Spectroscopic properties of molecules related to hindered isomers of retinal

V RAMAMURTHY and R S H LIU*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012
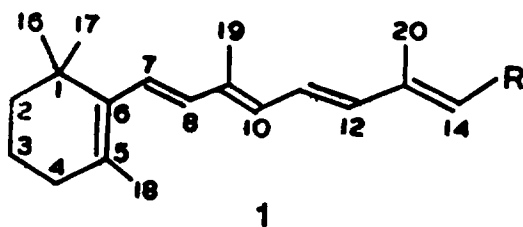* Department of Chemistry, University of Hawaii, Honolulu, USA

Abstract. Proton and ^{13}C NMR study of molecules related to retinal has been carried out. The characteristic differences in spectral behaviour among 7-*trans* and 7-*cis* isomers have been established which would be useful in determining the structure of new isomers and identifying components in a mixture. Through coupling constant measurements and DNMR study it is clearly established that 7-*cis* isomers of β-ionyl derivatives and in turn 7-*cis* isomers of retinyl derivatives prefer a non-planar arrangement and this non-planarity brings about resonance destabilisation.
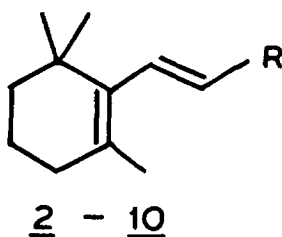
Keywords. ^{1}H; ^{13}C NMR study; DNMR of ionyl derivatives.

1. Introduction

Retinal 1, one of the biologically important molecules, theoretically can exist in sixteen geometrical isomeric forms. According to Pauling (1939, 1949) the possibility of forming *cis* double bonds at C_7 and C_{11} positions has to be discarded on account of the steric hindrance existing in these forms which would not allow the resonance phenomena. However, two hindered retinals having 11-*cis* configuration have since been synthesised (Orshnik 1956). Construction of the Dreiding models and spectroscopic data clearly indicate that the distortion of the side chain may partly reduce the possibility of resonance for these compounds (Patel 1969). On the other hand, all attempts to synthesise the 7-*cis* isomers through conventional means were unsuccessful (Wald *et al* 1955; Russel and Weeden 1969; Fagle and Karrer 1961). The rationale for the failure has been the lack of stability due to loss of resonance stabilisation brought about by the forced skewed geometry.

1

Recently, we have synthesised 7-*cis* isomers of retinal and related molecules through a novel "one way sensitised geometric photoisomerisation" (Ramamurthy and Liu 1976; Ramamurthy *et al* 1975). The ready availability of these molecules have allowed us to test the prediction of steric hindrance in these isomers. We have studied the 7-*cis* isomers of β-ionyl derivatives (2–10) possessing the basic framework of 7-*cis* retinals and the results are expected to show the fundamental structural features in the C_5–C_9 region of 7-*cis*-retinal isomers.

	2 R = CH₃CHOH
	3 = COOH
	4 = CH₂OH
	5 = CN
	6 = (CH₃)₂C-OH
	7 = C₆H₅
	8 = CH₃
	9 = CH₂CH₃
	10 = CH₂CHCHO.

2 – 10

In this paper we present our spectral data on these molecules which point out the existence of steric crowding resulting in non-planar molecules as was originally suggested.

2. Results and discussion

2.1. *Proton NMR study*

Molecules 2–10 were synthesised and purified by the published procedures (Ramamurthy and Liu 1976; Ramamurthy *et al* 1975). Proton and ^{13}C nmr data are presented in tables 1 and 2 respectively. The following general observations can be made on perusal of table 1. We believe that these gneralisations will be useful in determining the structure of new isomers and identifying components in a mixture.

   (i) The CH_3-18 and CH_3-19 of 7-*cis* isomers resonate at a higher field ($\triangle \delta$ 0·2 ppm) than *trans* isomers.

   (ii) Proton attached to C_7(H_7) is consistently shifted upfield in 7-*cis* isomers compared to 7-*trans* isomers.

   (iii) Proton attached to C_8 (H_8) is also shifted upfield in 7-*cis* isomers but only to a small degree.

It is not surprising to notice only a small difference in chemical shifts between 7-*trans* and 7-*cis* isomers for all other protons, except H_7, H_8, CH_3-18 and CH_3-19 as the geometry around chain and the ring would not be expected to affect their magnetic environments considerably. Had the 7-cis isomers been planar, the CH_3-18 and CH_3-19 would be expected to resonate downfield compared to 7-*trans* isomers, such shifts being due to very close steric proximity of these groups. On the other hand, the observed upfield shifts clearly rules out the steric crowding between CH_3-18 and CH_3-19 which must have been relieved by twisting about 6–7 bond. The upfield shift must be due to the shielding of CH_3-18 by the side chain which is out of plane with respect to the ring. The upfield shift of H_7 in 7-*cis* isomers compared to 7-*trans* isomers is also consistent with the twist

Table 1. NMR spectral characteristics of β-ionyl derivatives.

Compound	Chemical shifts					(Trans-cis)			
	H_7	H_8	CH_2-18	CH_3-19	$J_{7\,8Hz}$	H_7	H_8	CH_3-18	CH_3-19
2 *trans*	6·01	5·41	1·64	1·24	16				
cis	5·75	5·45	1·54	1·16	11·5	0·26	−0·04	0·10	0·08
3 *trans*	7·02	5·81	1·50	..	15·5				
cis	6·52	5·76	1·48		12	0·49	0·05	0·02	..
4 *trans*	6·04	5·51	1·80	4·12	16				
cis	5·79	5·57	1·42	3·90	11	0·25	−0·06	0·38	0·22
5 *trans*	7·10	5·30	1·82	..	17				
cis	6·84	5·46	1·76		11	0·26	−0·16	0·06	..
6 *trans*	6·03	5·53	1·66	1·34	16·2				
cis	5·71	5·46	1·70	1·23	12·5	0·32	0·07	−0·04	0·11
7 *trans*	6·60	6·35	1·80	..	17				
cis	6·00	6·34	1·54		12	0·60	+0·01	0·26	..
8 *trans*	5·73	5·25	1·60	1·72	16				
cis	5·83	5·55	1·48	1·62	12	−0·10	−0·30	0·12	..
9 *trans*	5·73	5·32	1·58	..	17				
cis	5·65	5·29	1·40		12	0·08	0·03	0·18	..
10 *trans*	5·91	5·19	1·60	1·12	16				
cis	6·02	5·28	1·52	1·06	11	−0·11	−0·09	0·08	0·06

around 6–7 bond. Because of this twist, a good overlap of π orbitals extends only from C_7 to the rest of the chain and under these conditions H_7 would be a terminal polyene proton and should appear at a higher field than if it were in the middle of a polyene chain. Thus proton nmr signals are consistent with non-planar 7-*cis* isomers.

2.2. ^{13}C NMR study

It is now well established that steric crowding and resonance effect play an important role in the ^{13}C resonance (Stothers 1972). Therefore, a correlation of ^{13}C chemical shifts of 7-*trans* and 7-*cis* isomers of β-ionyl derivatives is expected to reveal the presence of steric hindrance in 7-*cis* isomers, if any, and the nature of steric release. The following general procedure has been employed for the assignment of each of the ^{13}C spectra reported here. First an initial and possibly tentative assignment of the resonances in the noise decoupled spectrum was made based on comparison with model compounds and known substituent shifts

Table 2. ^{13}C chemical shifts of β-ionyl derivatives.

Carbon	R = CN (5)			R = COOH (3)		
	Trans	*Cis*	(T–C)	*Trans*	*Cis*	(T–C)
C_1	33·817	34·169	0·35	34·08	34·345	−0·265
C_2	39·629	38·748	−0·881	39·893	38·925	0·968
C_3	18·846	19·022	−0·176	18·977	19·022	0·045
C_4	33·288	32·232	1·05	33·640	31·879	1·76
C_5	136·324	132·802	3·52	136·456	129·632	6·82
C_6	135·619	134·739	−0·88	135·751	133·683	2·06
C_7	149·534	150·591	−1·057	146·364	0·043	0·043
C_8	100·570	101·803	−1·233	120·956	121·529	−0·573
C_9	117·655	116·422	−1·233	172·563	171·198	1·365
C_{16}	28·533	28·351	0·176	28·708	28·357	0·351
C_{17}	28·533	28·357	0·176	28·708	28·357	0·351
C_{18}	21·311	21·311	..	21·619	21·135	0·484

Carbon	R = CH$_2$CHOH (2)			R = (CH$_3$)$_2$C–OH (6)		
	Trans	*Cis*	(T–C)	*Trans*	*Cis*	(T–C)
C_1	34·0	34·036	..	33·993	34·433	−0·44
C_2	39·717	39·517	0·20	39·453	39·101	0·352
C_3	19·46	19·46	..	19·374	19·109	0·265
C_4	32·848	32·44	0·448	32·672	31·967	0·705
C_5	126·902	126·902	..	127·429	129·631	−2·202
C_6	136·765	135·00	1·765	123·643	122·410	1·23
C_7	126·401	126·902	−0·501	123·643	122·410	1·233
C_8	137·409	135·55	1·859	141·784	138·458	3·326
C_9	68·954	66·90	2·05	70·804	73·006	−2·202
C_{16}	28·796	28·5	0·296	28·709	30·646	..
C_{17}	28·796	28·5	0·296	28·709	29·413	..
C_{18}	21·75	21·7	0·05	21·311	22·368	1·057
C_{19}	23·877	..	..	29·942	28·973	..
C_{20}	..	..	..	29·942	28·709	..

(Jantelat *et al* 1970). An off resonance proton decoupled spectrum provides a check on the preliminary choice and separates the carbons according to their degree of substitution.
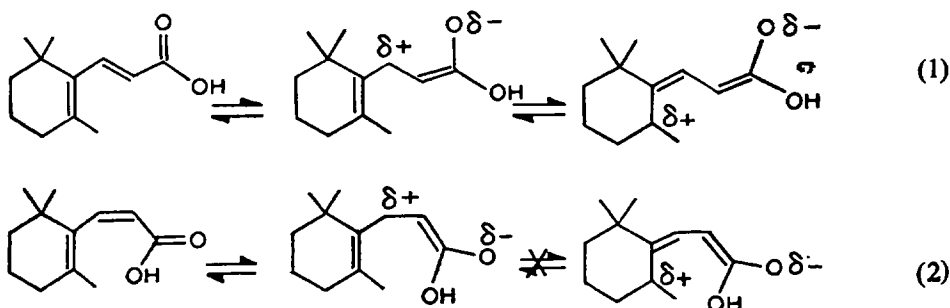
Inspection of table 2 reveals the following with respect to ^{13}C-spectral data of β-ionyl derivatives.

(i) The C_1 and C_3 chemical shifts are not considerably affected by the geometry around 7–8 double bond.

(ii) The C_1, C_4 and C_8 show a consistently small upfield shift for 7-*cis* isomers when compared to the *trans* isomers in all the compounds.

(iii) C_5 shows a large upfield shift for 7-*cis* isomers of 3 and 5 (R = COOH and CN) and downfield shift for 7-*cis* isomers of 2, 4 and 6 [R = CH$_3$CHOH, CH$_2$OH, (CH$_3$)$_2$C–OH].

(iv) C_7 does not show any consistency in its chemical shift differences between *cis* and *trans* isomers. On the other hand, C_8 is shifted upfield for 7-*cis* isomers of 2, 4 and 6 and downfield for 7-*cis* isomers of 3 and 5.

(v) C_9 shows a large upfield shift for all 7-*cis* isomers compared to 7-*trans* isomers.

(vi) C_{16}, C_{17} and C_{18} are not affected by the geometry around 7–8 double bond.

The nonplanarity of 7-*cis* isomers is clearly revealed by the independence of the chemical shifts of C_{16}, C_{17} and C_{18} of the geometry of 7–8 bond. Had it been planar, due to the large steric hindrance between these methyl groups and substituents on C_8 in 7-*cis* isomers, they would be expected to resonate at higher field. The large steric hindrance present in 7-*cis* isomers is relieved by twisting about 6–7 single bond as is clearly illustrated by the chemical shift data of C_5. The large upfield shift of C_5 in 7-*cis* isomers of $\underline{3}$ and $\underline{5}$ (R = COOH, CN) must be due to the absence of resonance effect resulting from twisting of 6–7 bond as shown in equations (1) and (2).

(1)

(2)

The upfield shift of C_8 in all 7-*cis* compounds compared to 7-*trans* isomers must be due to the steric crowding between C_8 and substituents at C_9 in the non-planar 7-*cis* isomers and in agreement with this C_9 also shows an upfield shift.

Thus both proton and ^{13}C nmr data are consistent with non-planar 7-*cis* β-ionyl derivatives with twisting around 6–7 single bond. Confirmation of this trend is provided by the DNMR (proton and ^{13}C) and coupling constant data as described below.

2.3. *Coupling constant measurements*

It is known from theoretical and experimental studies that long range proton couplings of the homoallylic type in which there are five intervening bonds are usually dominated by a π contribution such that

$$J_{HH^1} (cis) = J_{HH^1} = A \sin^2 \Phi \sin^2 \Phi', \qquad (3)$$

$$J_{HH^1} (trans) = J_{HH^1} + B = A \sin^2 \Phi \sin^2 \Phi' + B, \qquad (4)$$

where Φ and Φ' are dihedral angles and A is in the range of 5–8 Hz. We have attempted to use the above correlation to obtain the ring-chain dihedral angles in 7-*cis* isomers and the results are presented in table 3. The coupling between H_7 and CH_2–4, 4′ and CH_3–18 was extracted by decoupling experiments as illustrated in figure 1 for $\underline{6}$. The coupling of the methylene group CH_2–4, 4′ and the methyl group CH_3–18 with H_7 should be governed by the above equations (3) and (4) with Φ identified as the ring torsional angle and Φ' as that of the hydrogens in CH_2–4, 4′ or CH_3–18 relative to the C_4–C_5–C_6 plane or the CH_3–C_5–C_6 plane

Table 3. Torsional angle in β-ionyl derivatives.

R group	Isomer β-ionyl derivatives	Temperature (°C)	(Torsional angle)
CN (5)	trans	29	26·34
		−24	26·34
	cis	29	32–41
		−40	30–39
COOH (3)	trans	29	26–34
	cis	29	36–49
COOCH₃	trans	29	28–36
	cis	29	33–45
CH₂OCCH₃	trans'	29	28–36
	cis	29	37–50
CH₃CHOH (2)	trans	29	26–34
	cis	29	33–43
		− 7	32–42
(CH₃)₃–C–OH (6)	trans	27	28–36
	cis	40	40–53
		−40	37–51

respectively. These coupling constant results clearly demonstrate that the ring is twisted out of plane in both *cis* and *trans* isomers, although specific value for the angle must be regarded as approximate. The angles measured is an average over the torsional oscillations. The torsional angle for *trans* β-ionyl derivatives is independent of the substituents whereas for *cis*-isomers it seems to depend on them indicating the source of steric strain in 7-*cis* isomers to be the interaction of CH_3-18 or CH_3-16, 17 with substituents on C-8 (CH_3 group in the case of retinal).

2.4. *DNMR study*

The above results clearly demonstrate that *cis-β* ionyl derivatives and in turn 7-*cis* isomers of retinyl derivatives and carotenoids prefer the twisted ring chain conformation. The large steric hindrance in these molecules gives rise to a large barrier for the conformational equilibrium involving rotation around 6–7 single bond. DNMR spectroscopy has been extensively used in the study of fast exchange rate processes in cyclic as well as acyclic molecules (Binsch 1968). The applicability of the above technique to our system is readily realised, considering the magnetic non-equivalence of gem-dimethyl group (CH_3-16, 17) in the frozen conformation compared to the equivalence under fast rotation around 6–7 bond.
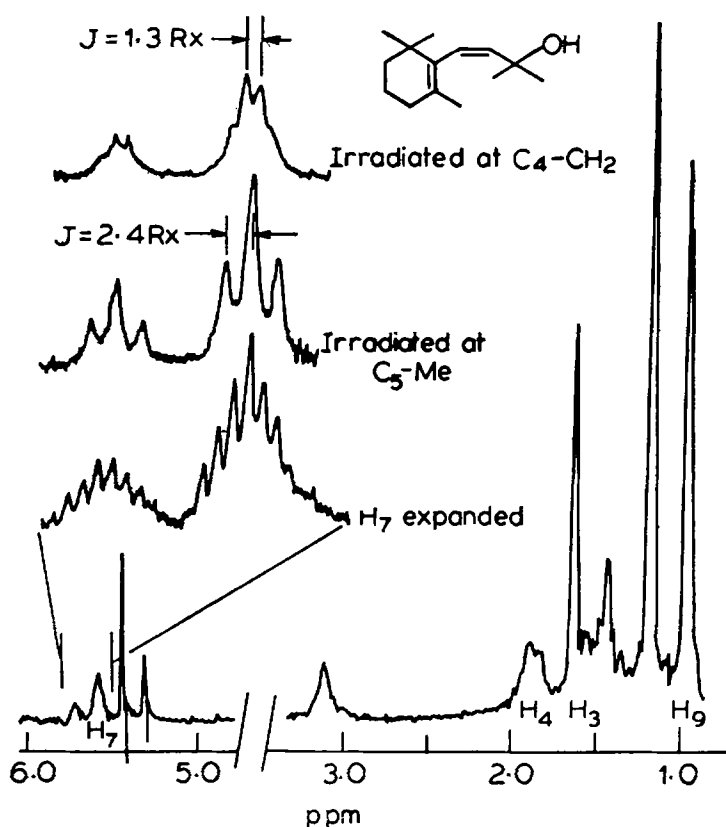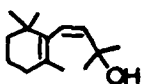
Figure 1. NMR spectrum of *cis* 6.

The geminal methyl groups (CH_3-16, 17) which appear as sharp singlet in pmr spectra at ambient temperature for $\underline{4}$ and $\underline{6}$ [R = CH_3CHOH and $(CH_3)_2C$-OH] turns into a doublet at low temperatures. Similarly C_{13} resonance of geminal methyl carbons of $\underline{4}$ and $\underline{6}$ show magnetic non-equivalence due to restricted rotation at low and room temperatures respectively by appearing as two singlets. The pmr spectra of these compounds ($\underline{2}$, $\underline{3}$, $\underline{4}$ and $\underline{6}$) were recorded at various temperatures and the $\triangle G^{+}$, the activation free energy for interconversion or exchange between the two structurally equivalent rotational isomers was calculated from their rate at the coalescence temperature (Ramamurthy *et al* 1972). The results are shown in table 4. The coalescence temperature as well as $\triangle G^{+}$ of these compounds seems to indicate the presence of large steric hindrance that is dependent on the size of the substituents at C-8.

The two rotamers of the two structurally equivalent rotational isomers of $\underline{6}$ must be enantiomers due to the production of molecular asymmetry. Based on the energy barrier calculated above, we did not expect this to be resolvable. Instead the presence of two enantiomers were shown by using an optically active shift reagent. The pmr spectra of $\underline{6}$ in the presence of fluoroshift and Eu-optishift reagents were recorded at 20° C (Whitesides and Lewis 1970; Goering *et al* 1971). The spectra show the expected downfield shift of signals in both cases (figures 2 and 3). In the former, geminal methyl signals (CH_3-16, 17) and the signals due

Table 4. Rotational barrier in cis-β-ionyl derivatives.

R	Solvent	Coalescence temperature	$v_B - v_A$ Hz	ΔG k. cal/mole
CH₂OH	Carbon disulphide	−60 C	4·0	11·2
	Vinyl chloride	−62	..	..
CH₃CHOH	Chloroform	−32	..	..
	Carbon disulphide	−35	..	..
(CH₃)₂C–OH	Chloroform	20	2·8	15·7
	Freon–12	20	..	..
	Vinyl chloride	22	..	..
COOH	Carbon disulphide	−50	15·6	11·0

Figure 2. NMR spectrum of *cis* 6 in the presence of fluoroshift reagent.

to CH₃-19, 19¹ appear as two doublets due to the frozen out conformation. On the other hand in the presence of Eu-optishift reagent, signals due to two enantiomers of 6 are clearly visible (H₈, two doublets; CH₃-18, two singlets; CH₃-19, 19′ two doublets) as shown in figure 3. Thus, the above DNMR and nmr results in the presence of shift reagents clearly demonstrate that 7-*cis* isomers of β-ionyl derivatives exist in non-planar forms with a twist around 6–7 single bond. This skewed geometry is expected to disfavour conjugation of the ring double bond with the rest of the chain. In confirmation of the above results we found that 7-*cis* β-ionol has a higher singlet excited state energy than 7-*trans* isomer (7-*cis*, 210 nm; 7-*trans*, 235 nm).

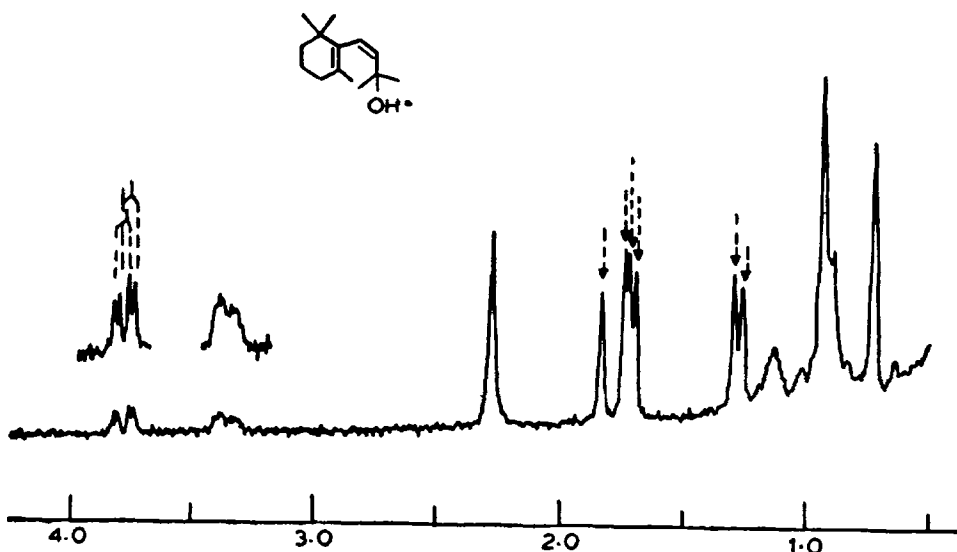**Figure 3.** NMR spectrum of *cis* 6 in the presence of Euro optishift reagent.

In conclusion we have clearly established that 7-*cis* isomers of β-ionyl derivatives and in turn 7-*cis* isomers of retinyl derivatives prefer a non-planar arrangement and this non-planarity brings about resonance destabilisation as was originally predicted.

Acknowledgements

References

Binsch G 1968 *Top. Stereochem.* **3** 97
Fagle H and Karrer P 1961 *Helv. Chim. Acta* **44** 1261
Goering H L, Eikenberry J N and Commer G S 1971 *J. Am. Chem. Soc.* **93** 5913
Jantelat M, Grutznev J B and Roberts J D 1970 *Proc. Natl. Acad. Sci.* **65** 288
Orshnik W 1956 *J. Am. Chem. Soc.* **78** 2651
Patel D J 1969 *Nature* **221** 825
Pauling L 1939 *Fortsch. Chem. Org. Naturst.* **3** 203
Pauling L 1949 *Helv. Chim. Acta* **32** 2241
Ramamurthy V, Bopp T T and Liu R S H 1972 *Tetrahedron Lett.* 3915
Ramamurthy V and Liu R S H 1976 *J. Am. Chem. Soc.* **98** 2935
Ramamurthy V, Tustin G, Yau C C and Liu R S H 1975 *Tetrahedron* **31** 193
Russel S W and Weedon B C L 1969 *Chem. Commun.* 85
Stothers J B 1972 *Carbon-13 NMR Spectroscopy* (New York : Academic Press)
Wald G, Brown P K, Hubbard R and Orshnik W 1955 *Proc. Natl. Acad. Sci.* **41** 438
Wald G, Brown P K, Hubbard R and Orshnik W 1956 *Proc. Natl. Acad. Sci.* **42** 578
Whitesides G M and Lewis D W 1970 *J. Am. Chem. Soc.* **92** 6976