bromoanthracene with adamantoyl chloride (Scheme 1).



2 **1**

Scheme 1. Preparation of compound **1**

The structural study of compound **1** includes the measure of the rotational barrier around the C_9–C_{11} bond. The dynamic study of rotation about this C_9–C_{11} bond (Scheme 2) by complete line shape analysis (CLASA) is not possible because $k<\Delta\delta$ and there are no changes in the spectra obtained at several temperatures. We have used the described[5] NOE transfer method to measure the kinetics shown in Scheme 2.



Scheme 2. Conformational equilibrium of compound **1**

We studied, at several temperatures, the change of the NOE on the H_1 and H_8 when the H_{11} was saturated. Table 1 shows the results obtained when we applied the NOEDIFF experiment. The relaxation constants are also given and were measured by the standard method of inversion–recovery.

Only from 340 K can we observe NOE on H_8, meaning that the exchange process between H_1 and H_8 becomes faster than the relaxation rates ($k \gg T_1^{-1}$). We can see that when the temperature increases, the NOE on H_1 decreases while on H_8 it increases. Applying the corresponding Eq. 1 we can calculate the kinetic constant and a very high energy of rotation for the indicated bond is obtained.

Table 1
Nuclear Overhauser effect at several temperatures measured on protons H_1 and H_8 of **1** when H_{11} is saturated

T /K	nOe /%		T_1 /s		R_{1l} /s^{-1}		k	$\Delta G^{\#}$
	H_1	H_8	H_1	H_8	H_1	H_8	/s^{-1}	/Kcal/mol
300	24.3	-	1.25	1.90	0.80	0.53	-	-
340	23.4	0.8	1.45	2.19	0.69	0.46	0.016	22.8
360	17.6	3.4	1.73	2.60	0.58	0.38	0.092	22.9

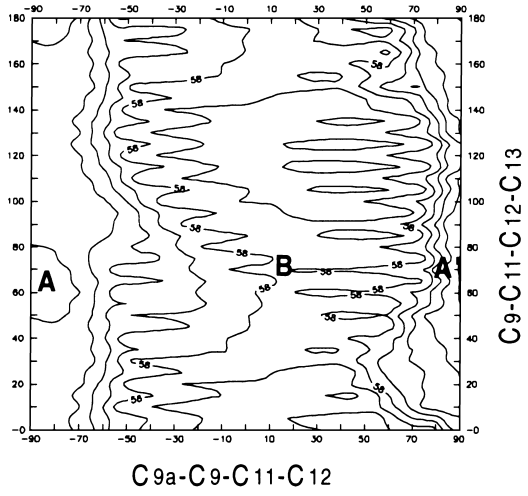


Figure 1. Potential energy surface for the rotation of ω_1 and ω_2 of **1**

$$\frac{f_{I8}(S)}{f_{I1}(S)-f_{I8}(S)}=\frac{k}{R_{I8}} \tag{1}$$

The $\Delta G^{\ddagger}$ for the described process is 1 kcal/mol higher than those measured[5] for the *tert*-butyl analogue, demonstrating a more important conformational rigidity for this adamantyl derivative.

The theoretical study based on molecular mechanics methodologies gives us the diagram in Fig. 1 where the potential energy is a function of the two dihedral angles ω_1 (C_{9a}–C_9–C_{11}–C_{12}) and ω_2 (C_9–C_{11}–C_{12}–C_{13}). The energy for the rotation of the C_9–C_{11} bond is calculated measuring the energy difference between the two rotamers (A and A′) and the transition state (B). The MM calculated value ($\Delta H^{\#}$) (22.3 kcal/mol) is in good agreement with the experimental value, suggesting that the entropic factor is very low.

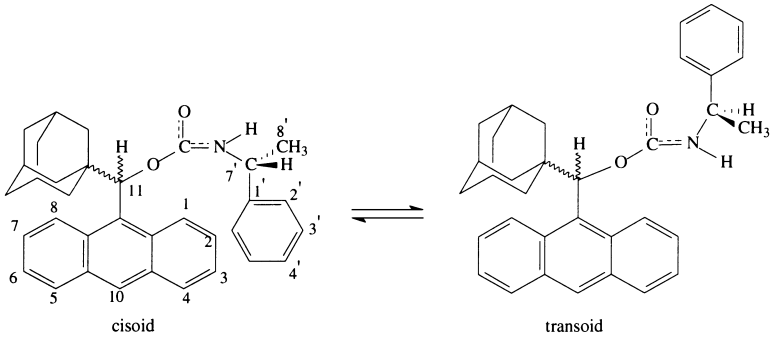
Racemic 1-adamantyl-9-anthrylmethanol **1** was resolved efficiently by two different processes. Directly, by preparative HPLC, with an (*R*,*R*)-Whelk-O1 semi-preparative column, using a flow of 4.5 ml/min of a mixture of hexane:isopropanol, 98:2. The two enantiomers were obtained at 28 ($[\alpha]_D^{25}=6.9\pm0.3$) and 31 min ($[\alpha]_D^{25}=-5.8\pm0.2$) retention times.

In an indirect way: we prepared the carbamate derivatives with 1(*R*)-phenylethylisocyanate. Its separation in flash chromatography gave us two diastereoisomers, **3** and **4**, that after hydrolysis yielded both enantiomers of **2**. The same carbamates were obtained directly from pure enantiomers (**3** from the first eluted and **4** from the second eluted).

The structural study of the isolated carbamates allowed us to determine the absolute configuration of the enantiomers of **2**. Each carbamate can be represented by the equilibrium between two forms (rotamers) around the C–N bond, *cisoid* and *transoid* (Scheme 3). The experiments of 1H{1H} NOE, that include the signals corresponding to saturation transfer, allowed us to correlate the signals corresponding of the two rotamers of each carbamate.

The ^{1}H NMR spectra at 265 K of each isolated carbamate present two important differences: the proportion (85:15 and 60:40 for **3** and **4**, respectively) and the difference in the chemical shifts of the two rotamers. Table 2 shows the chemical shifts of the protons of each rotamer of **3** and **4**, respectively.

We point out the great difference of chemical shift of H_8 between rotamers of compound **3**, owing to the distinct spatial disposition and proximity to the groups with magnetic anisotropy.



Scheme 3. Equilibrium between the *cisoid* and *transoid* rotamers of compounds **3** and **4**

Table 2
Chemical shifts of protons of carbamates **3** and **4** registered at 265 K

Compound		(*R*,*R*)-**3**			(*S*,*R*)-**4**	
Proton	Major	Minor	Difference	Major	Minor	Difference
H_1	8.60 (d)	8.60 (d)	-	8.58 (d)	8.58 (d)	-
H_2,H_3,H_6,H_7, $H_{2'}$,$H_{3'}$,$H_{4'}$	7.20-7.60	7.20-7.60	-	6.9-7.6	6.9-7.6	-
H_4	8.05 (d)	7.99 (d)	0.06	8.00 (d)	8.06 (d)	-0.06
H_5	8.01 (d)	7.88 (d)	0.13	7.99 (d)	7.63 (d)	0.36
H_8	9.05 (d)	8.27 (d)	**0.78**	9.06 (d)	8.89 (d)	0.17
H_{10}	8.52 (s)	8.43 (s)	0.09	8.47 (s)	8.54 (s)	-0.07
H_{11}	7.01 (s)	6.97 (s)	0.04	7.07 (s)	7.12 (s)	-0.05
$H_{7'}$	4.63 (m)	5.22 (m)	-0.59	3.94 (m)	4.68(m)	-0.74
$H_{8'}$	1.25 (d)	1.44 (d)	-0.19	1.39 (d)	1.36 (d)	0.03
Had	1.5-2.5	1.5-2.5	-	1.3-2.05	1.3-2.05	-

In a parallel way we have calculated the energy of rotamers of **3** and **4** (Table 3). Table 3 also displays the calculated distances that could justify the variation of chemical shift.

The difference between the distances of H_8 to the anisotropic points of the same compound ($C_{1'}$) in the two rotamers of two diastereoisomeric carbamates indicates that the carbamate of the first eluted enantiomer of the column **3** corresponds to the (*RR*)-isomer while the second **4** is the (*SR*)-compound, corresponding to the (*R*)-**2** and (*S*)-**2** alcohols, respectively.

2.2. Chiral induction activity

Substrate **2** was tested as a CSA in the presence of two racemic and non-racemic chiral compounds: 1-phenyl-1,2-ethanediol **5** and (α)-methoxyphenylacetic acid **6**. When (*S*)-**2** was added to a solution (0.13 M) of racemic **6**, we observed (Fig. 2), in addition to a general shielding effect, a separation in the signals corresponding to H_1 and H_3.

Table 3
Calculated internuclear distances and values of formation energies of compounds **3** and **4**

	E/Kcal/mol	$d(H_{11}\text{-}H_1)$/Å	$d(H_{11}\text{-}H_8)$/Å	$d(H_8\text{-}C_{1'})$/Å	$d(H_1\text{-}C_{1'})$/Å
SR-cisoid	159.2	1.87	3.81	3.67	6.61
SR-transoid	159.1	1.88	3.82	4.52	6.47
Difference	0.1	-	-	-0.85	0.14
RR-cisoid	161.0	1.87	3.81	3.02	7.03
RR-transoid	160.9	1.87	3.81	5.37	7.73
Difference	0.1	-	-	-2.35	-0.70

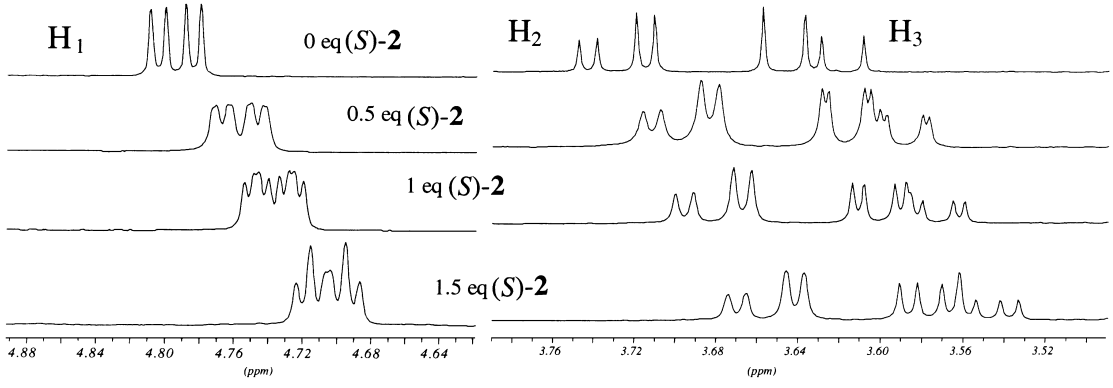


Figure 2. Part of NMR spectra of 1-phenyl-1,2-ethanediol **5** when (*S*)-**2** was added

The same experiment using each isolated enantiomer of **5** allows us to recognise that the enantiomer which shifted at the highest fields corresponds to (*R*)-**5**.

Since the conformational study of **5** by MM3[6] calculations gives a 90% population of II conformer, one could conclude that the proximity and solvation of two components takes place between the less steric hindered faces of anthracene rings, leaving the adamantane group outside the complex. Since the formation of the hydrogen bond and the π–π-stacking interactions are stabilising factors and since (*R*)-**5** is displaced to higher fields than (*S*)-**5** we can assume that, for the same kinetic factor, the complex (*S*)-2·(*R*)-**5** is more stable than the (*S*)-2·(*S*)-**5**.

The results are summarised in Table 4, where the maximum variation of the chemical shift for each enantiomer was observed when 1.5 equiv. of (*S*)-**2** was added. Also, in Table 4 the values obtained when (*S*)-**2** was added to a 0.11 M solution of α-methoxyphenylacetic acid **6** are included. Studying a non-racemic mixture we can deduce that the more shielded enantiomer also corresponds to the (*R*)-**6**.

Table 4
Differences of the chemical shifts of the protons for the two enantiomers (δ_S–δ_R) of **5** and **6** when several quantities of (*S*)-**2** were added

compound	1-phenyl-1,2-ethanediol **5**		(α)-methoxyphenylacetic acid **6**	
CAS added	$\Delta\delta H_{1'}$(ppm)	$\Delta\delta H_{3'}$(ppm)	$\Delta\delta H_1$(ppm)	$\Delta\delta H_{CH3}$(ppm)
0.5 eq **2S**	0	0.0037	0	0.0030
1.0 eq **2S**	0.0030	0.0059	0.0039	0.0049
1.5 eq **2S**	0.0081	0.0089	0.0078	0.0088

3. Experimental

*3.1. Synthesis: 1-adamantyl-9-anthrylmethanone **2***

A solution (1.6 M) of butyllithium (16 ml, 25.6 mmol) was slowly added to a diethyl ether (90 ml) solution of 9-bromoanthracene (4.75 g, 18.47 mmol) kept under N_2 continuous stirring. The reaction was completed after 3 h at room temperature. A diethyl ether solution of carbonyl adamantyl chloride (4.78 g, 25.06 mmol) was added dropwise. After 3 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:methylene chloride, 9:1 v/v): mp 167–170°C; IR (KBr) 2924, 2903, 1687 (C=O), 1447, 1349, 1265, 1194, 1173, 1145, 913, 892, 843, 737, 611 cm^{-1}; ^1H NMR: 1.64 (m, 3H), 1.98 (m, 12H), 7.45 (m, 4H), 7.69 (m, 2H), 8.00 (m, 2H), 8.43 (s); ^{13}C NMR ($CDCl_3$): 28.1, 36.4, 38.9, 48.3, 123.4, 125.3, 125.8, 125.9, 128.7, 127.5, 131.0, 136.5 and 217.5.

*3.2. 1-Adamantyl-9-anthrylmethanol **1***

A diethyl ether solution (15 ml) of $LiAlH_4$ (18 mg, 0.49 mmol) was slowly added to a diethyl ether (15 ml) solution of 1-adamantyl-9-anthrylmethanone (100 mg, 0.29 mmol) kept under N_2. Reduction was completed in 1 h. After adding ethyl acetate and water the organic layer was separated, dried and concentrated. The solid residue was purified (70% yield) by recrystallisation in cyclohexane: mp 165–168°C; IR (KBr) 3536, 3466, 3051, 2903, 2847, 1623, 1511, 1447, 1349, 1314, 1279, 1117, 1061, 1018, 892, 794, 730 and 597 cm^{-1}.

3.3. N-*(1-Phenylethyl)carbamates **3** and **4***

Carbamates were prepared according to the literature:[7] racemic 1-adamantyl-9-anthrylmethanol (100 mg, 0.30 mmol) and (*R*)-(+)-(1-phenylethyl)isocyanate 99% (0.15 ml, 1.07 mmol) were mixed and heated to 80°C while protected by a drying tube for 72 h. The mixture was chromatographed with toluene:methylene chloride (2:1) on a 2.5×20 cm column of silica gel. The first major fraction to be eluted was (*R*,*R*)-**3**. Crystallisation from hexane gave white needles. The second major fraction to be eluted was (*S*,*R*)-**4**.

3.4. NMR experiments

NMR experiments were conducted on a Bruker ARX400 spectrometer with a 5 mm QNP probe using CD_3COCD_3 and $CDCl_3$ as solvents. The operating frequency was 400.16 MHz for ^1H.

3.5. MM calculations

Calculations were carried out on a Silicon Graphics Indy computer with an R4000 processor. MM3*[6] force field as implemented in a MacroModel[8] and BatchMin version 5.0 were used throughout this work. All computations were carried out assuming a vacuum. Potential energy surfaces were calculated by increasing the selected dihedral angle by 10°.

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