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Application of a Shift Reagent in Nuclear Magnetic Resonance Spectroscopy. IV.[1] A Simple Method for Stereochemical Assignment and Simultaneous Determination of *cis-trans* Isomeric Trisubstituted Allylic Alcohols

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Relative shift values against a shift of an acetoxyl signal, estimated by employing a nuclear magnetic resonance shift reagent $Eu(DPM)_3$ on an acetylated sample, could yield valuable information for assigning the stereochemistry of *cis–trans* trisubstituted allylic alcohols and facilitate a simultaneous determination of these isomers in a mixture.

As is well known, nuclear magnetic resonance (NMR) spectroscopy has been proved to be most valuable for determining the stereochemistry of trisubstituted carbon-carbon double bonds of the type $-(CH_3)C{=}CH-$ which are frequently encountered in natural acyclic terpenes.[3] For elucidation of the stereochemical problems of those containing primary allylic alcohol together with methyl group(s), however, only a limited amount of information was obtained so far by a conventional NMR running. Hence, synthesis of the geometrical isomers of the compound under consideration or a suitable mixture of the two isomers was essentially requested for comparison and interrelating with the corresponding α,β-unsaturated acid, ester, or aldehyde has been usually recommended.[4]

In our preceding paper,[1] decisive information for characterizing *cis–trans* isomeric vitamin A acetates was obtained easily by employing tris(dipivaloylmethanato)europium $Eu(DPM)_3$, a typical paramagnetic shift reagent. In extension of our knowledge described above, a preliminary report[5] on a simple generalization of stereochemical arguments for trisubstituted allylic alcohols by using the same shift reagent on an acetate sample was subsequently published and the feature of our method was emphasized. We now give a full account of our results on stereochemical problems as well as simultaneous determination of these geometrical isomers in a mixture.

Result and Discussion

Geometrical Configurations

It is well established that geraniol has a *trans*-ol and nerol a *cis*-ol configuration[6] around the trisubstituted carbon-carbon double bond. Stereochemical assignment in such system containing $-(CH_3)C{=}CH{-}CH_2OH$ or $-CH{=}C(CH_3){-}CH_2OH$ has been frequently made by

1) Part III: K. Tsukida, M. Ito, and F. Ikeda, *Intern. J. Vit. Nutr. Res.*, **42**, 91 (1972).
2) Location: *Motoyama-cho, Higashinada-ku, Kobe.*
3) L.M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 119; *idem, Fortschr. Chem. Org. Naturstoffe*, **23**, 315 (1965).
4) *a*) J.W.K. Burrell, R.F. Garwood, L.M. Jackman, E. Oskay, and B.C.L. Weedon, *J. Chem. Soc.*, **1966**, 2144; *b*) K.C. Chan, R.A. Jewell, W.H. Nutting and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968).
5) K. Tsukida, M. Ito, and F. Ikeda, *Experientia*, **28**, 721 (1972); During our work was in progress, the limited discussion was made by de Haan, *et al.* on *Z-E* conformational isomerism of nerol and geraniol [J.W. de Haan and L.J.M. van de Ven, *Tetrahedron Letters*, **1971**, 2703].
6) With trisubstituted double bonds, the term *trans* and *cis* are used to designate the relative positions of the two largest substituents.

elegant synthetic studies of related compounds,[4a] while several pioneer works employing NMR spectroscopy have been also reported.[7] However, poor NMR resolution was usually obtained and a direct application of these proposals for a wide variety of compounds described above was prevented ,*i.e.*, difference in coupling constants or chemical shift values of appropriate protons attributable to the *trans* or the *cis* structure is often too small to make unambiguous stereochemical assignment and is also influenced obviously by other structural elements. Another proposal employing solvent shift values ($\Delta=\delta_{CDCl_3}-\delta_{C_6D_6}$) was found not always useful for the alcohols under consideration.[4b]

Our method is composed of acetylation of an alcohol sample, running NMR with and without an addition of $Eu(DPM)_3$ reagent, and reading of relative shift value(s) (ν_{rel}) of appropriate proton signal(s). As far as an approximate linear relationship is confirmed between shift of the signal and amount of the reagent, adoption of ν_{rel} value simplifies experimental descriptions and procedures considerably. Because of its characteristic chemical shift and sharpness of the signal, an excellent qualification of an acetoxyl peak as a reference signal[8] should be stressed repeatedly. Estimated ν_{rel} value can then be easily correlated to a pronounced, structural feature of one isomeric allylic acetate and a pure specimen of the other isomer or of its related compound is not necessary for comparison. The tabulated results clearly indicate that the stereochemistry of the isomeric trisubstituted allylic alcohols (types A and B in Tables I and II) can be definitely assigned by examining the following two points. Firstly, depending upon whether the compound is type A or B, there exists an obvious distinction on a splitting pattern of the proton signal attached to the carbon atom bearing

TABLE I. Relative Shift Values of the Acetates of Trisubstituted Allylic Alcohols

(1) Experimental Detail

type A: R_1 or $R_2=CH_3$, $R_3=H$

type B: R_1 or $R_2=H$, $R_3=CH_3$

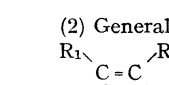
Parent alcohol[a]	Type	R_1	R_2	ν_{rel}[b] α CH_3	α H	β-*trans* CH_3	β-*trans* H	β-*cis* CH_3	β-*cis* H
Angelyl alcohol	B	H	CH_3	34.2			19.6	20.0	
trans-Crotyl alcohol	A	CH_3	H		c)	8.6			c)
cis-Crotyl alcohol	A	H	CH_3		c)		c)	18.1	
Geraniol	A	C_6H_{11}	CH_3		50.7			20.7	
trans-β-Ionylidene ethanol	A	$C_{11}H_{17}$	CH_3		48.5			19.2	
β-Methallyl alcohol	B	H	H	27.7			17.1		34.2
2-Methyl-2-penten-1-ol	B	C_2H_5	H	30.0					29.8
Nerol	A	CH_3	C_6H_{11}		52.3	10.9			
Phytol	A	$C_{16}H_{33}$	CH_3		48.8			19.6	
α-Santalol	B	H	$C_{11}H_{17}$	34.2			21.7		
β-Santalol	B	H	$C_{11}H_{17}$	33.9			21.1		
Tiglyl alcohol	B	CH_3	H	30.7		10.5			30.5
all-*trans* Vitamin A_1	A	$C_{16}H_{23}$	CH_3		50.1			19.1	
13-*cis* Vitamin A_1	A	CH_3	$C_{16}H_{23}$		c)	10.1			
9-*cis* Vitamin A_1	A	$C_{16}H_{23}$	CH_3		c)			19.6	
9,13-di*cis* Vitamin A_1	A	CH_3	$C_{16}H_{23}$		c)	9.6			

a) Compounds reported here in had correct spectral data.
b) 60 MHz, in CCl_4. The ν_{rel} refers to a relative paramagnetic shift against acetoxyl group ($\nu_{rel}=100.0$).
c) Could not be determined.

7) R.B. Bates and D.M. Gale, *J. Am. Chem. Soc.*, **82**, 5749 (1960); A.F. Thomas and M. Ozainne, *Chem. Commun.*, **1969**, 46; M. Kelly, S.A. Andresen, and S. Liaaen-Jensen, *Acta Chem. Scand.*, **25**, 1607 (1971).
8) K. Tsukida, M. Ito, and F. Ikeda, *J. Vitaminol.*, **18**, 24 (1972).

Table II. Relative Shift Values of the Acetates of Trisubstituted Allylic Alcohols

(2) General Survey



type A: R_1 or R_2=CH_3, R_3=H

type B: R_1 or R_2=H, R_3=CH_3

Relative position against $-CH_2OAc$ group	Type	ν_{rel}	Multiplicity of $-CH_2-O-$
C_α-CH_3	B	28—34	singlet
C_β-*cis*-CH_3	A,B	18—21	doublet (A type) singlet (B type)
C_β-*trans*-CH_3	A,B	9—11	doublet (A type) singlet (B type)
C_α-H	A	49—52	doublet
C_β-*cis*-H	B	30—34	singlet
C_β-*trans*-H	B	17—22	singlet

an acetoxyl group, and secondly, shift degree of an appropriate proton signal diminishes in the manner of geometric progression in the order of C_α–H>C_α–CH_3 and C_β-*cis*-H>C_β-*cis*-CH_3 and C_β-*trans*-H>C_β-*trans*-CH_3 (shift ratio is roughly 5: 3: 2: 1).

Simultaneous Determination of Isomers in a Mixture

Our method is very simple and potential as described above, a wide applicability of which can be foreseen not only for stereochemical assignment of natural products remaining unsolved, but also for simultaneous determination of *cis–trans* isomers in a mixture. Typical examples are given below.

Barnes, *et al.*[9] reported that a mixture of *cis* and *trans* crotyl alcohols gave a poor NMR resolution and their contents were estimated only by gas–liquid chromatographic analysis after attribution of the *trans* structure to the predominant form was established by infrared spectrum and by synthesis of the *trans* isomer. Our method using merely a few NMR running, however, revealed not only the expected shift difference between *trans* and *cis* β-methyl groups, but also a distinct separation in acetoxyl peaks of the isomers (shift ratio of *trans*: *cis*= 100: 88). Consequently, a content ratio (*trans*: *cis*=70: 30) of the isomers in a commercial sample was easily determined from the peak-height or peak-area ratio of the acetoxyl proton signals. This finding led us to propose a simple identification and simultaneous determination method of vitamin A isomers subsequently.[1]

Another example is an isomerization of the acetate of *trans*-β-ionylidene ethanol. When the acetate of *trans*-β-ionylidene ethanol was irradiated under an experimental condition in the presence of catalytic amount of iodine[10] and when the results before and after isomerization reaction were compared with each other, little information was able to obtain on a *trans*→*cis* isomerization of this compound from its NMR and thin-layer chromatographic behaviours. To the contrary, our method enables a distinct separation of the acetoxyl signals (shift ratio of *trans*: *cis*=100: 88) as well as olefinic methyl signals of the isomers in a mixture. A definite identification is now possible and a content ratio (*trans*: *cis*=67: 33) of the isomers in an irradiated acetate sample of *trans*-β-ionylidene ethanol can be easily estimated in a similar way. Our experimental results (ν_{rel} *trans*: 9-CH_3 19.0, 5-CH_3 2.4; *cis*: 9-CH_3 11.6, 5-CH_3 8.9; no indication of the third isomer) demonstrate that *trans*→*cis* isomerization occurs only around the $\Delta^{9,10}$-double bond and agree well with the previous interpretation[11] that β-ionone

9) D. Barnes, P.C. Uden, and P. Zuman, *Anal. Lett.*, **3**, 633 (1970) [*C.A.*, **74**, 82829 (1971)].

10) Under stirring in a flask, the hexane solution containing 0.1% iodine (sample acetate=100%) was exposed to the light of 40 cm long fluorescent lamp (20 W) from 30 cm distance for 30 min.

11) B. Honig, B. Hudson, B.D. Sykes, and M. Karplus, *Proc. Nat. Acad. Sci. USA*, **68**, 1289 (1971).

and its closely related compounds have generally the distorted, nonplanar *s-cis* configuration about the C_6–C_7 single bond with torsional angle in a definite range.

Experimental[12]

Materials——A shift reagent $Eu(DPM)_3$ was prepared primarily according to the method of Eisentraut and Sievers.[13] Sample acetates were prepared by refluxing the corresponding alcohols with equi-molar of acetic anhydride for 2 hr and were purified by distillation, column chromatography, or preparative GLC (10% Carbowax 20M-60/80 Chromosorb W column at 160° for geranyl acetate; 20% Reoplex 400-60/80 Chromosorb W column at 200° for α- and β-santalyl acetates). Parent alcohols were obtained commercially or synthesized by standard routes.

NMR Spectra——Relative shift values (ν_{rel}): see Table I. Chemical shift values (δ ppm) were given below in the order of C_α-CH_3, C_α-H, C_β-CH_3, C_β-H and acetoxyl proton and those which could not be determined were indicated by asterisk. Angelyl acetate: 1.70, —, 1.68, 5.43, 1.97; *trans*-crotyl acetate: —, *, 1.72, *, 1.96; *cis*-crotyl acetate: —, *, 1.73, *, 1.97; geranyl acetate: —, 5.30, 1.68, —, 1.95; *trans*-β-ionylidene ethyl acetate: —, 5.49, 1.87, —, 1.98; β-methallyl acetate: 1.75, —, —, 4.92 and 4.92, 2.00; 1-acetoxy-2-methyl-2-pentene: 1.64, —, —, 5.43, 1.98; neryl acetate: —, 5.32, 1.75, —, 1.95; phytyl acetate: —, 5.29, 1.69, —, 1.94; α-santalyl acetate: 1.71, —, —, 5.32, 1.97; β-santalyl acetate: 1.71, —, —, 5.32, 1.98; tiglyl acetate: 1.63, —, 1.63, 5.51, 1.97; all-*trans* Vitamin A_1 acetate: —, 5.57, 1.90, —, 1.98; 9-*cis* Vitamin A_1 acetate: —, *, 1.89, —, 1.98; 13-*cis* Vitamin A_1 acetate: —, *, 1.94, —, 1.98; 9,13-di*cis* Vitamin A_1 acetate: —, *, 1.94, —, 1.97.

Determination of a Content Ratio of *cis-trans* Isomers in a Mixture——NMR spectra with and without an addition of the shift reagent were run on a CCl_4 solution of an acetate sample. After the relative position of signals attributable to the *trans* and the *cis* structure was confirmed, a content ratio of the isomers were estimated from peak-height or peak-area ratio of the shifted and separated acetoxyl signals.

1) Commercial Crotyl Alcohol: Shift ratio of the acetoxyl peaks, *trans*:*cis*=100.0: 88.4. Content ratio of *trans* to *cis*, Found from peak-height 70.9: 29.1, 70.6: 29.4, 69.4: 30.6; Found from peak-area 71.0: 29.0, 68.8: 31.2, 67.9: 32.1.

2) An Irradiated Acetate of *trans*-β-Ionylidene Ethanol: Isomerization, see footnote 10. Shift ratio of the acetoxyl peaks, *trans*:*cis*=100.0: 88.4. Content ratio of *trans* to *cis*, Found from peak-height 65.4: 34.6, 68.0: 32.0; 66.2: 33.8; Found from peak-area 66.7: 33.3, 66.4: 33.6, 66.6: 33.4.

12) NMR spectra were recorded on a 60 MHz Varian A 60-D instrument in CCl_4 solutions, tetramethylsilane being used as an internal standard. Preparative gas–liquid chromatography (GLC) was performed using Varian Aerograph Gaschromatograph Model 90—75.

13) K.J. Eisentraut and R.E. Sievers, *J. Am. Chem. Soc.*, **87**, 5254 (1965).