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2-Fluoro-2-phenylacetic Acid as a Chiral Derivatizing Agent. PART VI[1]. Distinction of Configurations of its Esters with 2,2'-Dihydroxy-1,1'-binaphthyl and Some Derivatives by ^{19}F N.M.R.

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Abstract: The title compound was found to be useful as a chiral derivating agent in ^{19}F NMR spectroscopy, to determine the enantiomeric purity of 2,2'-dihydroxybinaphtyl and its monoether derivatives. The configurations of ether derivatives are easily deduced from that of known binaphthol, and a straightforward relationship is established between the configurations of the ethers and the δF chemical shifts. A molecular modelling analysis is consistent with the experimental and NMR results.

Introduction:

The axially-chiral derivatives of 2,2'-disubstituted-1,1'-binaphtyls and particularly the 2,2'-dihydroxy-1,1'-binaphthyl (binaphthol) have been widely used in organic synthesis as chiral inducers (asymmetric hydrogenation of olefins[2], reduction of ketones[3]), in selective complexation of enantiomers[4] or in liquid chromatography as chiral stationary phases[5]. There are relatively few methods for the determination of enantiomeric excess (ee) of binaphthyl systems such as substituted binaphthols. Actually this can be achieved by optical methods with the classical technique of crystallizing to constant rotation, by examination of the ^1H NMR spectrum of derivatives from Mosher's acid (α-methoxy-α-trifluoromethylphenyl acetic acid : MTPA) but run in the presence of $Eu(fod)_3$[6] or by chromatographic resolution on a Pirkle ionic column[7].

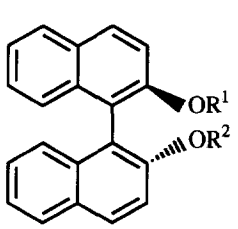
In previous papers, we have shown that several 2-fluoroacetic acids could be used as chiral derivatizing agents (CDA)[1]. Particularly the 2-fluoro-2-phenylacetic acid exhibited good qualities, in order to distinguish and to determine the configurations of secondary chiral alcohols and primary chiral amines, as their diastereoisomeric esters or amides, by means of ^{19}F NMR spectroscopy[8]. These compounds having one stereogenic center were clearly distinguished and our fluoroagent was as efficient as similar other one's described in literature during these five last years[9]. In order to extend these distinctions to a larger number of compounds we describe here, work relating to chiral compounds possessing a chirality axis and to do so binaphthyl structures were selected.

In this study we examined if the enantiomers of binaphthols are distinguished by their ^{19}F NMR chemical shifts through their diastereoisomeric esters with 2-fluoro-2-phenylacetic acid; then we observed the influence of the ether monosubstitution towards fluorine chemical shifts, and finally we could correlate the δF chemical shifts of binaphthol fluoroesters with the absolute configurations of binaphthol and its ether derivatives. We could also, determine the origin of the chemical shift non equivalence.

Results and Discussion:

Derivatization of binaphthol and binaphthol ethers with 2-fluoro-2-phenylacetic acid

The binaphthyl structures derivatized with the CDA were : 2,2'-dihydroxybinaphthyl **1** and its monoethers with R^2 = Me, Bn and iPr (**2** , **3** and **4**). These products and their esters are listed in figure 1. The monoethers came from the racemic or aR binaphtols.



1 $R^1 = R^2 = H$ **5** $R^2 = H$

2 $R^1 = H$ $R^2 = Me$ **6** $R^2 = Me$

3 $R^1 = H$ $R^2 = Bn$ **7** $R^2 = Bn$

4 $R^1 = H$ $R^2 = iPr$ **8** $R^2 = iPr$

9 $R^2 = PhCHFCO$

R^1 = PhCHFCO

Figure 1: 2,2'-dihydroxybinaphthyl and derivatives studied and their esters.

When **1** was esterified with two equivalents of distilled 2-fluoro-2-phenylacetic chloride two products, isolated by LC, were obtained : the monoester **5** (70 %) and the diester **9** (30 %). If an excess of acid chloride was used (four equivalents) we isolated only the compound **9**. Condensation of binaphthol or binaphthol ethers with acid, even in large excess, via the classical DCC (1,3-dicyclohexylcarbodiimide) method led to an incomplete transformation. Mono ethers **2** - **4** were derivatized in monoesters **6** - **8**. The different reactions were carried out from racemic substrates and from each enantiomer of binaphthol and acid chloride to point out the δF chemical shifts corresponding to the different diastereoisomeric fluoroesters.

Representative esterification

Binaphthol (40 mg, 0.14 mmol) and DMAP (22 mg, 0.18 mmol) were dissolved in 5 ml of a toluene/pyridine solution (10/0.5, v/v). Then 2-fluoro-2-phenylacetic chloride (29 mg, 0.18 mmol) dissolved in 2 ml of toluene was added slowly. The mixture was stirred during 24 h at room temperature. After this time the mixture was treated by a 10% HCl solution until acidic pH, filtered, and the two phases were separated. The organic phase was washed, first with an hydrogenocarbonate solution until pH 8, then, with water until neutrality. After drying, the organic solvent was evaporated. The mixture of monoester/diester (70/30) was separated on a silicagel column (eluent : $CHCl_3$/EtOAc, 4/1). The diester could be obtain, alone, by esterification with an acid chloride molar excess of 4. ^1H NMR analysis ($CDCl_3$/TMS); δ ppm, **5** : 6.8 to 8.2 (m, 17H); 5.65 and 5.55 (d, ^2JHF = 47, 1H, aRR/aSR). **9** : 6.8 to 8.2 (m, 22H); 5.52 and 5.57 (d, 2H, ^2JHF = 47, aRRR/aSRR/aRRS).

Fluorine NMR studies of esters deriving from binaphthols and 2-fluoro-2-phenylacetic acid

For monoesters **5** - **8** we observe one resonance (doublet ^2JHF = 47 Hz) for each aRR and aSR diastereoisomers. In the case of the diester **9** containing two fluorine atoms, we observe four resonances for the three expected diastereoisomers : one for each aRRR and aSRR configuration but two for aRSR (identical to aRRS) isomer. As a proof, the second phenolic function of the aRR monoester was esterified with the S-

acid chloride and we obtain only the aRRS diastereoisomeric ester which presents effectively two fluorine resonances.

Tables 1 and 2 list the δF chemical shifts and ΔδF chemical shifts differences observed for the monoesters **5** to **8**, on one hand and for the diester **9** on the other hand. For monoesters we define ΔδF as Δδ = δaRR - δaSR and for diester **9** Δδ = δaRRR - δaSRR where aR or aS and R or S are respectively the configurations of the chiral axis and of the acid moieties.

Table 1 : δF fluorine chemical shifts and ΔδF chemical shifts differences in the diastereoisomeric esters **5** - 8 (ppm/$CDCl_3$/C_6F_6).

	δaRR	δaSR	Δδ = δaRR - δaSR
5	- 17.65	- 16.80	- 0.80
6	- 18.85	- 17.72	- 1.13
7	- 17.52	- 15.68	- 1.84
8	- 18.36	- 15.57	- 2.79

Table 2 : δF fluorine chemical shifts and ΔδF chemical shifts differences in the diastereoisomeric diesters **9** (ppm/$CDCl_3$/C_6F_6).

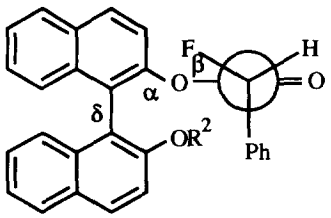
	δaRRR	δaRSS	δaRRS or δaRSR	Δδ = δaRRR - δaSRR
9	- 16.90	- 17.89	- 17.73 - 18.52	+ 0.99

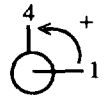
Large values of ΔδF were observed for monoesters : from - 0.8 to - 2.79 ppm and for diester **9** : + 0.99 ppm and the signal separation allows the determination of enantiomeric excess. A better distinction is found for the iPr group. Concerning the correlation between the sign of ΔδF and esters configuration, we note that ΔδF is negative for monoesters and positive for diester. The ΔδF are larger than those observed in alcohol series[8] (ΔδF from 0.4 to 1.3 ppm). The distinction of binaphthol configurations is better than that reached with MTPA diester derivatives : ΔδH = 0.18 ppm for the OMe protons[6] and ΔδF = 0 (this work).

Characteristic features of stable conformations

To understand the ΔδF origin and, later, to correlate the δF values with the absolute configurations in the esters, we used the molecular modelling. Energies of the different conformations for the two aSS and aSR configurations of monoesters **5** - **8** and for the three configurations of diester **9** were calculated with the help of the computer program : INSIGHT II / DISCOVER from BIOSYM.INC (station IBM RISC 340). The energies depend essentially on three dihedral angles α, β and δ defined as following and represented in table 3 : α : C_1-C_2–O–C(=O) β : O–C(=O)–C(HPh)–F δ : angle between the two naphthyls . The energies of the less stable conformations are all almost one kcal higher and represent less than 15 % of the total population.

Table 3 : Values of dihedral angles in esters **5** - **9** of binaphtols and 2-fluoro-2-phenylacetic acid.

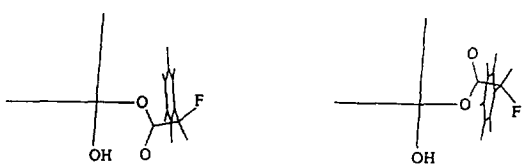




	configuration	dihedral angles		
		α	β	δ
monoesters	aSS	95 to 103	-55 to -60	89 to 101
	aSR	-87 to -103	59 to 67	82 to 92
diesters	aSSS	99	-57	93
	aSRR	-108	68	98
	aSRS	-89	55	94
		100	-55	94

The representation of the most stable conformation of aSR and aSS configurations of monoester **5** is given in figure 2. The characterisic features of stable conformations of mono and diesters are the following: - the angle δ between the two binaphtyl planes ranges from 80 to 110° (that observed for binaphtol is 70°)
- the phenyl group of an acid moïety is approximately perpendicular to its naphthyl group and always parallel to the other naphthyl group; the O-C=O group is in a plane perpendicular to naphthyl group; the C=O and F groups lie just about in a plane perpendicular to naphthyl groups planes, and they are in anti-position; the F atom is always close to the naphthyl plane which bears it; the acid moïety can be internal (as in aSR or aSRR configuration) or external (as in aSS or aSSS configuration) with respect to the quarter defined by the two naphthyls bearing the two functions. In aSRS configuration the S acid moïety is external and the R acid moïety internal; in the ether-esters we found close values for the weakest energy states coming from angular changes due to the position of the ether substituent.

Finally, the naphthyl / phenyl groups parallelism and the C=O / F anti position seem the fundamental criteria to obtain the most stable conformations.



aSR aSS

Figure 2 Stable conformation for monoester 5

Origin of the fluorine chemical shift non equivalence in diastereoisomeric esters

In alcohols and primary amines series we have shown, that the ΔδF could be related to the existence of one minor conformation where the phenyl group of the ester moiety lies in the plane of the C=O group, whereas F lies out of the plane. Then F is subject to different electronic effects[8c].

The existence of ΔδF in the binaphtol esters are well understood after modelling studies. In the binaphthol esters the fluorine nuclei lie in a different structural environment for each configuration, and F is either external (aSS, aSSS) or internal (aSR, aSRR). The F nucleus is sensitive to the structural changes and consequently it is subject to the electronic effects of other groups through space. Concerning the two F nuclei of the aSRS isomer, one is located in an external position, the other one in an internal position leading to two different δF values. The δF difference in aSRS configuration (0.8 ppm) results from an inversion of an acidic group from internal to external position and shows the great sensitivity of δF towards the nature of the other groups.

The large ΔδF variations according to the nature of the R^2 groups in the monoesters (from – 0.8 to -2.8 ppm) and the ΔδF sign inversion in the diester (+ 0.99 ppm) are not due to conformationnal modifications of the acidic moiety, since α, β, δ angles are similar in magnitude. The ΔδF differences can originate from different interactions of R groups, through space, recovering from two main causes : the electronic effects induced by R^2 as a function of their structure and the conformational changes of the OR^2 part as a function of its distance with F atom.

Conclusion

This work shows unambigously the great sensitivity of the F atom to its structural environment and confirms its use, in fluorinated CDA, for the recognition by means of ^{19}F NMR of the enantiomeric compositions and the determination of enantiomeric excess. In an homologous series (monoesters-ether) a strict correlation is obtained between the δF chemical shifts and the absolute configurations. Other works are in progress, concerning the study of binaphthyl structures diversely substituted on aromatic rings.

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