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# THE GEMINAL COUPLING AND PARAMAGNETIC SHIFT OF EXOMETHYLENE PROTONS IN THE α,β′-UNSATURATED γ-LACTONE GROUP OF SESQUITERPENE LACTONES CONTAINING $C_8$-α-HYDROXYL GROUPS

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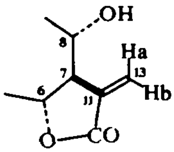
**Abstract**—Exomethylene protons ($H_{13a}$ and $H_{13b}$) in the α,β′-unsaturated lactone groups in sesquiterpene lactones which contain $C_8$-αOH groups exhibit NMR geminal coupling. In addition, $H_{13a}$ undergoes a paramagnetic shift relative to the corresponding compound which differs only in that it does not contain the $C_8$-α-hydroxyl group. Data are presented which indicate that the geminal coupling and concurrent paramagnetic shift mainly result from the van der Waal's proximity effect of the $C_8$-αOH group upon $H_{13a}$. The application of the phenomenon for making certain stereochemical and conformational assignments for sesquiterpene lactones is discussed.

IT IS well established[1] that allylic coupling occurs between the two $H_{13}$ exomethylene protons and the $H_7$ proton for all sesquiterpene lactones containing either a $C_6$ or $C_8$ α,β′-unsaturated γ-lactone ring; thus the signals for the $H_{13}$ protons (see partial structure A) typically appear as two doublets ($J$ = 1–4 c/s) in the range of 5–6 δ. However, for a number of sesquiterpene lactones which contain an α,β′-unsaturated $C_6$ γ-lactone and a $C_8$ α-OH group, each of the $H_{13}$ protons gives rise to a quartet. We have established by appropriate spin-decoupling experiments[2, 3] that this pattern results from geminal coupling in addition to the allylic coupling. We discuss here the structural, steric and electronic factors which are associated with the geminal coupling.



A

Examination of the NMR spectra of more than 290 sesquiterpene lactones* established that the geminal coupling ($J$ = about 1 c/s or more was only observed for $\alpha,\beta'$-unsaturated $C_6$- $\gamma$-lactones which also contained a $C_8$-$\alpha$-hydroxyl group. Moreover, the signal for $H_{13a}$ in sesquiterpene lactones which exhibit geminal coupling† always appears at lower field than the $H_{13a}$ signal for compounds which differ only in that they do not contain a 8-$\alpha$-OH group.

We propose that the geminal coupling and the concurrent paramagnetic shift for $H_{13a}$ mainly results from the van der Waal's proximity effect of the $C_8$-$\alpha$-hydroxyl group $H_{13a}$. This postulation is supported by the following observations and compilations:

(1) The calculated chemical shift values and distances between an influenced proton and a perturbing OH group (Table 3) are compatible with the experimental data presented in Table 4. Table 3 summarizes (according to results of Zürcher)[4] the calculated ranges in ppm for the van der Waal's paramagnetic shifts; these chemical shift ranges correspond to distances between an influenced proton and a perturbing OH group. Table 4 shows the ranges of experimentally observed chemical shifts and the distances between $H_{13a}$ and the $C_8$-$\alpha$-OH group as measured on Dreiding molecular models of $C_8$-$\alpha$-hydroxy-eudesmanolides; these latter compounds were used for this measurement because their *trans* decalin rings are held in a rigid chair form.

(2) The $H_{13a}$ paramagnetic shifts observed for both the $C_8$-$\alpha$-hydroxy compounds and their trimethylsilyl ethers were similar and less than 1 ppm; this is as expected if the shifts are due to van der Waal's forces.[5]

(3) When the $C_8$-$\alpha$-hydroxy compounds are acetylated, the $H_{13a}$ protons exhibit a diamagnetic shift; this result is as expected since acetyl groups delocalize the non-bonding electrons on the $C_8$-$\alpha$-O atoms. Similar results have been reported for the van der Waal's shifts of the C-methyl signals of the steroids.[5]

(4) The magnitude of the geminal coupling varies directly with the paramagnetic shift, therefore the geminal coupling appears to be dependent upon the same factors which influence the paramagnetic shift. Thus, since van der Waal's forces mainly influence only the $H_{13a}$ shift, the major factor causing the geminal coupling must be the distortion of the angle between $H_{13a}$ and $H_{13b}$.

The magnitudes of the paramagnetic shifts and the geminal couplings are to some degree dependent upon the nature of solvent.‡ Taking these solvent effects into account, we wish to point out that the paramagnetic shift and the geminal coupling data can be used for the following stereochemical and conformational assignments:

(a) The stereochemistry for a $C_8$-OH group in $C_6$-$\alpha$-lactones in eudesmanolides

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* Many investigators of sesquiterpene lactones contributed either samples or NMR spectra for this compilation which is presently being prepared for publication: H. Yoshioka, T. J. Mabry and B. N. Timmermann, *Sesquiterpene Lactones*, Hirokawa Publishing Co., Ltd., Tokyo, Japan.

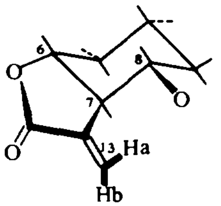
† The assignment of the signals of the $H_{13}$ protons is based upon findings that in $\alpha,\beta'$-conjugated carbonyl systems the $\beta'$-protons which are *cis* to the carbonyl function resonate at lower fields than the ones which are *trans*. However, there may be exceptions for some sesquiterpene lactones whose $H_{13a}$ protons exhibit a large paramagnetic shift (geminal coupling on the order of 1–2 c/s) and thus give rise to signals in the region where the signals for $H_{13b}$ occur. This matter is currently under investigation.

‡ Larger shifts are usually observed in pyridine-$d_5$ relative to other solvents. This may result from the electron donating nature of pyridine to the $C_8$-$\alpha$-hydroxyl groups. The similar "pyridine-induced" solvent shifts have been reported on methyl groups in steroids.[6]

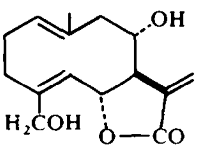
and the elemanolides can be assigned. For example, in these classes of compounds a paramagnetic shift of 0·4–0·7 ppm with concurrent geminal coupling of about 1 c/s denotes an α-orientation for the $C_8$-OH group; other results determine a β-orientation (Tables 4 and 5). Similarly, the presence or absence of the paramagnetic shift and the geminal coupling for all the available examples of germacranolides, guaianolides and pseudoguaianolides are also compatible with the known stereochemistry at $C_8$ (Tables 1 and 2).

(b) When the absolute stereochemistry of a germacranolide or guaianolide is known, the shift-geminal coupling data can be used for conformational analysis. For example, a 0·5–0·6 ppm paramagnetic shift for $H_{13a}$ for germacranolides such as salonitenolide require a distance of 2·0–2·5 Å between the $C_8$ α-O atom and $H_{13a}$ (Tables 3 and 4); this distance is possible only when the conformation in the $C_6$-$C_7$-$C_8$ system is as shown in Fig 1; furthermore the conformation for the $C_6$-$C_7$-$C_8$ unit usually determines the conformation for the remainder of the molecule.

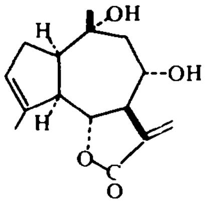
The shift and the geminal coupling data as described above did not appear to be applicable to the $C_6$-α-hydroxy-$C_8$-α-germacranolides and pseudoguaianolides which are lactonized to $C_8$ and contain a $C_6$ α-OH group; the former compounds exist in more than one conformation in solution and give poorly resolved NMR spectra.[3]



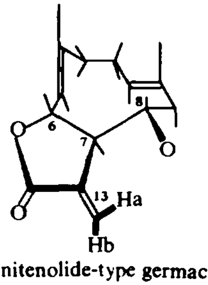
Eudesmanolides and elemanolides*



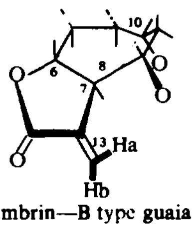
Salonitenolide



Cumambrin—B.



Salonitenolide-type germacranolide



Cumambrin—B type guaianolide†

FIG 1. The paramagnetic shift data for $H_{13a}$ determine the conformation for the $C_6$-$C_7$-$C_8$ portion of the sesquiterpene lactone and consequently the carbocyclic ring conformations as shown here.

* This conformation has been confirmed for the elemanolide vernolepin structure by X-ray analysis.[7]

† The pseudo-axial disposition of the $C_{10}$-α-hydroxyl group has been shown by the NMR proximity effect between the $C_{10}$ O atom and $H_7$.

TABLE 1. AVERAGE CHEMICAL SHIFTS AND GEMINAL COUPLING CONSTANTS OF $H_{13a}$ AND $H_{13b}$ FOR $C_8$-α-OXY-$C_6$-LACTONES[a]

| Classes of sesquiterpene lactones (No. of examples employed) | Chemical shifts |  | Geminal coupling constants |
|---|---|---|---|
|  | $H_{13a}$ | $H_{13b}$ | $^2J_{13a,b}$ |
| $C_8$-non-substituted-$C_6$-α-germacranolides (6) | 5·57 $\binom{+0·08}{-0·03}$ | 6·27 $\binom{+0·06}{-0·04}$ | ≲0·5 |
| $C_8$-non-substituted-$C_6$-eudesmanolides (12) | 5·45 $\binom{+0·10}{-0·07}$ | 6·10 $\binom{+0·07}{-0·08}$ | ≲0·5 |
| $C_8$-non-substituted-$C_6$-α-guaianolides (6) | 5·55 $\binom{+0·07}{-0·07}$ | 6·28 $\binom{+0·04}{-0·15}$ | ≲0·5 |
| $C_8$-non-substituted-$C_6$-pseudoguaianolides(11) | 5·58 $\binom{+0·09}{-0·19}$ | 6·25 $\binom{+0·05}{-0·10}$ | ≲0·5 |
| $C_8$-non-substituted-$C_6$-α-elemanolides(2) | 5·30 $\binom{+0·03}{-0·03}$ | 5·96 $\binom{+0·02}{-0·02}$ | ≲0·5 |
| $C_8$-α-hydroxy-$C_6$-α-germacranolides (5) | [6·09–6·40][b, c] | [6·17–6·52][b, c] | 1·6–2·2 |
| $C_8$-α-trimethylsilyloxy-$C_6$-α-germacranolides (4); | 6·06 $\binom{+0·06}{-0·04}$ | 6·32 $\binom{+0·11}{-0·05}$ | 1·4–2·0 |
| (9) | [5·89–6·12][d] | [6·06–6·43][d] |  |
| $C_8$-α-hydroxy-$C_6$-α-eudesmanolides(2); | 6·06 $\binom{+0·06}{-0·03}$ | 6·18 $\binom{+0·00}{-0·00}$ | 0·7–0·9 |
| (4) | [6·03–6·33][e] | [6·18–6·33][e] |  |
| $C_8$-α-hydroxy-$C_6$-guaianolides (11) | [5·96–6·44][c] | [6·03–6·55][c] | 0·7–1·8 |
| $C_8$-α-trimethylsilyloxy-$C_6$-α-guaianolides (2) | 5·95 $\binom{+0·22}{-0·22}$ | 6·29 $\binom{+0·10}{-0·10}$ | 0·8–0·9 |
| $C_8$-α-hydroxy-$C_6$-β-pseudoguaianolides(1); | 5·95 | 6·33 | 1 |
| (3) | [5·95–6·30][f] | [6·09–6·46][f] |  |
| $C_8$-α-trimethylsilyloxy-$C_6$-β-pseudoguaianolide (1) | 5·75 | 6·35 | 1 |
| $C_8$-α-hydroxy-$C_6$-elemanolide (1) | 6·08 | 6·25 | 1–1·2 |
| (3) | [6·04–6·23][g] | [6·10–6·25][g] |  |
| $C_8$-α-acyloxy-$C_6$-α-germacranolides (9); | 5·80 $\binom{+0·10}{-0·16}$ | 6·30 $\binom{+0·05}{-0·06}$ |  |
| (14) |  |  | 0·6–1·5 |
|  | [5·62–5·90][h] | [6·05–6·35][h] |  |
| $C_8$-α-acyloxy-$C_6$-α-eudesmanolides (6); | 5·56 $\binom{+0·06}{-0·05}$ | 6·15 $\binom{+0·05}{-0·04}$ | ≲0·5 |
| (8) | [5·51–5·68][e] | [6·11–6·23][e] |  |
| $C_8$-α-acyloxy-$C_6$-α-guaianolides (3); | 5·65 $\binom{+0·19}{-0·13}$ | 6·25 $\binom{+0·09}{-0·07}$ | 0–0·6 |
| (4) |  |  |  |
|  | [5·52–5·84][e] | [6·18–6·34][e] |  |
| $C_8$-α-acyloxy-$C_6$-β-pseudoguaianolide (1); | 5·66 | 6·32 | ≲0·5 |
| (2) | [5·66–5·72][i] | [6·18–6·32][i] |  |
| $C_8$-α-acyloxy-$C_6$-α-elemanolide (1) | 5·62 | 6·21 | ≲0·5 |

[a] All NMR spectra were measured only in $CDCl_3$ unless otherwise noted.

[b] Numbers in brackets parentheses indicate ranges of chemical shifts obtained when different solvents were employed for the examples.

[c] In this instance, $CDCl_3$, acetone-$d_6$, pyridine-$d_5$ and DMSO-$d_6$ were employed.

[d] Solvents employed: $CDCl_3$, acetone-$d_6$, DMSO-$d_6$, $CCl_4$ and $CS_2$.

[e] Solvents employed: $CDCl_3$ and pyridine-$d_5$.

[f] Solvents employed: $CDCl_3$, pyridine-$d_5$ and DMSO-$d_6$.

[g] Solvents employed: $CDCl_3$, acetone-$d_6$ and pyridine-$d_5$.

[h] Solvents employed: $CDCl_3$, acetone-$d_6$, DMSO-$d_6$ and $CCl_4$.

[i] Solvents employed: $CDCl_3$ and acetone-$d_6$.

TABLE 2. AVERAGE CHEMICAL SHIFTS AND GEMINAL COUPLING CONSTANTS OF $H_{13a}$ AND $H_{13b}$ FOR $C_8$-PSEUDOGUAIANOLIDES

| Type of pseudoguaianolide (No. of examples) | Chemical shifts $H_{13a}$ | Chemical shifts $H_{13b}$ | Geminal coupling constants; $^2J_{13a,b}$ |
|---|---|---|---|
| $C_6$-non-substituted-$C_8$-lactonized (4) | $5{\cdot}66\begin{pmatrix}+0{\cdot}10\\-0{\cdot}11\end{pmatrix}$ | $6{\cdot}28\begin{pmatrix}+0{\cdot}07\\-0{\cdot}08\end{pmatrix}$ | $\lesssim 0{\cdot}5$ |
| $C_6$-hydroxy-$C_8$-lactonized (4) | [5·55–5·86][a] | [6·15–6·39][a] | $\lesssim 0{\cdot}5$ |
| $C_6$-acyloxy-$C_8$-lactonized (4) | $5{\cdot}45\begin{pmatrix}+0{\cdot}20\\-0{\cdot}34\end{pmatrix}$ | $6{\cdot}30\begin{pmatrix}+0{\cdot}12\\-0{\cdot}08\end{pmatrix}$ | $\lesssim 0{\cdot}5$ |

[a] In addition to examining these substances in $CDCl_3$, a solvent employed for all the compounds in this table, these examples were also examined in acetone-$d_6$ and DMSO-$d_6$; thus only chemical shift ranges are indicated.

TABLE 3. PARAMAGNETIC SHIFTS FOR $H_{13a}$ CALCULATED FOR SELECTED RANGES OF DISTANCES BETWEEN $H_{13a}$ AND THE $C_8$-O ATOM

| Calculated $H_{13a}$ paramagnetic shift (ppm) | Selected distances between $H_{13a}$ and the $C_8$-O atom (Å) |
|---|---|
| 0·2–0·6 | 2·0–2·5 |
| 0·0–0·1 | 3·0 |
| 0·0 | 3·5–4·0 |

TABLE 4. OBSERVED $H_{13a}$ PARAMAGNETIC SHIFTS AND MEASURED DISTANCES BETWEEN $H_{13a}$ AND $C_8$-O ATOMS FOR SESQUITERPENE LACTONES

| Type of sesquiterpene lactone | Observed $H_{13a}$ paramagnetic shifts in ppm | Measured distances between $H_{13a}$ and $C_8$-oxygen atoms using molecular models | | Stereochemical assignments of the $H_{13a}$-$C_8$-O atom system comparing data here with calculated values in Table 3 |
|---|---|---|---|---|
| | | for equatorial conformation | for axial conformation | |
| $C_6$-α-lactone-$C_8$-α-hydroxy-eudesmanolides<br>elemanolides | 0·4–0·6 | 2·0–2·5 | * | equatorial |
| germacranolides<br>guaianolides | 0·4–0·6 | 2·0–2·5 | 3·5–4·0 | equatorial |
| $C_6$-α-lactone-$C_8$-β-hydroxy- | | | | |
| eudesmanolides | 0·0–0·1 | * | 3·5–4·0 | axial |
| germacranolides | 0·0–0·1 | 2·0–2·5 | 3·5–4·0 | probably axial |

* Impossible conformation.

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