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STUDIES ON AZETIDINE DERIVATIVES III[1)]

CONFIGURATIONAL ASSIGNMENT WITH A SHIFT REAGENT

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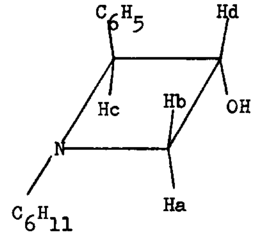
Recently, tris(dipivalomethanato)europium(III), Eu(DPM)$_3$, has attracted special attention because it produces magnified chemical shifts of protons in NMR spectra of alcohols and other lone pair containing organic compounds and provides valuable information for assignment of the configuration or the structure.[2-6)]

As for the determination of the stereochemistry of azetidine derivatives, no reliable method has so far been established.[7,8)] It has recently been reported that amino or hydroxyl groups can be coordinated with Eu(DPM)$_3$ more strongly than other functional groups.[2,4)] However, it was not known whether a hydroxyl oxygen or an amino nitrogen would be preferentially coordinated with Eu(DPM)$_3$.[9)]

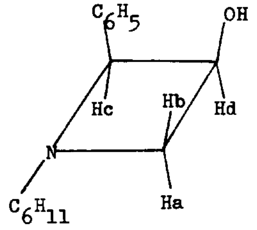
This has prompted us to study the application of Eu(DPM)$_3$ for the configurational assignment of diastereomeric 1-cyclohexyl-2-phenylazetidin-3-ols,[1)] compound I, mp 138-140°C, and compound II, mp 101-102.5°C. Both the diastereomers have two possible coordination sites, a hydroxyl group and a ring nitrogen atom, in the molecule.

Figure 1 shows the conventional 100 MHz spectra of compounds I and II (A and C) and the spectra in the presence of Eu(DPM)$_3$ (B and D). The observed chemical and paramagnetic shifts are summarized in Table I.

The signal of the hydroxyl proton undergoes the largest shift, followed by that of the carbinol methine proton, Hd (Table I). Further investigation of the diastereomeric 3-cyano-1-cyclohexyl-2-phenylazetidines revealed that



I



II

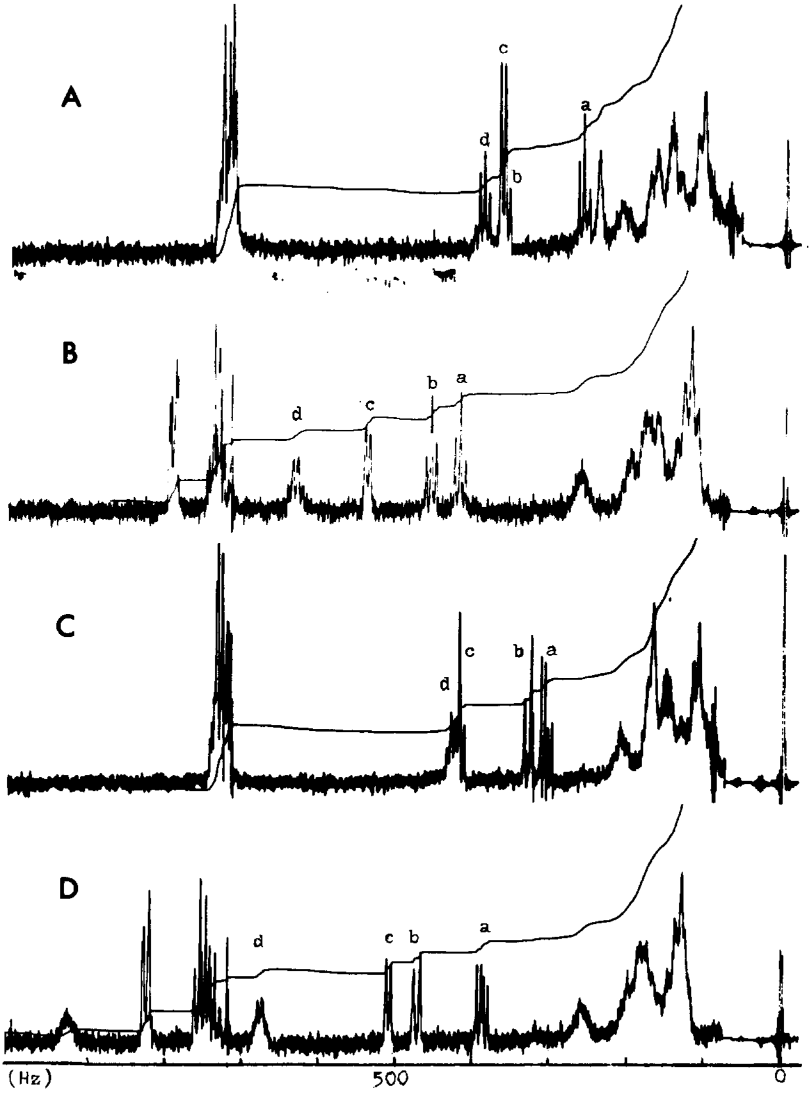


Figure 1. 100 MHz Spectra of trans- and cis-1-Cyclohexyl-2-phenylazetidin-3-ol, I and II, respectively.

A: Spectrum of I (0.05 M) in $CDCl_3$.

B: Spectrum of I (0.05 M) and $Eu(DPM)_3$ (0.0084 M) in $CDCl_3$.

C: Spectrum of II (0.05 M) in $CDCl_3$.

D: Spectrum of II (0.05 M) and $Eu(DPM)_3$ (0.0084 M) in $CDCl_3$.

The proton assignment shown was confirmed by the decoupling at 100 MHz.

the NMR spectra of these compounds are unaffected by the addition of Eu(DPM)$_3$.

Table I. Chemical and Paramagnetic Shifts with Eu(DPM)$_3$

	Proton	a	b	c	d	OH
I						
Chemical Shift*	(Hz)	266	368	371	400	244
Paramagnetic Shift	(Hz)	161	97	177	241	938
II						
Chemical Shift*	(Hz)	311	315	413	419	ca.170
Paramagnetic Shift	(Hz)	80	162	101	264	ca.742

* Downfield shift from internal standard TMS.

This fact together with the aforementioned results obtained with compounds I and II indicates that the metal is coordinated with the hydroxyl oxygen but not with the ring nitrogen of these compounds.

It was expected that the signal of the proton Hc of the trans-isomer would be more strongly shifted than that of the cis-isomer from inspection of the molecular model[10)] since the proton of the trans-isomer is located closer to the metal than that of the cis-isomer. A reverse shift relationship should apply to the phenyl protons which are located on the opposite site of the azetidine ring with respect to the proton Hc. In fact, the signal of the proton Hc of I is shifted more strongly than that of II (Table I) and the signals of the phenyl protons of II are shifted more strongly than those of I (Figure 1B and 1D). These findings provide good evidence for the conclusion that compound I is trans-1-cyclohexyl-2-phenylazetidin-3-ol and compound II is the cis-isomer.

Similar results have been obtained in these laboratories with other related azetidine derivatives in which functional groups can be coordinated with Eu(DPM)$_3$ and will be reported elsewhere in the future.

The present technique with a paramagnetic shift reagent appears to be the first instance and provides a valuable tool for the configurational assignment of four-membered cyclic compounds.

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References

1) Part I and Part II of this series which describe the synthesis and the reaction of the compounds mentioned in this communication will be published elsewhere.

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9) An example of the preferential coordination with $\mathrm{Eu(DPM)_3}$ to two functions has recently been reported.6)

10) For the puckered azetidine rings two conformations are possible through ring flipping, so the distance between a ring proton and the coordinated metal may be different for each conformation. With respect to this point, from a molecular model it has been confirmed that the relative distances between the protons, Ha, Hb and Hc, and the coordinated metal are practically the same for the two conformations.