DOI 10.5012/bkcs.2011.32.6.2076

NMR-based Enantiodifferentiation of Chiral *trans*-2-Phenylcyclopropane Derivatives Using a Chiral Lanthanide Shift Reagent

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Received February 1, 2011, Accepted April 7, 2011

Key Words : Chiral lanthanide chemical shift, Chiral *trans*-2-phenylcyclopropane derivatives, Optical purity, Absolute configuration

NMR techniques are well adapted for determining the enantiomeric purity of chiral compounds in the presence of a chiral lanthanide shift reagent (CLSR).[1] In contrast with optical methods,[1] there is no need to characterize the pure enantiomers. Instead, the NMR method makes use of chiral reagents that convert a mixture of enantiomers into a mixture of diastereomeric complexes. Integration of the resulting NMR spectra yields a direct measurement of enantiomeric purity as long as there is a sufficiently large difference between the chemical shifts of the two diastereoisomeric complexes to produce baseline-resolved peaks. Absolute enantiomeric configurations can also be determined using this method.

Chiral lanthanide shift reagents have been used since the 1970s[1] to form addition complexes with various compounds through interactions with electron donor sites. Lanthanide-induced, pseudo-contact shifts[2] (LIS) are a function of the distance, *r*, between the nuclei under observation and the lanthanide center, and the angle, θ, between the line connecting the metal ion with the observed nucleus and the line representing the CLSR magnetic axis (generally assumed to be the bond between the lanthanide ion and the electron donor site).

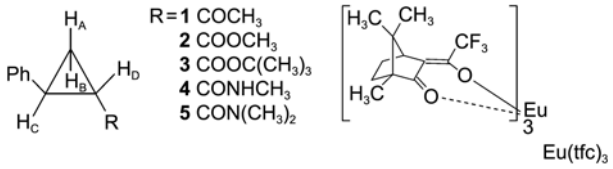
$$\mathrm{LIS} = C\frac{3\cos^2\theta - 1}{r^3}$$

The resulting addition complex is in fast exchange on the NMR time scale, with the unassociated compound.[3] As a result, the observed signals are generally devoid of any fine structure and the line broadening is proportional to the square of the difference between shifts.[4]

All living matter is built of L-amino acids and D-sugars. Stereochemical considerations, including the optical isomerism of biomolecules, are thus of high importance in understanding biochemical and physiological mechanisms. Chiral phenylcyclopropane derivatives exhibit fungicidal,[5] pharmacological,[6] and human *anti*-breast cancer activities,[8] and have been used as NMDA receptor antagonists[7] and in tumor imaging with positron emission technologies.[9] Since chiral phenylcyclopropane derivatives represent various biological activities, it is useful to determine their optical purities and absolute configurations by NMR with the simple addition of CLSR. The current study reported the chiral lanthanide chemical shift on the several 2-*trans*-phenylcyclopropane derivatives with the addition of CLSR, tris[(3-trifluorohydroxymethylene)-(+)-camphorato]europium(III) ($Eu(tfc)_3$).

Results and Discussion

The following 2-phenylcyclopropane derivatives were investigated.



NMR spectra were acquired after doping solutions of each of the above compounds with $Eu(tfc)_3$. Spectra of the compound **1** racemate in the presence of $Eu(tfc)_3$ are shown in Figure1. All compounds exhibited downfield shifts.

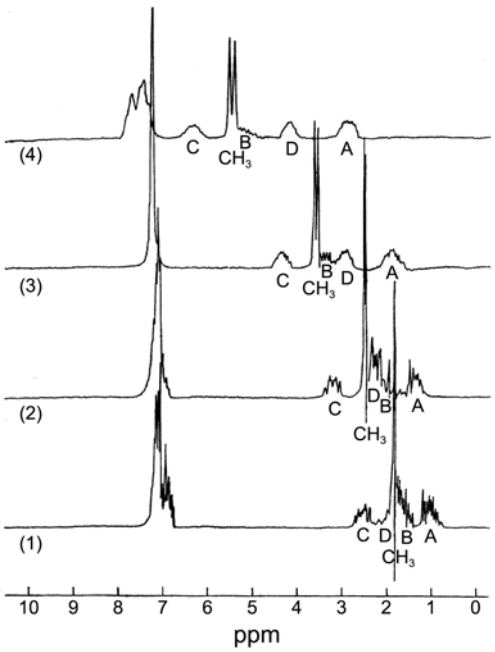


Figure 1. Downfield shifts were observed in the proton resonances of a racemic mixture of compound **1** with the addition of $Eu(tfc)_3$. The $[Eu(tfc)_3]$/[substrate] molar concentration ratios were as follows: (1) 0.00, (2) 0.04, (3) 0.06, (4) 0.21.

Table 1. Diastereoisomer discrimination in ^{1}H NMR spectra by complexation with Eu(tfc)$_3$

Compound	Proton	[L]/[S]	Induced Chemical Shift (Δδ, ppm)	Enantiomeric Shift Difference (ΔΔδ, ppm)	Absolute Configuration
1	CH_3	0.18	3.04, 3.15	0.11	R,[a] S
2	CH_3	0.25	2.83, 2.98	0.15	R,[a] S
3	CH_3	0.64	2.33, 2.40	0.07	R,[a] S
4	CH_3	0.08	3.47, 3.67	0.20	R,[a] S
5	CH_3	0.18	1.21, 1.31, 2.94, 3.04	0.15, 0.1	R,[a] S

[a]Peaks corresponding to the R enantiomer were observed upfield.

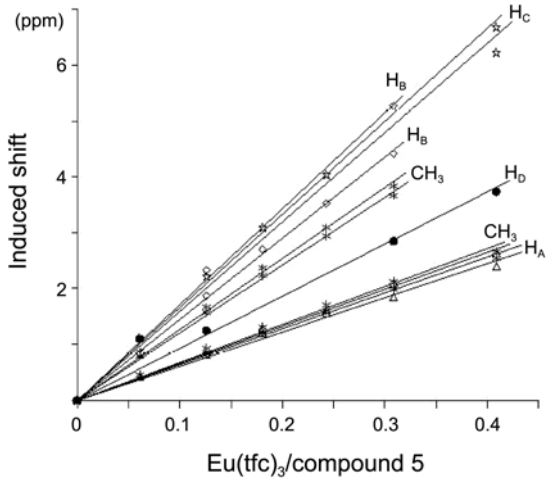


Figure 2. Induced chemical shifts are shown as a function of the concentration ratio of Eu(tfc)$_3$ to compound **5** racemate.

The lanthanide induced shift, as defined by the difference in chemical shift in the presence or absence of Eu(tfc)$_3$, is plotted as a function of the concentration ratio of the substrate to Eu(tfc)$_3$. This relationship is generally linear at mole ratios up to 0.6,[10] as demonstrated by all five substrates studied here. The plots corresponding to compound **5** are shown in Figure 2.

Addition of Eu(tfc)$_3$ to solutions of **1-5** resulted in baseline resolved differentiation of the methyl protons, which allowed accurate NMR integration (Fig. 1). Table 1 shows the induced chemical shifts of the methyl enantiomers (Δδ), the enantiomeric shift difference ΔΔδ (*i.e.*, the difference between the chemical shifts of the enantiomers), the chemical shifts of the absolute configuration, and the molar ratios (CLSR/substrate) at which the spectra were acquired. The optical purity can be determined by integration of the methyl peak in the presence of Eu(tfc)$_3$. As shown Figure 1, peaks corresponding to other hydrogen atoms were not sufficiently resolved to determine optical purity due to line broadening.

Differences in chemical shifts observed for different enantiomers in the presence of a chiral shift reagent may arise from differences in equilibrium constants of formation or complex geometry of the various possible diastereomeric complexes.[1] The coordination site is the same carbonyl group in each of the substrate compounds, the chelation of which generally influences basicity and the stereochemical properties of the substrate.[1] The minimum mole ratio of substrate to Eu(tfc)$_3$ required to determine optical purity increases as *N*-methyl amide < *N,N*-dimethyl amide < methyl ketone < methyl ester < *t*-butyl ketone. This order can be influenced by the formation of complex with Eu(tfc)$_3$ and its structural differences. It is not directly related with either the basicity of carbonyl groups or steric effect for the formation of complex with Eu(tfc)$_3$. Thus, this result was controlled by not only the formation of complexes but also the absolute structures of complexes. The absolute structures of complexes are greatly influenced to be resolved.

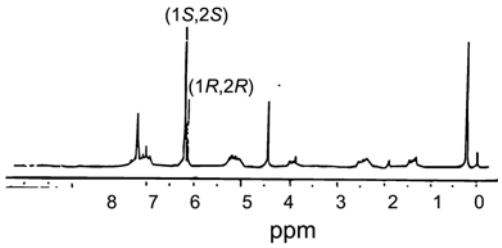


Figure 3. Proton magnetic resonances of partially resolved (1*S*, 2*S*)-methyl 2-phenylcycloproanecarboxylate in the presence of Eu(tfc)$_3$.

The chemical shifts of absolute configurations shown in Table 1 were determined from compounds prepared from partially resolved (1*S*,2*S*)-2-phenylcyclopropane carboxylic acid (Figure 3). Direct correlations between absolute configuration and chemical shift differences (ΔΔδ) are not straightforward. ΔΔδ represents the rapid equilibrium between substrate and CLIS and the structure of the substrate-CLIS complex. Care is required in determining absolute configurations based on empirical correlations of chemical shifts in the presence of chiral shift reagents. While several studies have determined absolute configurations based on ΔΔδ,[11-19] there are cases in which the sign of ΔΔδ changes within the same series of compounds.[20,21] In the current study, absolute configurations are considered accurate because the differences in the patterns of R and S enantiomeric methyl chemical shifts (ΔΔδ) were the same (*i.e.*, the downfield chemical shift of the S enantiomer matches the upfield chemical shift of the R enantiomer).

Experimental Section

Experiment of Chiral Lanthanide Chemical Shift. Chiral shift reagent runs utilize incremental method[20,22] in which the shift reagent was successively added to a $CDCl_3$ solution

containing the substrate. The concentration of the shift reagent was determined gravimetrically by means of weighing the sample tube after each addition. Volume of sample tube was calibrated by the standard measured nmr tube. The spectra of each compound have been obtained from the ca. 10 different concentration of shift reagent, $Eu(tft)_3$.

$Eu(hft)_3$ was purchased from Aldrich and dried (100 °C below 1 mmHg) and stored in vacuum desiccator over P_2O_5 prior to use.

(1*S*,2*S*) and racemic-*trans*-2-phenylcyclopropanecarboxylic acid,[23] (1*S*,2*S*) and racemic-*trans*-2-phenylcyclopropanecarbonyl chloride[24] and (1*S*,2*S*) and racemic-methyl *trans*-2-phenylcyclopropanecarboxylate (**2**)[24] were followed previous procedure.

The specific rotation[25] of (1*S*,2*S*)-*trans*-2-phenylcyclopropane carboxylic acid is $[\alpha]_D^{22} = +314.0$ ($c = 1.776$, EtOH).

Partially Resolved (1*S*,2*S*) and Racemic-methyl *trans*-2-Phenylcyclopropyl Ketone (1)[26]. *Trans*-2-phenylcyclopropanecarboxylic acid (0.5 g, 3×10^{-3} mole) or partially resolved *trans*-2-phenylcyclopropanecarboxylic acid dissolved in 30 mL ether and methyl lithium solution, 3.2 mL (1.25 M, 6.6×10^{-3} mole) added to the above acid solution. The reaction mixture was stirred at room temperature. The end point of the reaction was checked by TLC. The salt was filtered off and the ether solution was washed with saturated NH_4Cl solution. The ether solution was dried with $MgSO_4$ and distilled off all solvent to obtain crude product. This crude product was Kugelrohr distillated under 1 mmHg and product was collected at 70-80 °C. 0.25 g (51%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21 (5H, m, Ph), 2.50 (1H, m, H_C), 1.83 (3H, s, CH_3), 1.80 (1H, m, H_D), 1.57 (1H, m, H_B), 0.97 (1H, m, H_A).

Partially Resolved (1*S*,2*S*) and Racemic-*t*-butyl *trans*-2-Phenylcyclopropanecarboxylate (3). It followed the procedure of methyl *trans*-2-phenylcyclopropanecarboxylate.[24]

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21 (5H, m, Ph), 2.53 (1H, m, H_C), 1.80 (1H, m, H_D), 1.67 (4H, m, H_B), 1.37 (9H, s, 3Me), 0.97 (1H, m, H_A).

Partially Resolved (1*S*,2*S*) and Racemic-*N*-methyl *trans*-2-Phenylcyclopropanecarboxamide (4). It was followed the procedure of *trans*-2-phenylcyclopropanecarboxamide.[24] Compound (**4**) was prepared by stirring *trans*-2-phenylcyclopropanyl chloride with the gas forming from 40% aqueous methylamine solution. mp 122-125 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19 (5H, m, Ph), 6.9 (1H, s, NH), 2.91 (3H, d, CH_3), 2.75 (1H, m, H_C), 1.61 (2H, m, H_B and H_D), 1.28 (1H, m, H_A).

Partially Resolved (1*S*,2*S*) and Racemic-*N*,*N*-dimethyl *trans*-2-Phenylcyclopropanecarboxamide (5). mp 58-60 °C (dec.). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20 (5H, m, Ph), 2.73 (3H, s, CH_3), 2.47 (3H, s, CH_3), 2.57(1H, m, H_C), 2.83 (1H, m, H_D), 1.81 (9H, m, H_B), 1.30 (1H, m, H_A).

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