ml of 6N NaOH. The reaction mixture was stirred at room temperature for 24 hours, diluted with 130 ml of water, and extracted with 2×60 ml of hexane. The combined hexane layer was washed with 2×20 ml of water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified on a silica gel column to afford the epoxyketone (3, 1.7g, 67% yield). NMR (CDCl$_3$); δ 1.9~2.4 (m, 2H) 1.09~1.80 (m, 28H), 0.70~1.09 (t, 6H).

13-Eicosyn-10-one (2). To a magnetically stirred solution of the epoxyketone (3, 394 mg, 1.28 mmole) in 4 ml of dichlormethane and 2 ml of acetic acid at 0° was added p-toluenesulfonylhydrazide (238 mg, 1.28 mmole) in one portion. After stirring for 3 hours at 0° and 3hours at ambient temperature, the mixture was poured into 10 ml of water and the organic layer was washed with 3×10 ml of water followed by 5 ml of saturated sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to give a pale yellow oil which consisted of two major products by TLC. Less polar product turned out to be the desired acetylenic ketone (2) (344 mg, 83% yield) after column chromatographic separation. NMR (CDCl$_3$); δ 1.88~2.61 (m, 6H), 1.14~1.80 (m, 24H). 0.70~1.14 (t, 6H).

(Z)-13-Eicosen-10-one (I). A solution of the ynone (2, 200mg, 0.68 mmole) in 25 ml of methanol containing 500μl of pyridine was shaken under a slight positive pressure of hydrogen gas over 175 mg Lindlar catalyst (5% Pd on CaCO$_3$ poisoned with Pb). The hydrpgenation was complete in about 1 hour as checked by TLC analysis. The catalyst was removed by filtration and the solution was diluted with hexane, washed with 2×10 ml of 2N HCl, water, and brine, dried over anhyd-

rous magnesium sulfate, and concentrated in vacuo. Pure product (1, 167 mg, 83% yield) was obtained by column chromatographic separation.
IR; 1450cm^{-1}, 1710cm^{-1}. NMR (CDCl$_3$); δ 5.18~5.45 (m, 2H), 1.66~2.39 (m, 8H), 1.05~1.66 (m, 22H), 0.73~1.05 (t, 6H).

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cis-trans Isomeric and Substituent Effects on the Lanthanide Induced Shifts in 2-Phenylcyclopropanic System

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LIS's of *cis* and *trans*-methyl-2-phenylcyclopropanecarboxylate, *cis* and *trans-t*-butyl-2-phenylcyclopropanecarboxylate, *cis* and *trans*-N,N-dimethylcyclopropanecarboxamide, *trans*-2-phenylcyclopropyl methyl ketone and *trans*-2-phenylcyclopropyl *t*-butyl ketone have been studied. The LIS's hold the McConnell–Robertson relation and are mainly influenced by the steric effect. LIS's of *trans* isomers are larger than those of *cis* isomers. In *trans* isomers, the LIS's decrease in the following order: methyl ketone > methyl ester > N, N-dimethyl amide > *t*-butyl ketone ~ *t*-butyl ester.

Introduction

Since Hinckley[1] reported on the use of a lanthanide shift reagent (LSR) to analyze NMR spectra, literally hundreds of papers[2~7] have appeared, dealing with both theoretical and practical aspects of reagents. LSR's have proved to be a

valuable development in the use of NMR spectroscopy for organic structure determination. While LSR's can be used qualitatively to simplify and interpret spectra patterns, more recent works[8–14] are directed at a quantitative comparison of experimental lanthanide induced shifts (LIS) with values predicted *via* the pseudocontact equation[15] such as given
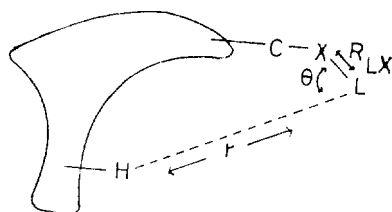
Figure 1. Representation of the geometric relationship between the lanthanide ion L and a hydrogen atom in terms of distance and angle from the magnetic axis for a complex of an organic substrate where X is the binding site.

below:

$$\Delta\delta_i = k(3\cos^2\theta - 1)/r_i^3 \qquad \text{(equation 1)}$$

This is for a hypothetical LSR-substrate complex[16] such as illustrated in Figure 1. Thus, the induced shift, $\Delta\delta_i$, depends on: (1) r_i, the distance between the metal ion and the nucleus of interest, (2) θ_i, the angle subtended by the line connecting the metal ion and the observed nucleus and the line representing the LSR magnetic axis (assumed here to be equivalent to the bond between the lanthanide ion and the heteroatom X) and (3) a constant, k, which should be a characteristic property of particular LSR. The predicted LIS's for some proposed structure are compared with the experimental LIS's. A statistical comparison of both, which is usually composed of the crystallographic agreement factors is used to assess the validity of the proposed structure. In order to obtain values of θ_i and r_i it is necessary to specify the geometric coordinates of both the metal ion and the observed nucleus relative to the hetero atom. It is difficult to specify the exact location of the observed proton with reasonable accuracy because one cannot ignore different available conformations. LIS studies partly have succeed in making reliable assessment of proposed structures. The LIS technique might be developed into a liquid state structure elucidation method like a crystallographic technique had already been used for a solid state structure elucidation. Unfortunately this possibility has not yet been realized.[8–14]

For rigorous and accurate assessment of a proposed structure, more careful studies are required on not only the sterochemistry for the formation of complexes, substrate-LSR but also k. They are valuable for the accurate assessment of a proposed structure and also for the interpretation of simplified spectra. This research thus has been attempted to investigate the influencing factors of the LIS's which are especially depended on the functionalities and stereochemistry of the substrates. The different conformations of organic molecules make this study complicated. To overcome this difficulty, it was necessary to make careful selections of substrates which are conformationally restricted and partially flexible molecules,[17] such as 2-phenylcyclopropane derivatives. Because the cyclopropane ring is conformationally restricted, 2-phenylcyclopropane derivatives have geometric isomers. Therfore we were able to investigate the effects of functionalities, geometric cis and trans isomers and partially conformational changes on the LIS. Our approach is to compare the

relative values of the induced shifts of 2-phenylcyclopropane derivatives using tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium (III) as LSR, which can be abbreviated as Eu (fod)₃ and has proven particularly useful LSR.

Experiment

Gas–liquid chromatography (GLC) analysis and preparative GLC were performed on Yanago Model G-180 chromatograph (Thermal conductivity detector).

All proton nuclear magnetic reasonance spectra were obtained by Varian EM-360A spectrophotometer at ambient probe temerature of ca. $30\pm1°C$. All spectra were recorded 600 Hz widths, chemical shifts were measured relative to internal standard of Me₄Si. When the widths of spectra exceeded the sweep widths, offset spectra were recorded.

Experimental LIS. Shift reagent runs utilized the incremental method[17] in which the shift reagent was sucessively added to a C₆D₆ solution containing the substrate. The concentration of shift reagent was determind gravimertrically by means of weighing the sample tube after each addition. The spectra of each compound has been obtained from the ca. 10 different concentrations of shift reagent. Eu (fod)₃ was purchased from Aldrich, resolve-Al, EuFOD, 160938 and it was dried (100°C, below 1 Torr.) by dry gun and stored in vacum desicator over P₂O₅ prior to use.

C₆D₆ was dried by storing over 4A molecular sieves.

Preparation of cis and trans–Ethyl-2-phenylcyclopropanecarboxylate. A mixture of approximately 3: 2 trans to cis ethyl ester was prepared by the method of Aratani.[18] Under nitrogen atmosphere, ethydiazoacetatecyclohexane solution was added dropwise during 10–12 hrs, to styrene and cupric sulfate cyclohexane solution at reflux temperature. The reaction mixture was distilled under reduced pressure (75–80°C, 2mmHg). The distillate which has been spearated by GLC (10% carbowax 20M) was a mixture of cis and trans ester (2:3) with the yield of 40–60%.

Each pure stereoisomer was then hydrolyzed by alkaline aqueous ethanol (1:1) under reflux (during 10hrs) to prepare cis and trans–2-phenylcyclopropanecarboxylic acid[19], cis and trans–2-phenylcyclopropanecarboxylic acid chloride were prepared from the reaction of[20] the corresponding acid with thionyl chloride. Cis and trans methyl ester were obtained from the reaction[21] of corresponding acid chloride with methanol room temperature. When the above reaction was carried out with the mixture of cis and trans acid, the mixture of cis and trans methyl ester was separated by GLC (10% carbowax 20M).

Preparation of cis and trans–t-Butyl-2-phenylcyclopropane-carboxylate. cis and trans–t-butyl-2-phenylcyclopropanecarboxylate were prepared by the previously described method. The mixture of cis and trans t-butyl ester was separated by GLC (10% OV-1).

Preparation of cis and trans–N,N–Dimethyl-2-phenylcyclopropanecarboxamide[22]. cis and trans–N,N–dimethyl-2-phenylcyclopropanecarboxamide were prepared from the reaction of the corresponding acid chloride with dimethyl

amine at room temperature. The mixture of *cis* and *trans* amide was separated by GLC (10% carbowax 20M).

*Preparation of trans-2-Phenylcyclopropyl Methyl Ketone*[19].

trans-2-Phenylcyclopropyl ketone was prepared from the reaction of *cis* and *trans* acid methyl lithium (Aldrich 1.2M ether solution). *trans*-2-phenyl-cyclopropyl methyl ketone was purified by GLC (10% FFAP).

Preparation[19] *of trans-2-Phenylcyclopropyl t–butyl Ketone*. *trans*-2-Phenylcyclopropyl *t*-butyl ketone was prepared by the previously described method.
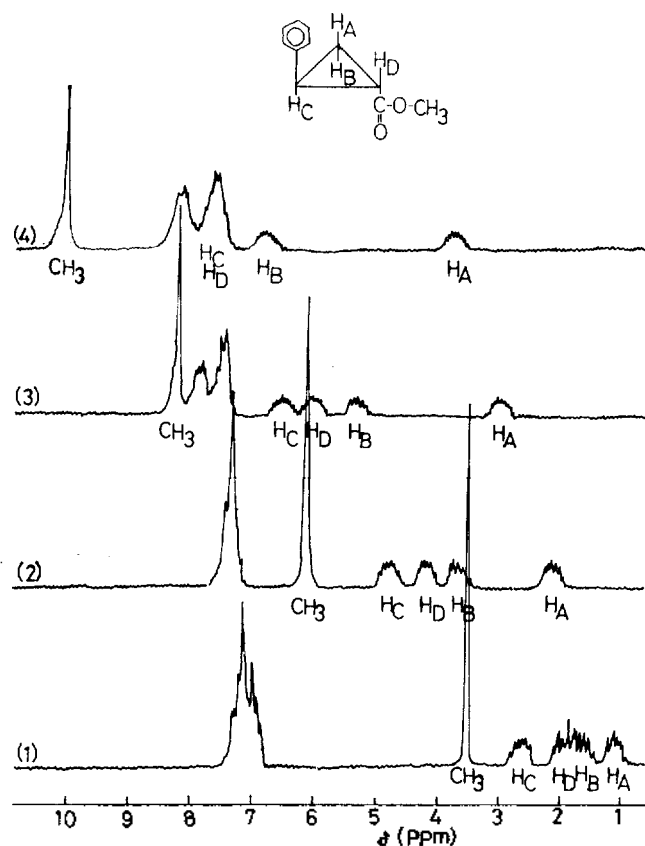
Results and Disscution

The following 2-phenylcyclopropane derivatives has been studied.
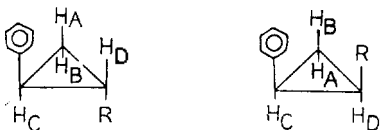
(1) R=CO₂Me (2) R=CO₂*t*-Bu, (3) R=CONMe₂
(4) R=COMe (5) R=CO*t*-Bu, (6) R=CO₂Me
(7) R=CO₂*t*-Bu (8) R=CONMe₂

The structures of *cis* and *trans* isomer are determined by either the chemical shift of methyl group[21] or comparision[23~25] with the standard spectra. The ring protons of cyclopropane

Figure 2. Variations in chemical shifts for the different protons of *trans*-methyl-2-phenylcyclopropanecarboxylate in the presence of Eu(fod)₃. [Eu(fod)₃]/[*trans*-ester] (1) 0.00, (2) 0.09, (3) 0.20. (4) 0.35.

are verified by chemical shifts[21] and LIS's[23-25] which hold the distance relationship of equation 1 (McConell–Robertson Relation). NMR spectra were successively recorded after each doping of Eu (fod)₃. The sets of spectra measured for the compound 1 and compound 6 in the presence of Eu (fod)₃ are presented as Figure 2 and Figure 3 respectively. The LIS's for each compound were plotted as $\Delta\delta$ (the difference of chemical shifts are observed in either presence or absence of Eu(fod)₃ *vs*. the concentration ratio of the compound to Eu(fod)₃. The plots of compound 1 and compound 6 are shown on Figure 4 and Figure 5, repectively.

The LIS's used for this study are presented in the slopes of
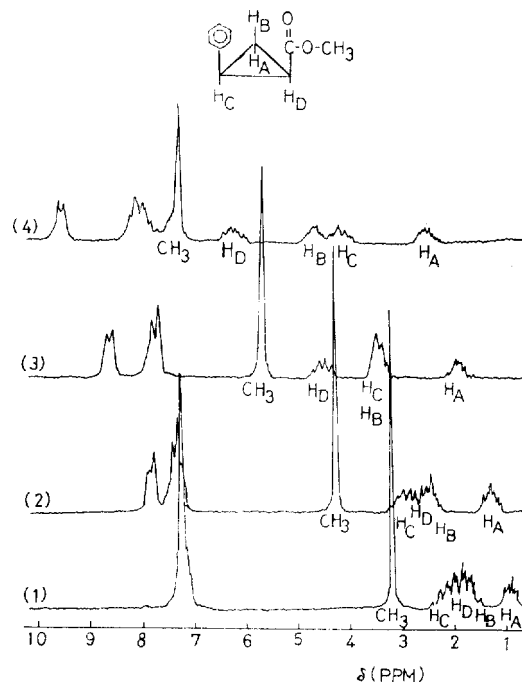
Figure 3. Variations in chemical shifts for the different protons of *cis*-methyl-2-phenylcyclopropanecarboxylate in the presence of Eu(fod)₃. [Eu (fod₃]/[*cis* ester] (1)0.00 (2)0.10 (3) 0.20, (4)0.35.
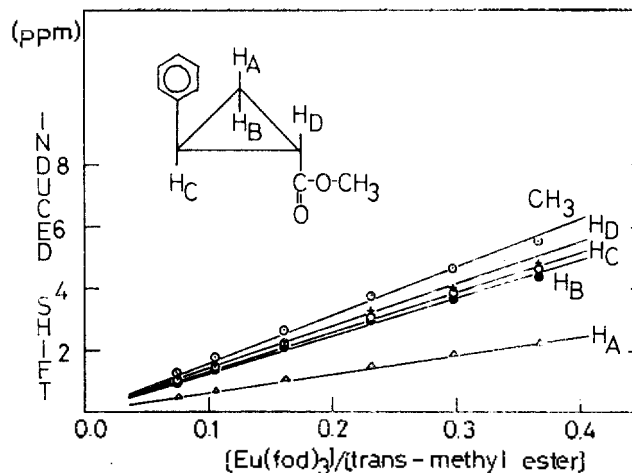
Figure 4. Plots of induced chemical shifts of proton reasonances of *trans*-methyl-2-phenylcyclopropylcarboxylate in the presence of Eu(fod)₃.
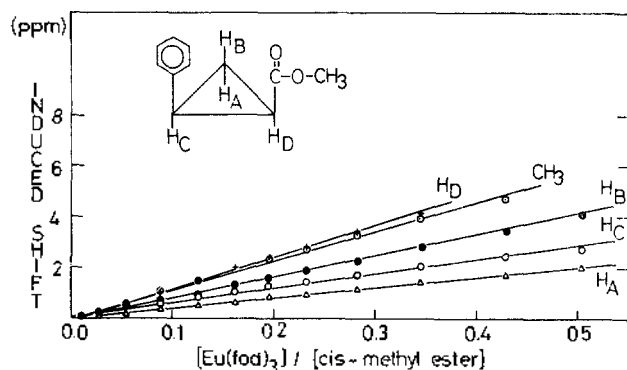
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Figure 5. Plots of induced chemical shifts of proton reasonances of cis–2–methyl–2–phenylcyclopropylcarboxylate in the presence of Eu(fod)₃.

the chemical shifts vs. the mole ratios of LSR to substrates. The mole ratios of Eu(fod)₃ to the substrates used in this work are below 0.5. The range of 0–0.6 mole ratio is[17] usually known to give good linear correlation between $\Delta\delta$ and mole ratio. This means that [LSR–substrate] shows linearly proportioned increase to the increase of [LSR].

To determine the best straight line through each set of data, a linear least-squares analysis was carried out. The slope which could be obtained from this least-squares line was then used as the LIS. Due to the definition of "slopes" these LIS's represent the changes in chemical shifts extrapolated to a mole ratio of 1.0. The correlation coefficients for the least-squares lines were greater than 0.98 in all cases. The LIS data obtained from cis isomers and trans isomers are shown in Table 1 and 2.

The observed shift, δ, of a given proton is a concentration-weighted average of chemical shift of substrate and complex species in solution. It is also time-averaged spectra of fast-exchange type.[17] The concentration of complex is derived from the association constant involving the LSR and the substrate. Formation of Eu(fod)₃–substrate complex is resulted from the expansion of the coordination number of the Eu(fod)₃ from six to seven.[26] Since Eu(fod)₃ is a large molecule, not only the electronic but also the steric consideration are required to understand the formation of LSR–substrate complex.

The magnetitudes of the induced shifts being provided in Table 1 and 2 hold the relationship of McConnell–Robertson equation. The closer the observed proton to the site of complexation is the greater the induced shift. In other words, LIS of B hydrogen is greater than of a hydrogen or C hydrogen in case of cis isomers, similarly, in case of trans isomers, LIS of B hydrogen or C hydrogen is greater than that of A hydrogen.

t–Butyl group has greater hyperconjugative effect than methyl group, at inductive point, the formations of complexes with t–butyl compounds are expected to be easier than with methyl compounds. But the methyl compounds have relatively larger LIS than t–butyl compounds in the same geometric isomer. It can concluded that the amounts of LIS of t–butyl compounds are smaller than those of methyl com-

TABLE 1: Relative Lanthanide Induced Shifts[a] of cis-2-Phenylcyclopropane Derivatives

Proton	Compound		
	Methyl ester	t–Butyl ester	N,N–Dimethyl amide
H_A	4.2	3.4	4.8
H_B	8.1	5.5	7.7
H_C	5.5	3.9	4.8
H_D	12.0	12.0	13.0
CH₃	11.0	6.4	4.3[b]
			10.7[c]

[a] LIS was measured in parts per million; [b] cis proton to complexation; [c] trans proton to complexation.

TABLE 2: Relative Lanthanide Shifts[a] of trans-2-Phenylcyclopropane Derivatives

Proton	Compound				
	Methyl ester	t–Butyl ester	N,N–Dimethyl amide	Methyl ketone	t–Butyl ketone
H_A	5.9	3.4	5.1	8.8	3.5
H_B	11.7	6.4	7.9	17.4	6.3
H_C	12.4	6.8	10.6	17.0	6.7
H_D	13.1	9.6	13.4	11.4	5.0
CH₃	14.6	5.8	6.3[b]	19.8	4.6
			14.5[c]		

[a] LIS was measured in parts per million; [b] cis proton to complexation; [c] trans proton to complexation.

pounds is due to the steric effect of t–butyl group.

In trans isomers, the LIS's of ketones esters and amide decrease in the following order: methyl ketone$>$ methyl ester$>$ N,N–dimethyl amide$>$ t–butyl ester$\sim$t–butylketone. Even though the coordinate sites of esters,[27] amide[28, 29] and ketones[30] toward LSR are equal to the oxygen atom of the carbonyl group, the relativity of D hydrogen's LIS to B or C hydrogen in ketones is clearly different from that of LIS in esters and amide. It can be understood by the previous reports[27–30] in which the geometric coordination position of europium toward ketone is not same as the position toward ester and amide. The basicities of funtional groups are generally followed in the following order; amide$>$ ketone $>$ ester. The magnitudes of LIS follow the basicities of functionalities, that may be influenced by steric consideration. Since carbon nitrogen bond of amide has double bond character, it can't rotate freely. The oxygem atom of amide group has much more steric hinderance than methyl ester and methyl ketone. Since phenylcyclopropyl group is large group and and Eu(fod)₃ is also large, LIS's of this study are mainly influenced by the steric hinderance. The similar result has been reported[31] for a series of 2–alkyl substituted phenols in which the induced shift are clearly dominated by steric rather than electronic consideration.

The difference of LIS between cis and trans isomers can be illustrated by the following. The pKa's[32] of acrylic acid, cis cinnamic acid and trans–cinnaimic acid are respectively 4.25, 3.89 and 4.44. Phenyl group reacts as electron withdrawing in cis isomer and as electron donating in trans isomer. Since carbon–carbon bond of cyclopropane ring has bond charac-

ter, the phenyl group can be expected to have similar character in *cis* and *trans* cinnamic acid. This fact and steric hinderance of phenyl group explains the case that *cis* isomers are not favorable to form the LSR–substrate complexes. The relativities of D hydrogen's LIS to B hydrogen in *cis* isomers are different from those in corresponding *trans* isomers. These phenomena partly be influenced by geometric changes in complexations. The steric effect of phenyl group can be considered by the results of the steric hinderance of the formations of complexes or of the steric changes of complexations. Although we are now studying equilibria between substrates and Eu(fod)$_3$ and the bound shift[33] of each proton, we are expecting to explain the effect of phenyl group somewhat clearly, so far LIS's of *cis* compounds can be considered as mainly steric hinderance like *trans* isomers.

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