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Conformational Analysis of MNCB (MBNC) Esters and Amides: Promising Chiral Reagents for Stereoselective Applications

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ABSTRACT: Calculations (MM, AM1/PM3, *ab initio*) and DNMR experiments indicate that 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (**MNCB**) and 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (**MBNC**) esters and amides exist in solution as two conformers in equilibrium: one of them (*sp*) has synperiplanar Ar_1-Ar_2 and C=O bonds, and another one (*ap*) has antiperiplanar bonds.

Due to the close populations of the forms only a part of large shielding effects attributed to the ***ap*** form is transformed into observed high field shifts in NMR experiments. Thus, the low population of the "***ap***" conformer and the low selectivity of the aryl ring anisotropic influence on the alcohol (amine) moiety are limitations of the efficiency of **MNCB** (**MBNC**) in their use as reagents for absolute stereochemistry determination of alcohols and amines by NMR. The way to increase the efficiency of this type of reagent has been revealed on the basis of these findings. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The growth of interest in stereoselective synthesis and drug design necessitates effective and reliable methods to control enantiomeric purity and absolute stereochemistry of chiral compounds. Therefore essential efforts have been directed towards developing methods to analyze optically active compounds.[1] Up to now the NMR based method [2] is one of the most attractive ones: it is based on the derivatization of enantiomers (indistinguishable in terms of NMR) into diastereomers by corresponding chiral derivatizing reagents (CDR) followed by analysis of their NMR spectra.

Since the first pioneering work of Raban and Mislow several chiral reagents were proposed and were found to be useful in determination of absolute configuration of secondary alcohols.[3] All of them contain a chiral center and an aryl ring, the asymmetric, anisotropic influence [4] of which in diastereomers leads to the differentiation of esters in NMR. Differences were interpreted using empirical models and rules for determination of absolute configuration were formulated.

Later, in a similar way, several new classes of chiral compounds were studied by NMR: primary and secondary alcohols, primary amines and carboxylic acids.[5]

Recently the main factors that determine the efficiency of the method in the case of secondary alcohols were established and the basic rules for designing new reagents were formulated.[6] It was shown that structures and populations of the main forms are of great importance in this method. New reagents and preferable conditions were proposed on the basis of these findings.

At the same time, during the last years several examples of axially chiral reagent applications were dem-

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onstrated.[7] Sterically hindered bi-aryls are axially chiral due to the high barrier of rotation around the aryl-aryl bond, which can be easily separated in enantiomerically pure form. They can react with alcohol and amines without racemization. Thus the derived diastertomeric esters and amides can be analyzed by NMR (Fig. 1).

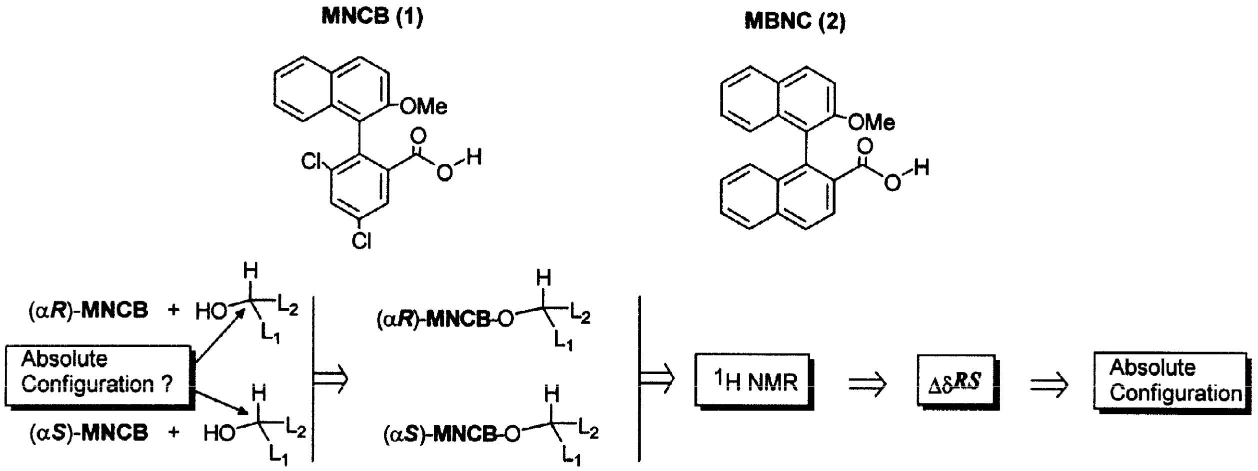


Figure 1. Derivatization of secondary alcohols by MNCB or MBNC

The essential shielding effects were observed on alcohol and amine moiety in esters and amides of 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (**MNCB, 1**) and 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (**MBNC, 2**). Namely, high field shifts were found to be different for diastereomers and empirical model was proposed to correlate chemical shifts with the absolute configuration of the alcohol (Fig. 2). However, in spite of large shielding effects, the NMR differentiation of the diastereomers ($\Delta\delta^{RS}$) [8] is not high enough, although one could expect much higher separation.

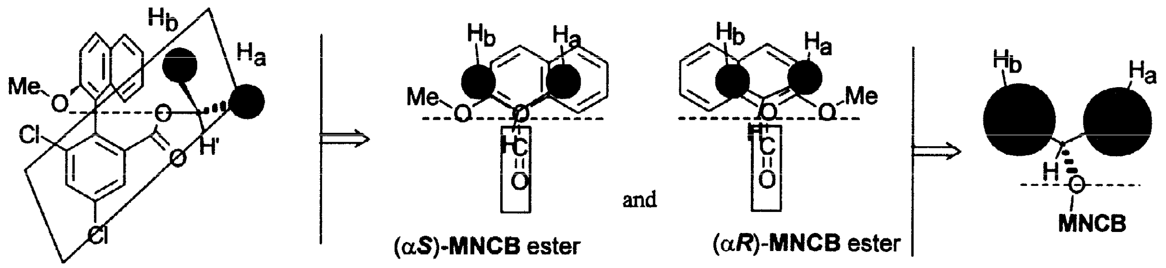


Figure 2. Model to correlate NMR chemical shifts and stereochemistry of the MNCB (MBNC) derivatives.

It is very likely that this occurs due to unfavorable conformational properties. However, no conformational analysis in solution is available for the title compounds to our knowledge.

The determination of factors which govern the equilibrium of MNCB and MBNC esters and amides may provide an opportunity to tune conformational parameters for the rational design of new similar acids to obtain all the intrinsic advantages of this type of the reagent. Moreover, if peculiarities of the conformational equilibrium were known, new applications of these compounds as chiral auxiliaries in a variety of reaction types would be found, i.e. as a steric barrier in some stereoselective reactions.

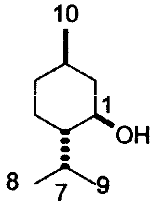
This work was undertaken with the purpose of gaining insight into the conformational properties of **MNCB** (**MBNC**) esters and amides. Some results of calculations and DNMR experiments are presented. The aromatic shielding effect calculations confirm the conclusions. Scope and limitations are discussed.

RESULTS

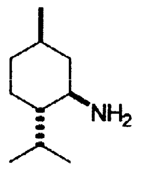
Calculations

Initial geometries were minimized using the Molecular Mechanics (MM) method and then were used as starting structures in semiempirical (PM3 or AM1) quantum chemical calculations. *Ab initio* (HF 3-21 G//HF 3-21 G) calculations were performed for the simplest model systems (**1-4**, Fig.3) to check geometries and energies obtained by simpler methods (MM and PM3/AM1). The main results are summarized in Table 1.

Acid	X	R	Compound
MNCB	O	H	1
MBNC	O	H	2
MNCB	NH	H	3
MBNC	NH	H	4
MBNC	O	i-Pr	5
MBNC	NH	i-Pr	6
MNCB	O	(-) menthol	7
MBNC	O	(-)-menthol	8
MNCB	NH	(-)-menthylamine	9



(-)-menthol



(-)-menthylamine

Figure 3.

It was found that esters and amides of **MNCB** and **MBNC** have very similar conformational parameters. All the main peculiarities in the geometry and in the energy which were found for **MNCB** derivatives were also revealed for **MBNC** ones (see Table 1). Therefore only the main results for **MNCB** derivatives will be discussed in detail unless otherwise noted.

Table 1. Comparison of MM, PM3/AM1 [a] and *ab initio* Energies (kcal/mol) of Main Conformers Around Ar-CO Bond of **MNCB** (**MBNC**) Esters and Amides (**1-4**).

ester/amide	acid	conformer	MM [b]	PM3 [c]/AM1 [d]	HF3-21G//HF3-21G
ester	**MNCB**	*sp*	0.00	0.00 [d]	0.00
	MNCB	*ap*	1.21	0.70 [d]	0.90
	MBNC	*sp*	0.00	0.00 [c]	0.00
	MBNC	*ap*	1.41	0.90 [c]	2.02
amide	**MNCB**	*sp*	0.00	0.00 [c]	0.00
	MNCB	*ap*	1.72	0.12 [c]	1.45
	MBNC	*sp*	0.00	0.00 [c]	
	MBNC	*ap*	1.93	0.98 [c]	

[a] AM1 was used when PM3 failed to find an energy minimum corresponding to one of the conformer; [b] pcff91 force field, ε=8; [c] PM3method; [d] AM1 method

According to the results of MM calculations MNCB (MBNC) esters (amides) are in equilibrium in the form of two conformers obtained by rotation around the Ar_1-CO bond (schematically shown on Fig. 4): one (*sp*) conformer has the synperiplanar Ar_1-Ar_2 and C=O bonds, and another (*ap*) conformer has antiperiplanar bonds. In both conformers the aryl plane (Ar_1), C=O and $C_{1'}$-H' bonds are approximately co-planar while the second aryl (Ar_2) ring is almost perpendicular to the first aryl ring.

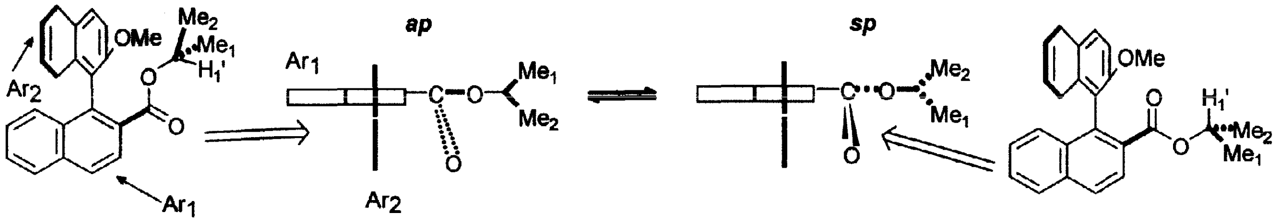


Figure 4. Conformational equilibrium of MBNC esters.

Thus, the alcohol (amine) moiety protons are located in the area of the aromatic shielding cone of the second aryl (Ar_2) ring in the *ap* conformer. Only slight effects for some of the protons can be expected in the *sp* conformer. It follows from comparison with AMAA [6] derivatives that the aryl (Ar_2) ring is much closer to the alcohol (amine) fragment and its orientation is more preferable to produce shielding effects (the main conformers of (α*R*)-MBNC amide of (-)-menthyl amine are shown on Fig. 5).

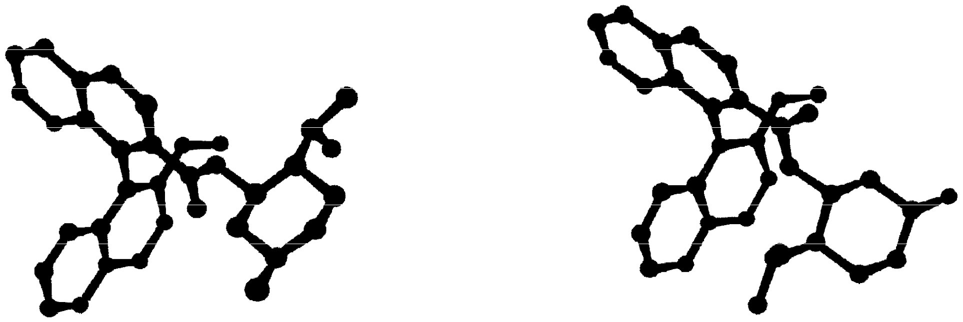


Figure 5. Structures of (α*R*)-MBNC amide of (-)-menthylamine in the *sp* and *ap* conformations.

According to MM calculations the *sp* conformer is more stable than the *ap* one for almost all MNCB (MBNC) derivatives (Table 1). The barrier of interconversion between these conformers is ca. 11 kcal/mol.

Usually MM calculations predict reasonable structures but the energy data is less accurate. Moreover, according to the protocol of calculations, the full force-field parameter-set is unavailable for some structural fragments. Therefore we carried out calculations on the semiempirical level of the theory (AM1/PM3) and, in general, similar results were obtained.

These results do not coincide with results of previous studies [7] in which only the *ap* form was considered and the dominance of the other form was not expected. Therefore, to confirm the results obtained, the calculations of the energy on the non-empirical level of the theory were performed for the simplest systems.

For a variety of molecular systems, it was already shown by Pople [9] that *ab initio* optimization reproduces well gas-phase geometry. There are many examples [10] showing that solvent effects on the geometry of the conformers are insignificant and only an influence on the populations of the forms can be expected. In addition, we found that the minima on the potential energy profile around the Ar-CO bond in the systems under investigation is very sharp and therefore the position of energy minimum will be hardly changed due to medium effect. Therefore it can be expected that the *ab initio* produced geometry should be close to the solution phase one.

For our compounds we found that in general MM and *ab initio* geometries are in good agreement. This proximity of MM and *ab initio* results for models allows us to expect that MM generated geometries for molecules used in DNMR experiments also should be close to the real solution state structures.

The analysis of energy distribution of the ester array for the simplest model shows that all three methods give preference to the ***sp*** conformer that has not been taken into consideration before. The energy gap is ca. 0.1-0.9 kcal/mol.

It is important that PM3 (AM1)and *ab initio* results for the models coincide with each other. Therefore semiempirical methods can be used to analyze the conformational energy distribution of compounds prepared for DNMR experiments.

The calculations (MM and PM3 (AM1)) on the ***R***- and ***S*-MNCB** (**MBNC**) esters of (-)-menthol (**7, 8**) predict similar energy distributions (PM3 or AM1) and geometries.

As a whole, the results of the calculations allow a partial explanation of the available experimental data: remarkable shielding effects may be due to a "good" orientation of the aryl ring with respect to an alcohol (amine) moiety in the ***ap*** form.

At the same time thermodynamic (small energy difference between the ***ap*** and ***sp*** rotamers (PM3/AM1)) and geometric (low selectivity of the shielding effects of Ar_2 on the alcohol's protons) parameters result in the loss of the essential part of the indicative $\Delta\delta^{RS}$ difference. Namely, in each diastereomer, due to the ***ap-sp*** equilibrium, shielding effects are produced for both groups (i.e. on Fig. 6a the L_1 in the ***sp*** and the L_2 in the ***ap***) and even in ***ap*** conformer orientation of the second aryl is such that shielding effects are produced on both groups L_1 and L_2 (i.e. on Fig. 6b). Thus both sides (L_1 and L_2) of the alcohol (amine) moiety are shifted to high fields and therefore NMR differentiation ($\Delta\delta^{RS}$) should be small.

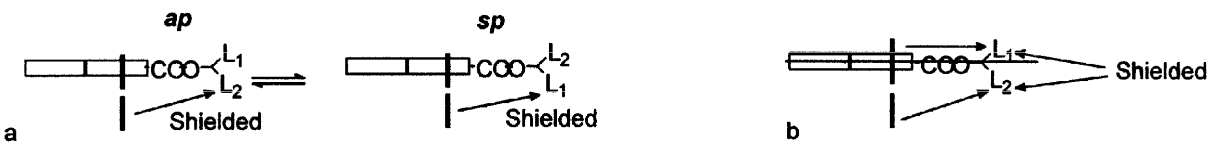


Figure 6. Geometries of the main forms and distribution of the shielding effects on alcohol moiety.

It is highly necessary to have an experimental proof of the theoretically revealed unexpected peculiarities of the conformational equilibrium of **MNCB** (**MBNC**) esters and amides. DNMR should be an effective

method in solving this task. Analysis of shielding effects on the moiety substrate and modification of the line-shape with temperature can be used as probes of the geometry and energy distributions of the main forms.

MNCB (MBNC) esters and amides of (-)-menthol and (-)-menthyl amine were prepared as suitable models for DNMR experiments. These compounds were selected because in accordance with the calculations performed the geometry of derivatives suggests remarkable shielding increments for a variety of protons.

^{1}H NMR studies

In all cases, temperature variations produce modifications of the spectra. Variable temperature NMR data is summarized in the Table 2 and the spectra of (α***R***)-**MNCB** ester of (-)-menthol (***R*-7**) are given in Fig. 7.

Table 2. Selected ^{1}H NMR Data for **MNCB** (**MBNC**) Esters of (-)-Menthol (**7, 8**) and Amides of (-)-Menthylamine (**9**).

config	solvent	T, K	H(1)	H(2)	H(5)	$H(6_e)$	$H(6_a)$	H(7)	Me(8)	Me(9)	Me(10)	NH
MNCB-(-)-Menthol												
R	CS_2	300	4.302	0.607	1.136	1.208	-0.202	1.278	0.669	0.408	0.653	
		165	4.328	0.921	1.288	1.489	0.218	1.5	0.792*	0.313	0.728*	
	$CDCl_3$	300	4.40	0.63	1.16	1.26	-0.23	1.33	0.68	0.42	0.64	
S	CS_2	300	4.325		1.18	1.416	0.124	1.063	0.483*	0.428*	0.743	
		173	4.303		1.2	1.563	0.398	1.2	0.495	0.429	0.771	
	$CDCl_3$	300	4.44	0.41	1.22	1.48	0.13	1.11	0.50	0.46	0.73	
MBNC-(-)-Menthol												
S	CS_2	300	4.365	0.632	1.16	1.26	-0.201	1.16	0.693	0.46	0.656	
		173	4.330			1.428	-0.071	1.22	0.776*	0.336	0.680*	
MNCB (-)-Menthyl Amine												
R	CS_2	300	3.291	0.362	1.098	0.9	-0.297	1.146	0.655	0.533	0.626	5.084
		183	3.297	0.577	1.098	0.85?	-0.147	1.093	0.702*	0.535	0.643*	5.5
	$CDCl_3$	300	3.42	0.39	1.15	1.01	-0.30	1.20	0.68	0.57	0.62	
	$(CD_3)_2CO$	323	3.394	0.712		1.24	0.251		0.639	0.421	0.712	6.100
		300	3.395	0.75	1.24		0.329	1.24	0.627	0.378	0.725	6.288
S	CS_2	300	3.326	0.198	1.219	1.412	-0.011	0.423	0.198*	0.385*	0.744	5.080
		173	3.353	0.272	1.240	1.408	0.155	0.570	0.046	0.335	0.751	5.462
	$CDCl_3$	300	3.47	0.21	1.27	1.52	0.04	0.43	0.39	0.25	0.74	
	$(CD_3)_2CO$	300	3.408	0.634	1.22	1.563	0.349	0.993	0.576*	0.294*	0.742	6.212
		183	3.385	1.09		1.577	0.649	1.22	0.759	0.226	0.747	7.216

*- assignment can be interchanged.

The evolution of the spectra was very similar for **MNCB** and **MBNC** esters. As a rule decreasing the temperature produces low field shifts for most of the protons.

(α*R*)-MNCB ester of (-)-menthol (*R*-7): The decrease in temperature leads to an upfield shift of Me(9’), downfield shifts of Me(8’) and Me(10’), H(2’), and H(6’$_a$), H(6’$_e$), H(1’), H(5’), H(7’) protons. The most spectacular modification of NMR resonance occurs for H(6’$_a$): it is shifted from ca. -0.2 ppm (300 K, CS_2 + CD_2Cl_2 - 3/1) to +0.2 ppm (173 K)..

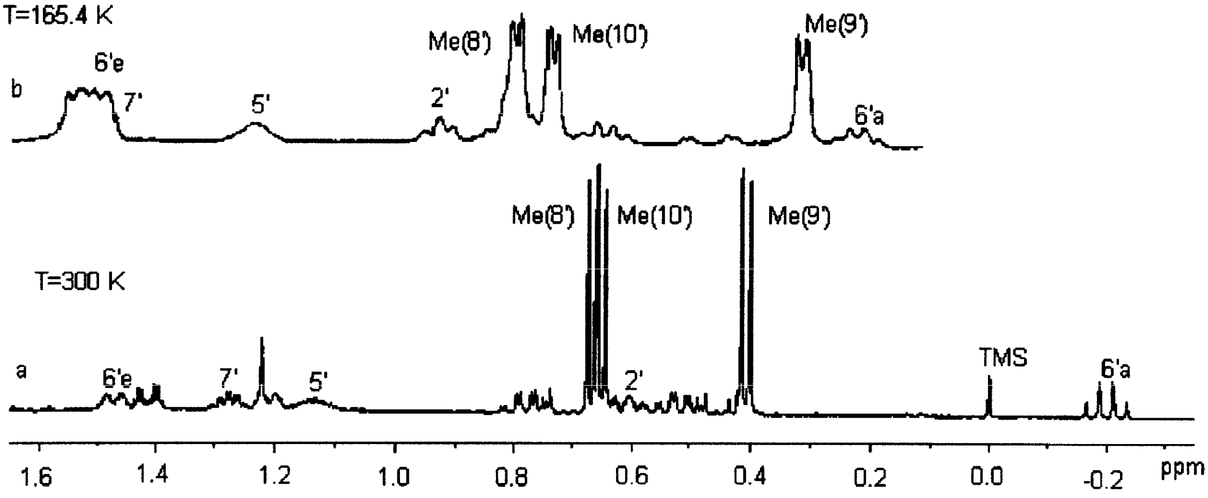


Figure 7. Partial ^{1}H NMR spectra of (α*R*)-**MNCB** ester of (-)-menthol at room (a) and low temperatures (b).

At low temperature (ca. 163 K) the broadening of almost all lines was observed. Therefore we concluded that the exchange rate is close to "slow exchange limit" on the NMR time scale (ca. 11 kcal/mol according to calculations) and, it seems that a coalescence of the spectrum is to be observed at ca. 143-133 K. But after further decreases in temperature, the compound precipitated and no spectra were observed at 153 K.

(α*S*)-MNCB ester of (-)-menthol (*S*-7): Downfield shifts were observed for H(1’), H(5’), H(6’$_a$), H(6’$_e$), H(7’), Me(10’) protons, while there were almost no changes for Me(8’) and Me(9’).

(α*S*)-MBNC ester of (-)-menthol (*S*-8): The modifications in the spectra were very similar to those for (α*R*)-**MNCB** derivative: upfield shift for Me(9’) and downfield shift for Me(8’), Me(10’), H(6’$_a$), H(6’$_e$) protons, respectively.

For amides, in general, very similar changes with temperature were obtained. The main differences are that the line broadenings at low temperature was more extensive.

(α*R*)-MNCB amide of (-)-menthylamine (*R*-9): almost all protons moved to lower field on decreasing the temperature. Only for Me(9’) doublets with almost no changes were observed.

We found that in acetone most of protons resonate at the lower field than in CS_2. Only Me(8’) and Me(9’) signals showed the reverse - in acetone they appeared at higher field. Moreover, low temperature NMR experiments with (α*S*)-**MNCB** amide of (-)-menthylamine (*S*-9) in acetone demonstrated that the observed solvent-induced up and downfield shifts increase when the temperature is decreased.

DISCUSSION

Evolution of the spectra with temperature corresponds to an equilibrium of the conformers which are close in energy and reflects the variation of their populations with temperature. Moreover, the geometry of the minor conformer is suitable for aromatic shielding effects for most of protons, while in the major one only 8'- and 9'-methyls are affected by this effect. Thus, at low temperature the population of the more stable conformer increases and, therefore, most of the resonances move to low field, while Me(9') moves to high fields.

In addition, in the amides, the N$\underline{H}$ proton chemical shifts and their strong shift with temperature support above mentioned assumptions. In the ***ap*** form N$\underline{H}$ protons are affected by strong anisotropic effect (ca. 3 ppm) while in the ***sp*** form only deshielding effects (ca. - 0.5 ppm) take place. So, the low field shift of N$\underline{H}$ protons is due to the increase of the population of the main ***sp*** conformer that is in full agreement with the calculations and results obtained by analysis of the shielding effects for other protons.

Moreover, the low energy non-shielding producing conformer of amide is more stable in polar solvent. The comparison of chemical shifts in CS_2, $CDCl_3$ and acetone reveals this effect. The gradual decreasing of shielding effects for the most significant resonances reflects less shielding contribution as solvent is varied from CS_2, $CDCl_3$ to acetone. Only for Me(9') notable shielding's increase was in acetone that is in full agreement with the model describing equilibrium.

Thus, all of these data support the results of the calculations. There is an equilibrium of two types of conformer: one leads to the shielding effects for most of the protons, while the second one is only for 9'(8')-methyl's. The shieldings producing ***ap*** conformers are less stable.

Aryl Shielding Effects

A comparison of the experimental and theoretical aromatic shielding effects is used as an additional proof of the structures and energy distribution of the main conformers. The shielding increments were calculated (summarized in Tables 3-4) for all low-energy structures. Experimental shielding increments were calculated as the difference of the chemical shifts in ester (amide).[11]

The analysis of Tables reveals that observed values are intermediate between the values for the two main conformers. In general a good approximation is that the ***ap*** form's population is less than 50 % and the dominant contribution is due to the ***sp*** form. These contributions explain high field shifts of 9'(8') methyl protons and the temperature evolution of their chemical shifts. In most cases the observed essential shielding increments are reproduced theoretically. For example, there are H(2'), H($6'_a$), H($6'_e$), H(7') proton chemical shifts.

Thus, analysis of the aromatic anisotropy effect corroborates the results derived above. The correlation between theoretical and experimental values is observed.

Really, several examples were reported in which the aromatic shielding effects were successfully used to justify the theoretically derived geometry. It was found that the theory gives a good prediction on the quantitative level of theory if only the geometry is correct. In this case, although theoretical results are in qualitative agreement with the experiment (see Fig. 8), some discrepancies for several protons were observed. Attempts to get best-fit geometry by variation of the force-field constants did not improve essentially a correlation. In particular, the most notable disagreement was observed in the case of the amides.

Table 3. Calculated [a] and Experimental [b] Shielding Increments (in ppm) for the Principal Conformers of the ***R***- and ***S***-MNCB and MBNC Esters of (-)-Menthol (7, 8).

	MNCB						MBNC					
config.	***R***	***R***	***R***	***S***	***S***	***S***	***S***	***S***	***S***	***R***	***R***	***R***
confor.	*sp*	*ap*	EXP	*sp*	*ap*	EXP	*sp*	*ap*	EXP	*sp*	*ap*	EXP
H(5)	0.16	0.39	0.26	0.21	0.23	0.20	0.19	0.40	0.22	0.21	0.24	0.14
H(6_e)	0.12	0.73	0.70	0.34	0.24	0.48	0.20	0.77	0.56	0.35	0.26	0.28
H(6_a)	0.08	2.05	1.18	0.12	0.56	0.82	0.07	2.11	1.13	0.13	0.59	0.68
H(1)	0.43	0.59		0.29	0.52		0.36	0.60		0.29	0.53	
H(2)	0.12	1.66	0.48	0.04	1.70	0.69	0.06	1.61	0.62	0.05	1.72	0.86
H(3_e)	0.15	0.34	0.18	0.05	0.41	0.22	0.08	0.32	0.16	0.05	0.42	0.19
H(3_a)	0.25	0.36	0.21	0.10	0.39	0.22	0.14	0.36	0.18	0.10	0.39	0.21
H(4_e)	0.10	0.29	0.19	0.09	0.20	0.17	0.08	0.28	0.10	0.09	0.20	0.07
H(4_a)	0.08	0.53	0.32	0.07	0.30	0.30	0.06	0.59	0.26	0.09	0.30	0.22
Me(10)	0.06	0.30	0.29	0.13	0.09	0.20	0.07	0.30	0.18	0.10	0.08	0.06
H(7)	0.40	0.64	0.84	-0.02	2.26	1.06	0.04	0.59	0.32	-0.02	2.20	0.75
Me(8)	0.07	0.10	0.23	-0.00	0.68	0.41	0.03	0.07	0.14	0	0.65	0.37
Me(9)	0.89	0.30	0.39	0.03	0.42	0.35	0.17	0.20	0.22	0.03	0.43	0.24
ΔE(AM1)	0.00	0.81		0.00	1.01		0.0	1.28				
ΔE(PM3)										0.0	1.06	

[a] according to the semiclassical model, both aryl rings were taken into account; [b] in $CDCl_3$ at T=298 K, free menthol was taken as reference [7b];

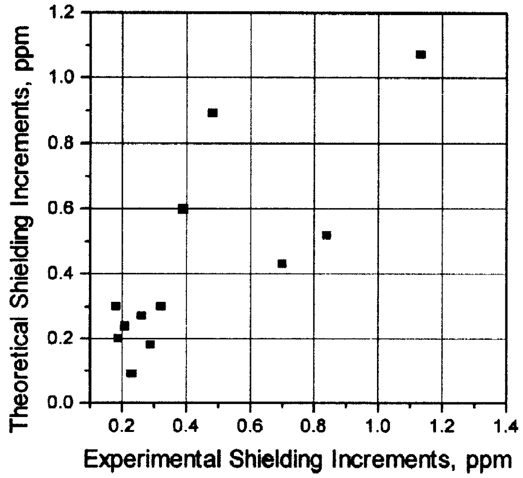


Figure 8. Correlation of experimental and calculated shielding increments for (α***R***)-MNCB ester of (-)-menthol.

Table 4. **Calculated** [a] **and** Experimental [b] Shielding Increments **(in ppm) for the principal Conformers of the *R*-** and ***S*-MNCB Amides of** (-)-**Menthylamine (9).**

config.	*R*	*R*	*R*	*S*	*S*	*S*
conform.	*sp*	*ap*	EXP	*sp*	*ap*	EXP
H(5‘)	0.16	0.37	0.27	0.13	0.25	0.15
H(6‘$_e$)	0.12	0.71	0.95	0.10	0.30	0.44
H(6‘$_a$)	0.08	1.80	1.37	0.04	0.66	0.91
H(1‘)	0.44	0.58		0.30	0.54	
H(2‘)	0.14	1.40	0.72	0.03	1.55	0.90
H(3’$_e$)	0.16	0.30	0.16	0.06	0.39	0.23
H(3’$_a$)	0.26	0.34	0.14	0.13	0.38	0.19
H(4’$_e$)	0.11	0.26	0.14	0.06	0.21	0.12
H(4‘$_a$)	0.09	0.46	0.30	0.04	0.30	0.27
Me(10‘)	0.07	0.27	0.31	0.05	0.10	0.19
H(7‘)	0.59	0.64	0.67	0.02	1.97	1.44
Me(8‘)	0.13	0.09	0.23	0.0	0.57	0.52
Me(9‘)	0.97	0.20	0.18	0.27	0.39	0.51
NH	0.03	3.54		-0.05	3.30	
ΔE(PM3)	0.00	0.44		0.00	0.31	

[a] according to the semiclassical model, both aryls rings were taken into account; [b] in $CDCl_3$ at T=298 K, free menthol was taken as reference [7b];

The main source of this discrepancy is incorrect geometry. A revision of the protocol of the calculations supports this conclusion: there is no full set of force field constants, in particular, those that are responsible for the description of the interaction between C=O and the aryl ring, to determine the overall geometry.

In the ***ap*** conformers in both diastereomers the gradient of the secondary magnetic field is very strong in the area of the alcohol (amine) moiety, therefore a small disagreement in the geometry leads to notable differences in the observed and calculated values. Thus this "incorrectness" explains some discrepancies.

These results are not unexpected: there are almost no studies concerning conformational properties of these compounds, in particular in the solution state.

A bigger discrepancy for the amides may be explained by an additional contributions in NMR spectra of the conformers around the CO-NH bond. [5b]

Summarizing, these results strongly support the prediction: in solution, these compounds exist in a conformational equilibrium of two forms. The ***sp*** conformer is dominant, although the population of the ***ap*** conformer is essential, in particular in the non-polar solvent. The observed temperature effects are explained in the framework of this equilibrium of the two main conformers.

Only some part of the large shielding effects is transformed to the observed high field shifts in NMR experiments. There is a qualitative agreement between theory and experiment if it is supposed that the shielding producing conformer is ca. 50% or less populated. Thus, the low population of the ***ap*** conformer and low selectivity of the aryl ring influence on alcohol (amine) moiety are the limitations of the efficiency of MNCB (MBNC) in their application as reagents for absolute stereochemistry determination of alcohols and amines.

Final Remarks and New Reagent Design

Once conformational properties are established, the rational design of new more effective CDR with a chirality axis can be undertaken. Obviously the new reagent has to be composed from two aromatic rings linked by a single bond and an acid fragment: the interaction of aromatic rings leads to the perpendicular orientation of the Ar_1 and Ar_2 rings. This structure together with the co-planar orientation of the C=O bond and the Ar_1 ring and the Ar_2 ring having its shielding cone directed with respect to the alcohol moiety gives an overall structure (Fig. 9). In addition, these aromatic systems must be hindered enough to exist for a long time as an axially chiral form.

But this is not enough for the reagent to be efficient. It is necessary to modify a reagent in order to increase the selectivity of anisotropic effects on the substrate moiety in the shielding-producing conformer either and/or to increase the population of the shielding-producing form (*ap*).

In the first approach an increase in the efficiency of the reagents ($\Delta\delta^{RS}$) would be achieved by tuning the geometry of the shielding producing form (*ap*). At present the available reagents' (MNCB and MBNC) aryl ring (Ar_2) is very close to the symmetry axis (Fig. 9a, b). Therefore its influence is distributed somehow in a similar manner on both groups (L_1 and L_2).

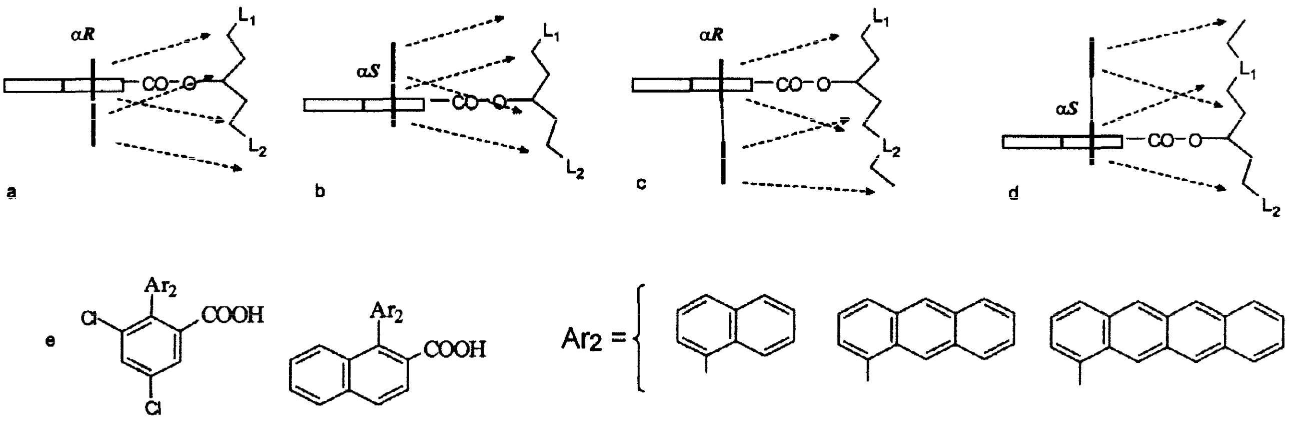


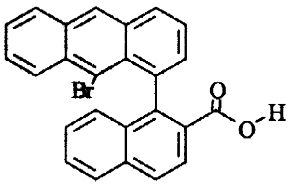
Figure 9.

Thus it is now clear that the second aryl has to be more extended from the side of the symmetry planar plane and that it should be more asymmetric with respect to the Ar_1-Ar_2 axis (Fig. 9c, d). While in the area near symmetry axes protons are going to be affected in both dieastereomers, most of remote protons will feel the shielding effect only in one diastereomer. That leads to new reagents having 1-anthryl as a second aryl (Fig. 9e).

Our preliminary results support this conclusion. 1-(10-bromo-1-anthryl)-2-naphthoic acid was synthezed (BANA) [12] and its esters of (-)-menthol were prepared (Fig. 10). Although the $\Delta\delta^{RS}$ values in these derivatives

are of the same order, the sign distribution around the chiral center in BANA derivatives is more correct than in MNCB esters. Therefore, it seems, BANA should be a useful reagent and **additional investigations are highly** neccesary.

BANA (11)



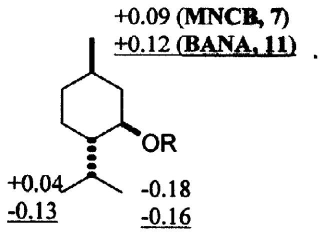


Figure 10. $\Delta\delta^{RS}$ values (ppm, $CDCl_3$) for **MNCB** and **BANA** derivatives of (-)-menthol.

Another complimentary and more efficient way is to bias an equilibrium in favor to the form of our interest to modify the populations of the conformers. Some results for *o*- and *m*-substituted benzaldehydes [13] support this idea. Indeed, the conformational equilibrium around the Ar-CO bond depends on the position of substituents and its nature. Therefore, perhaps, a modification of the reagents could be achieved by the introduction of substituents to the aryl ring (Ar_1). These hypotheses are the subjects of our future projects.

EXPERIMENTAL SECTION

Computational methods. Molecular mechanics (employing the pcff91 force fields [14]) and PM3 (AM1) molecular orbital calculations were performed by the Insight II package on a Silicon Graphics Iris (SGI) computer. Initial molecular geometries were originated from the Builder Module of Insight II; 3D coordinates were then generated from the bond lengths, bond angles and dihedral angles by the DG-II package.[15] Calculation of the energy barriers between these conformers were carried out by MM with an additional harmonic term of the form $k(1+\cos(n\theta-\theta_0))$ included in the force field. The energies of conformations were minimized by the block-diagonal Newton-Raphson method; minima corresponded to rms energy gradients < 0.001 kcal/mol Å. The ground state energies of the geometries were then calculated by PM3 (AM1) using the MOPAC 6.0 program. Full geometry optimization used the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method and the PRECISE option.[16] *Ab initio* calculations (at the restricted Hartree-Fock level of theory) were performed using GAUSSIAN 92/94.[17] Internal coordinates were optimized by Berny algorithm.

Shielding Effects calculations were carried out by the program (written on Fortran 77) based on the semi-classical model of Bovey and Johnson.[4] π-Current loops are separated by 1.39 Å.[4b, f]

NMR Spectroscopy. ^1H NMR spectra of samples in 4:1 CS_2/CD_2Cl_2, $CDCl_3$ or $(CD_3)_2CO$ (ca. 2-3 mg in 0.5 mL) were recorded on a Bruker AMX 500 NMR spectrometer. Chemical shifts (ppm) are internally referenced to TMS (0 ppm) in all cases. 1D- and 2D NMR spectra were measured with standard pulse sequences.

1D ^1H NMR spectra. Size 32 K, pulse length 2.8 ms (30°), 16 acquisitions.

2D COSY spectra: D_1-90-t_1- G_1-90-G_2-AQ; relaxation delay D_1=1 s, 90° pulse 8.5 μs, gradient ratio 1:1.

2D TOCSY spectra. Relaxation delay D_1=2 s; mixing time 41.3 ms; 90° pulse 8.5 μs; TPPI-mode, NS=64.

2D Proton-detected heteronuclear multiple quantum correlation (HMQC) experiments. Sequence: $D_1 90(^1H)$-D_2-$90(^{13}C)$-$t_1/2$-G_1-$180(^1H)$-G_2-$t_1/2$-$90(^{13}C)$-G_3-D_2-AQ (GARP(^{13}C)), relaxation delay D_1=2s; D_2=3.45 ms; 90° pulse (^{1}H) 8.5 μs; 90° pulse (^{13}C) 10.5 μs, gradient ratio 5:3:4.

For DNMR spectroscopy, the probe temperature was controlled by a standard unit calibrated using a methanol reference; samples were allowed to equilibrate for 15 min at each temperature before recording spectra.

General. Preparations of the diastereomeric esters/amides from the corresponding alcohols/amines and MBNC/MNCB were carried out with DCC and 4-pyrrolidinopyridine. For experimental details see reference.[18]

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8. $\Delta\delta^{RS}$ represents the difference between δ(ppm) in the (*R*)- and in the (*S*)-ester [$\Delta\delta^{RS} = \delta(R) - \delta(S)$].

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