Tetrahedron. Vol. 32, pp. 229 to 231. Pergamon Press 1976. Printed in Great Britain

^{13}C NMR SPECTRA OF TOCOPHEROLS AND 2,2-DIMETHYLCHROMANOLS†

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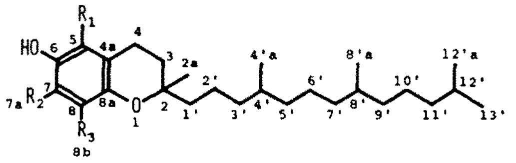
(*Received in Japan* 20 *August* 1975; *Received in UK for publication* 18 *September* 1975)

Abstract—Carbon-13 NMR signals have been assigned for α-, β-, γ- and δ-tocopherols, and their model compounds, 2,2-dimethylchromanols. The ^{13}C spectra of α-tocopherol-5-CD$_3$ and -8-CD$_3$ afforded the evidence of the assignments of Me-carbon signals. It was found that previous tentative assignments for C-6 and C-8a of α-tocopherol are not correct. Steric compression shifts have been observed at several Me-carbons and at the methylene-carbons of C-4 in their compounds.

In recent years it has become easier to obtain high-resolution ^{13}C NMR spectra of complex molecules as large as tocopherols by the introduction of pulsed Fourier transformation technique. However, the full utility of ^{13}C NMR in structure determination is not yet established because of the difficult task of assigning the ^{13}C resonances. We attempted to assign all the ^{13}C signals in natural-abundance ^{1}H-noise-decoupled ^{13}C FT NMR spectra of tocopherols and their model compounds, 2,2-dimethylchromanols. The structure of five 2,2-dimethylchromanols and four tocopherols (*d*-α-, *dl*-β-, *d*-γ- and *d*-δ-tocopherols) examined is shown in Fig. 1 and their chemical shifts (δ_c) are presented in Tables 1 and 2. The spectrum of α-tocopherol (vitamin E) shown in Table 2 has already been known though the signals were not fully assigned.[1] The spectra of tocopherols except the isoprenyl side-chain were quite analogous to those of the model compounds.

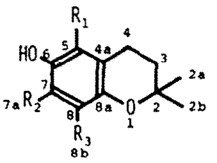
2,2-Dimethylchromanols. Since 2,2-dimethylchromanols are the model compounds of tocopherols studied here, we found it important to establish the ^{13}C signal assignments in their spectra. In almost all cases unambiguous assignments were made by comparing observed peak positions and by the use of off-resonance decoupling technique and a shift reagent, Eu(fod)$_3$. With a few exceptions of unresolved two-carbon Me singlets from C-2a and C-2b in each model compound, and from C-7 and C-8 in 2,2,7,8-tetramethylchromanol, all the peaks were well separated for the assignment. As is apparent from Table 1, the carbon resonances of the chromanols can be grouped into three regions which correspond to aromatic, aliphatic, and Me-carbons attached to the aromatic ring.

The two kinds of oxygenated carbons (phenolic C-6 and ethereal C-8a) of the chromanols were distinguished by Eu(fod)$_3$-induced shift since the europium ions coordinate selectively to the phenolic oxygen.[2,3] On using Eu(fod)$_3$, their peaks moved downfield and the magnitude of the induce shift was about five times larger at the phenolic carbon than at the ethereal one in each model compound. In 5,7-dimethyl, 5,8-dimethyl and 5,7,8-trimethyl compounds, phenolic carbons were slightly shielded relative to ethereal carbons. Further, the europium-induced shift method was applied to determine whether peaks arise from carbons *ortho* or *meta* to the phenolic carbon. The shifts at the *ortho* carbon peaks were relatively large. Off-resonance decoupling technique provided indication of protonated or substituted aromatic carbons; the latter signal was at lower field than the former one because of a deshielding effect of the adjacent Me or methylene group.[4] Chemical shifts of the protonated aromatic carbons in this system increased in the order of C-5, C-7 and C-8. In 2,2-dimethylchromanol without a Me group in the aromatic ring, the peaks of the three protonated carbons at δ 114·5, 115·5 and 117·6 were assigned to C-5, C-7 and C-8, respectively. A similar trend was apparent for the substituted aromatic carbons at C-5 (δ 119·4 in 5,8-dimethylchromanol) and C-7 (121·8 in 7,8-dimethylchromanol). The substituted aromatic carbon resonances for C-4a appeared over the range of δ 116·9–121·7, which were assigned by referring to the chemical



Tocopherols

Type	α	β	γ	δ
R$_1$	Me	Me	H	H
R$_2$	Me	H	Me	H
R$_3$	Me	Me	Me	Me



Chromanols

Type	triMe (α)	diMe (β)	(γ)		none
R$_1$	Me	Me	H	Me	H
R$_2$	Me	H	Me	Me	H
R$_3$	Me	Me	Me	H	H

Fig. 1.

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†Presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai (Apr. 1974); Contribution TMIG-RI No. 1.

Table 1. ^{13}C chemical shifts and $Eu(fod)_3$-induced shifts in 2,2-dimethylchromanols[a]

	2,2-Dimethylchromanols									
Type	triMe (α)		5,8-diMe (β)		7,8-diMe (γ)		5,7-diMe		none	
Carbon No.	δ^b	◂ Eu^c	δ^b	◂ Eu^c	δ^b	◂ Eu^c	δ^b	◂ Eu^c	δ^b	◂ Eu^c
8a	145.5	0.9	145.9	1.0	145.7	1.2	147.2	1.0	147.5	1.3
6	144.4	5.2	145.6	5.3	146.1	6.9	145.0	4.8	148.4	7.6
8	122.4	1.4	123.8	1.3	125.6	1.3	116.1^d	1.3	117.6^d	1.4
7	121.1	2.6	115.5^d	2.7	121.8	2.0	122.4	2.5	115.5^d	2.9
5	118.6	2.7	119.4^d	1.7	112.3^d	3.7	122.0	2.5	114.5^d	2.3
4a	116.9	1.3	120.0	1.1	117.9	1.5	117.8	1.2	121.7	1.4
2	72.3	0.4	72.4	0.4	73.3	0.4	72.6	0.4	74.0	0.4
3	33.1	0.3	33.0	0.4	33.0	0.3	33.0	0.3	32.8	0.4
4	21.1^e	0.5	21.1^e	0.5	22.6	0.3	20.8^e	0.4	22.6	0.5
2a 2b	26.7	0.2	26.6	0.2	26.9	0.2	26.5	0.2	26.7	0.3
7a	12.1^e	2.2	-	-	11.9^e	2.4	16.0	2.0	-	-
8b	11.8^e	0.4	15.8	0.3	11.9^e	0.6	-	-	-	-
5a	11.3^e	2.2	11.0^e	1.9	-	-	11.4^e	2.0	-	-

(a) Each compound (1 mmol) was disolved in $CDCl_3$ (1 cm^3), and $Eu(fod)_3$ (200 mg) was added to the solution after determination of δ values. (b) Chemical shifts in ppm for TMS. (c) ◂Eu[the differential shift value induced by $Eu(fod)_3$] = $\delta_{Eu} - \delta$. (d) Chemical shift values for protonated aromatic carbons. (e) A steric effect was observed.

Table 2. ^{13}C chemical shifts and $Eu(fod)_3$-induced shifts in tocopherols[a]

	Tocopherols							
Type	α		β		γ		δ	
Carbon No.	δ^b	◂ Eu^c	δ^b	◂ Eu^c	δ^b	◂ Eu^c	δ^b	◂ Eu^c
8a	145.4	0.9	145.7	1.1	145.5	1.1	145.8	1.1
6	144.4	4.7	145.5	6.1	146.0	5.8	147.5	7.0
8	122.3	1.2	123.8	1.4	125.5	1.1	127.1	1.2
7	121.0	2.5	115.4^d	3.2	121.5	1.9	115.8^d	2.4
5	118.5	2.5	119.2	2.0	112.0	3.3	112.7^d	2.6
4a	117.0	1.2	120.1	1.2	118.0	1.2	121.1	1.1
2	74.3	0.4	74.4	0.4	75.3	0.4	75.5	0.3
1'	39.8	0.3	39.8	0.3	40.0	0.3	40.0	0.2
11'	39.4	0.1	39.4	0.1	39.4	0.1	39.4	0.0
3' 5' 7' 9'	37.5	0.1	37.4	0.1	37.5	0.1	37.5	0.0
4' 8'	32.7	0.1	32.7	0.1	32.8	0.0	32.7	0.1
3	31.6	0.3	31.5	0.4	31.4	0.3	31.4	0.3
12'	28.0	0.1	28.0	0.1	27.9	0.1	28.0	0.0
10'	24.8	0.1	24.8	0.1	24.8	0.1	24.8	0.0
6'	24.5	0.1	24.5	0.1	24.4	0.1	24.5	0.0
2a	23.8	0.2	23.8	0.3	24.0	0.2	24.0	0.2
12'a 13'	22.6	0.1	22.7	0.0	22.6	0.0	22.7	0.0
2'	21.0	0.2	21.0	0.2	21.0	0.2	21.0	0.2
4	20.8^e	0.4	20.8^e	0.5	22.3	0.4	22.7	0.3
4'a 8'a	19.7	0.1	19.7	0.1	19.7	0.1	19.7	0.0
7a	12.1^e	2.1	-	-	11.9^e	2.0	-	-
8b	11.8^e	0.4	15.8	0.3	11.9^e	0.5	16.0	0.4
5a	11.2^e	2.0	11.0^e	2.2	-	-	-	-

See Table 1 for footnotes a to e.

shift of C-4a (δ 117·8) in 5,7-dimethylchromanol. These results enabled the assignment of the substituted aromatic carbons in 5,7,8-trimethylchromanol; i.e. C-4a at δ 116·9, C-5 at 118·6, C-7 at 121·1 and C-8 at 122·4.

The assignment of four kinds of aliphatic carbons at C-2, C-3, C-4 and C-2a and -2b (unresolved) was straightforward. A steric effect[5] was found at C-4 in the chroman ring methylated at C-5. The C-4 methylene signals in the 5-methylated chromanols were about 1·5 ppm upfield from those in the 5-protonated compounds.

The carbon resonances of three Me groups (C-5a, C-7a and C-8b) bonded to an aromatic ring were in the region of δ 11·0–16·0. The C-8b absorptions in 5,8-dimethyl-, 7,8-dimethyl- and 5,7,8-trimethylchromanols were easily distinguished by their small $Eu(fod)_3$-induced shifts. The unresolved peak due to C-7a and C-8b in 7,8-dimethylchromanols appeared at δ 11·9. The C-5a and C-7a absorptions in 5,7-dimethyl- and 5,7,8-trimethylchromanols were assigned by reference to the chemical shift values of C-5a (δ 11·0) in 5,8-dimethylchromanol and C-7a (11·9) in 7,8-dimethylchromanol. As will be mentioned later, these signal assignments on Me-carbons attached to the aromatic ring were supported by analysis of the spectra of α-tocopherol-5-CD_3 and -8-CD_3. Steric compression shifts were observed at the congested Me-carbons of C-5a, C-7a and C-8b.[4,5] Their Me-carbons flanked with a Me or a methylene group resonated at δ 11·0–12·1, while those with an *ortho* proton were less shielded (δ 15·8 and 16·0). In this case the difference was about 4·0 ppm.

Tocopherols. The signals due to C-2, C-2a, C-3, C-4, C-6, C-8a, and carbons of the isoprenyl side-chain in α-tocopherol have previously been assigned.[1] The signal assignments in the isoprenyl part were strongly supported by ^{13}C NMR data of a polyisoprenoid of phytol already reported.[6] We found that the $Eu(fod)_3$-induced shift in the isoprenyl side-chain of tocopherols (from C-2' to C-13') was quite small; this is useful for assigning the peaks of the isoprenyl carbons. The spectra of the isoprene moieties in tocopherols examined were superimposable with each other. The carbon resonances of tocopherols except the isoprenyl side-chain were assigned by analogy with the model compounds. An earlier assignment[1] that the most downfield peak at δ 145·4 of α-tocopherol is caused by the phenolic carbon was not correct. It was clear by a concentration variation method of $Eu(fod)_3$ that the lowest peak should be assigned to the ethereal carbon and the second lowest peak to the phenolic carbon (Table 2). It is also the case with *p*-methoxyphenol.[3,4] On the other hand, the phenolic carbon in γ- and δ-tocopherols absorbed at the most downfield (δ 146·0 and 147·5). In α-tocopherol, the assignments of C-5a, C-7a and C-8b signals were confirmed by comparison with the spectra of α-tocopherol-5-CD_3 and -8-CD_3. Peaks at δ 11·2 and 11·8 disappeared in the spectra of α-tocopherol-5-CD_3 and -8-CD_3, respectively. The peak at δ 11·2 corresponds to C-5a and the one at 11·8 to C-8b. The remaining peak at δ12·1 was thus assigned to C-7a. In β-tocopherol, a Me-carbon of C-5a absorbed at δ 11·0 and another of C-8b at 15·8. An unresolved peak due to C-7a and C-8b in γ-tocopherol appeared at δ 11·9. A Me peak of C-8b in δ-tocopherol was found at δ 16·0. These assignments were also proved from the data of the europium-induced shift. A steric compression shift was observed at the congested methylene and Me-carbons at C-4, C-5a, C-7a and C-8b in tocopherols, as observed in the model compounds. The C-2a signals in tocopherols were at about 2·5 ppm upfield relative to C-2a and -2b in the respective model compounds. This may be attributed to the steric effect of the isoprenyl group.

EXPERIMENTAL

dl-β-Tocopherol, *dl*-γ-tocopherol and 2,2-dimethylchromanols were prepared in our laboratory according to the usual methods,[7] and *d*-α-, *d*-γ- and *d*-δ-tocopherols were the gifts from Messrs. Ano and Abe (Eisai Research Laboratories, Tokyo, Japan). $Eu(fod)_3$ was purchased from Dojin Co, Ltd. (Kumamoto, Japan). $CDCl_3$, DCDO, DCl and TMS were obtained from E. Merck AG (Darmstadt, West Germany). *dl*-α-Tocopherol-5-CD_3 was synthesized from *dl*-γ-tocopherol and DCDO in the presence of DCl and $SnCl_2$ in isopropyl ether, and *dl*-α-tocopherol-8-CD_3 from *dl*-5,7-dimethyltocol by the same method.[8] All 10-mm sample tubes employed were obtained from Varian Associates (Palo Alto, U.S.A.).

All ^{13}C FT NMR spectra were recorded on a Varian XL-100-12 wide-gap spectrometer, equipped with a Varian 620/L computer, operating at 25·2 MHz at about 30°. An 8 k data-set was used in the computer controlled Fourier transform system. The Fourier transformations were based on 8192 data points. The spectra were taken at a 5 kHz spectral width using a 3 kHz noise band width at 95% high power operation of the decoupler; normally 10 k transients were taken using an aquisition time of 0·8 sec, and a 15 μsec pulse width. Under these conditions, computer-measured chemical shifts were corrected to ± 0·05 ppm and narrow peaks as close as 0·1 ppm could be resolved.

The compound (1 mmol) was dissolved in $CDCl_3$ (1 cm^3) containing TMS (0·1 cm^3) as internal standard. $Eu(fod)_3$ varying from 0·01 to 0·2 mmol was added to the solution. Field-frequency lock was established by the deuterium resonance of the solvent.

Acknowledgements—The authors thank Messrs. K. Ano and K. Abe of Eisai Research Laboratories for the gifts of *d*-α, *d*-γ- and *d*-δ-tocopherols, and Dr. Y. Kawazoe of National Cancer Center Research Institute for his useful advice, and also Messrs. S. Yamanoi and Y. Tahara of this Institute for their technical assistances.

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