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THE GINKGOLIDES. V[1, 2].

SOME ASPECTS OF THEIR NMR SPECTRA

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As a result of studies reported briefly in the preceding communications[1, 3, 4, 5], the structure and stereochemistry of the four ginkgolides (GA, GB, GC and GM) have been determined. In this paper we describe in more detail some aspects of the NMR of the ginkgolides and their derivatives which played an important role in elucidating the structures of these compounds.

"GA triether". One of the more important derivatives was the so-called "GA triether" (actually a tetraether) which had been prepared through reduction of GA with $LiAlH_4$ and pyrolysis of the product[4]. Its molecular formula, $C_{20}H_{30}O_6$, and the absence of any carbonyl absorption in the infrared, suggested that it might be a dihydroxy-tetraether which differed from GA only in the replacement of all lactone carbonyls by CH_2 groups. This suggestion was fully substantiated by an analysis of its NMR spectrum.

The 100 Mc spectrum of "GA triether" in $CDCl_3/D_2O$, together with the structure of "GA triether" and the assignment of all proton signals, is shown in Fig. 1. When measured in DMSO-d_6, the "triether" exhibits additional signals, a singlet at 4.93 ppm (tert-OH) and a doublet at 5.03 ppm (sec-OH) with $J_{I,OH}$=4 cps, as well as increased complexity in the I-proton signal which now shows as a sextet.

The chemical shifts and coupling constants for all protons (apart from OHs) are tabulated in Table 1 which also gives a summary of the results of decoupling experiments that enabled the assignments to be made; the assignments were checked by measuring the spectrum of "GA triether" in $CDCl_3$-C_6H_6.

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* from Varian Associates.

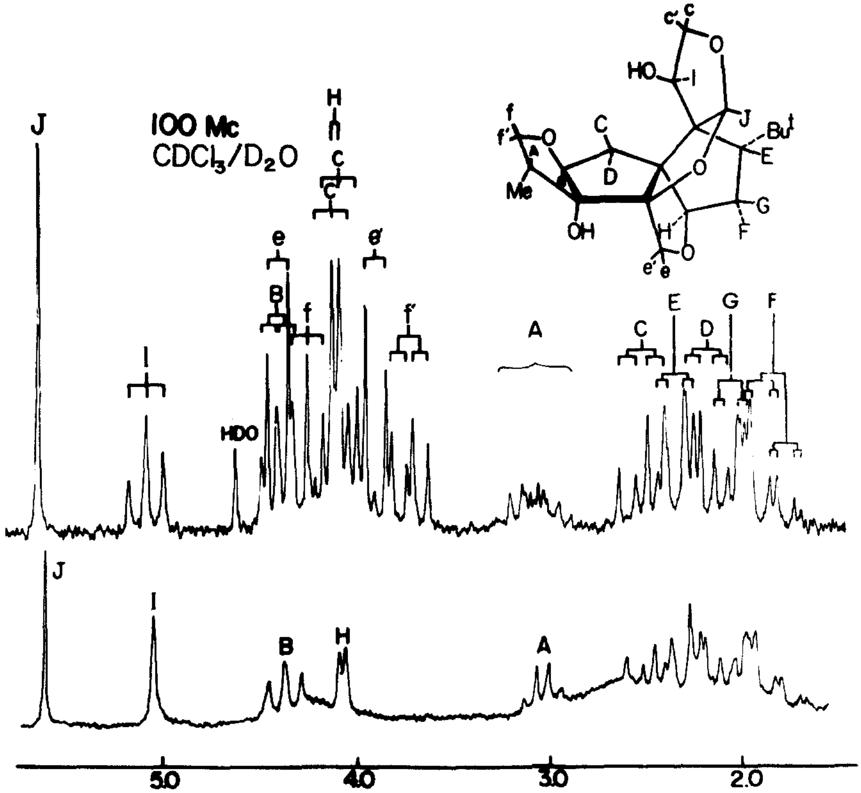
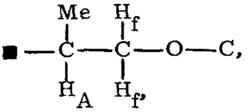
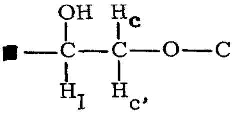


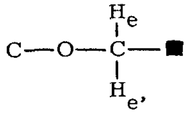
Fig. 1 Upper: "GA triether" Lower: hexadeuterio- "GA triether"

From the decoupling experiments and data given in Table 1, it is apparent that the protons B-D, E-H and J are in the same partial structures as in GA, whereas the remaining protons, apart from the tert-OH and tert-Bu, must be present in "GA triether" in the part-structures,

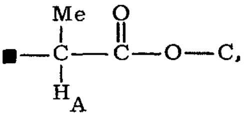

$$\blacksquare-\underset{\text{H}_A}{\overset{\text{Me}}{\text{C}}}-\underset{\text{H}_{f'}}{\overset{\text{H}_f}{\text{C}}}-\text{O}-\text{C},$$

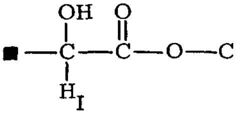

$$\blacksquare-\underset{\text{H}_I}{\overset{\text{OH}}{\text{C}}}-\underset{\text{H}_{c'}}{\overset{\text{H}_c}{\text{C}}}-\text{O}-\text{C}$$

and

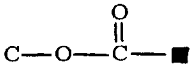

$$\text{C}-\text{O}-\underset{\text{H}_{e'}}{\overset{\text{H}_e}{\text{C}}}-\blacksquare$$

which must have originated from the three lactones in GA, namely,


$$\blacksquare-\underset{\text{H}_A}{\overset{\text{Me}}{\text{C}}}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-\text{C},$$


$$\blacksquare-\underset{\text{H}_I}{\overset{\text{OH}}{\text{C}}}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-\text{C}$$

and


$$\text{C}-\text{O}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\blacksquare$$

In particular, it should be noted that, because of its very low-field position, proton J must be on a carbon bearing two oxygen atoms both of which must be ether oxygens, and that proton I is on a carbon bearing both a hydroxyl group and a lactone carbonyl in GA. Proton I should

TABLE 1

Analysis of Spectrum of "GA triether" in $CDCl_3/D_2O$.

Couplings (J in cps)		Protons	δ in ppm	Multiplicity of signal	Decoupling Experiments The arrow indicates the proton irradiated.		
1)		tert-Bu	1. 07	s			
2)	6. 5	sec-Me	1. 04	d	←	d	←
	11	A	3. 04	d, d, q	d,d(8, 11)	d, q (?)*	d (11)
	8	f'	3. 71	d, d	d, d	←	?
	8	f	4. 23	d, d	d, d	d (8)	←
3)	8. 5	B	4. 38	d, d	←		
	7. 5 14. 5	C	2. 47	d, d	d (14. 5)		
		D	2. 18	d, d	d (14. 5)		
4)	13. 5	E	2. 31	d, d	?	d, d	
	5	F	1. 83	d, d, d	←	d, d (13, 13. 5)	
	3. 5 13	G	2. 02	d, d(br)	←	d, d (5, 13)**	
	1	H	4. 09	d, d	s	←	
5)	8. 5	I	5. 08	d, d	←	s	
	8. 5	c'	4. 10	d, d	d (?)*	←	
	8. 5	c	4. 07	d, d	d (?)*	←	
6)	10. 5	e	4. 36	d	←	s	
		e'	3. 89	d	s	←	
7)		J	5. 61	s			

Note: This table shows seven distinct groups of protons. Couplings between protons within each group are indicated by lines connecting the protons in question, the coupling constant being shown next to the connecting line in the first column; no evidence of coupling between protons in different groups was found. The results of irradiating a particular proton, or in some cases simultaneous irradiation of two or more protons within one group, are indicated in the columns headed "decoupling experiments"; the figures in parentheses are the splittings in the resulting signals. Abbreviations: d=doublet, s=singlet, br=broad, and d, d=doublet of doublets. Coupling constants have been assumed to be equal to the observed splittings.

* Pattern not clear due to incomplete decoupling.

** The broad lines were sharpened due to removal of the small J_{HG}.

be subject to a rather large deshielding effect[6)] due to compression by the closely situated tert-Bu group; similarly proton C is at appreciably lower field than proton D because of its compression by the sec-OH.

When the reduction of GA was carried out with $LiAlD_4$ instead of $LiAlH_4$, pyrolysis of the product afforded the corresponding hexadeuterio-"GA triether"[4)], the spectrum of which is shown in Fig. 1. A comparison of the two spectra in Fig. 1 not only confirms the assignments in Table 1 but also indicates that it is very unlikely that any skeletal rearrangements had occurred during formation of the "triether" from GA, since the spectra of GA[4)] and hexadeuterio-"GA triether" are strikingly similar, the only changes being those associated with reduction of all carbonyls to CD_2 groups. The significant up-field shifts[4)] of protons B (5. 10 to 4. 38 ppm) and H (5. 04 to 4. 09 ppm) in going from GA to the "triether" are in accord with these two protons being α to lactone oxygens in GA.

An intramolecular nuclear Overhauser effect. While searching for small couplings, which might have revealed relationships between the isolated proton systems discussed in the second paper[4)] of this series, it was found that irradiation of the tert-Bu signal, in the spectra of GA, GB and GC, caused significant increases in the heights of the signals due to protons I, J, E and F (cf. Fig. 1 in Part II[4)]) without appreciable decrease in the band width at half-height (W 1/2). Integration, both before and during irradiation, showed that a significant increase in the signal area or intensity had occurred. Examples of this effect are shown in Fig. 2; it should be noted that the signals of I, J, E, and F are the only ones affected by irradiation of the tert-Bu. Table 2 summarizes the results obtained; in some cases, although increases in the heights of signals E and F were apparent, reliable measurements could not be made due to either overlap of signals or the signal being too close to the position of irradiation. Anet and his coworkers reported[7)] having found evidence for the occurrence of an intramolecular nuclear Overhauser effect in certain cage molecules having two protons very close together in space but separated by five bonds. Irradiation (saturation) of one of these two protons caused an increase in the intensity of the signal of the other.

It is apparent that a similar mechanism must be operating in the case of the ginkgolides, i. e. the tert-Bu protons offer an efficient pathway for relaxation of the I, J, E and F protons; hence saturation (by irradiation) of the tert-Bu protons causes the I, J, E and F proton signals to experience a significant increase in intensity (an intramolecular nuclear Overhauser effect). Moreover, since this Overhauser effect is observed with ginkgolides in TFA solution (i. e. an abundant supply of protons and fluorine nuclei are present), it appears that the tert-Bu group also serves to insulate the I, J, E and F protons from close approach of solvent molecules which would otherwise contribute significantly to the relaxation of these protons.

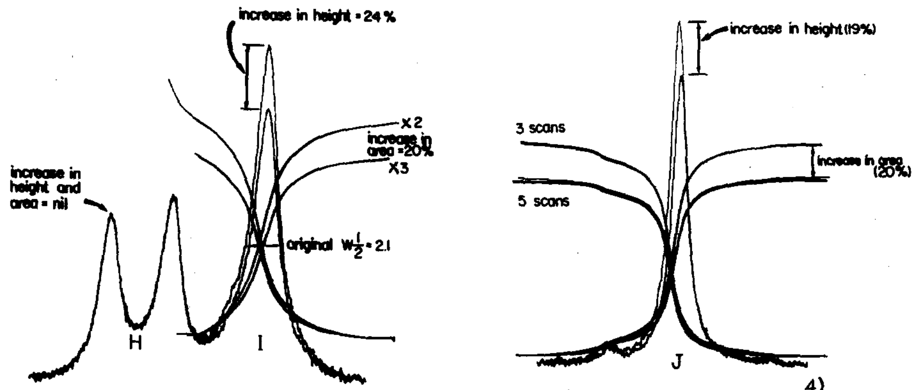


Fig. 2 Effect of irradiating the tert-Bu group in GC (cf. Fig. 1 in Part II4)). Spectra taken at 100 Mc: TFA solution, TMS field/frequency lock; recorded at 50 cps/500 secs, integrals at 50 cps/100 secs. Figure shows superimposed spectra with and without irradiation of tert-Bu.

TABLE 2

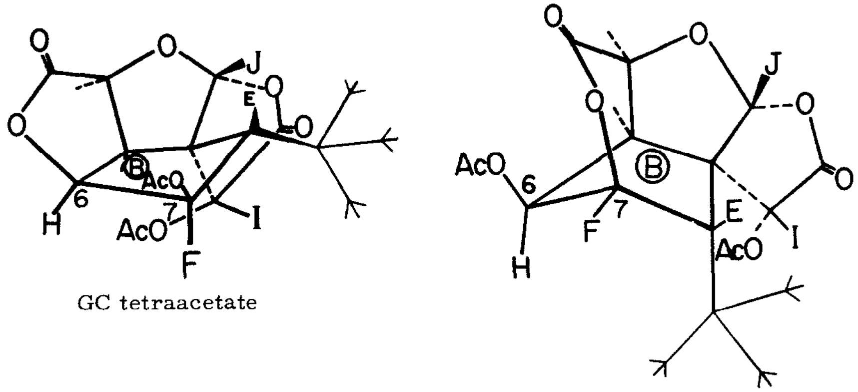
NUCLEAR OVERHAUSER EFFECTS*

H obs	H irr	GA	GB	GC	GC tetra OAc	iso GC tetra OAc	iso GC tri OAc
I	tert-Bu	30[32]	25[24]	20[24]	33[36]	27[37]	30[32]
J	〃	22[22]	21[23]	20[19]	22[21]	nil	nil
F	〃	-	-	4[10]	16[13]	19[22]	24[23]
E	〃	-	-	-	6[16]	13[17]	14[14]
H	〃	nil	nil	nil	nil	6[10]	12[15]
J	E	-	-	nil	nil	10[17]	7[21]
E	J	-	-	nil	nil	23[30]	20[27]

* Given as the percent increase in integrated intensity on irradiation; the figure in parenthesis is the percent increase in height of the signal. Solutions were in TFA; signals were recorded at 50 cps/500 sec sweep and integrated at 50 cps/100 sec sweeps, on a Varian HA-100.

The essential requirement that protons I, J, E and F be very close to the tert-Bu group was of great value in deducing the structure and stereochemistry of the ginkgolides1, 5). As can be seen from Fig. 3, which shows the spatial arrangement of these four protons and the tert-Bu group in GC tetraacetate, the tert-Bu group is in fact very close to all four protons, provided that ring B is in the conformation shown, i. e. with the tert-Bu in a quasi-equatorial position, otherwise the distance between proton J and the tert-Bu becomes too great for the intramolecular nuclear Overhauser effect to operate.

In iso GC tetraacetate (see Part IV1)), proton J is no longer effected by irradiation of the tert-Bu and instead the proton H signal shows a significant increase in area (see Table 2). These changes are in complete accord with a shift of the lactone ring from C_6 to $C_7$1) which causes a change in the conformation of ring B such that the tert-Bu group now adopts a quasi-



GC tetraacetate

iso GC tetraacetate

Fig. 3

axial position, thus bringing the tert-Bu grouping close to proton H and away from proton J; at the same time proton E is forced into a position closer to proton J (see Fig. 3) and these two protons can now participate in an intramolecular nuclear Overhauser effect.

REFERENCES

1) Part IV. M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, Y. Takagi and K. Nakanishi, Tetrahedron Letters, this issue.

2) Supported by the National Institutes of Health, Public Health Service Research Grant No. CA08394.

3) Part I. M. Maruyama, A. Terahara, Y. Itagaki and K. Nakanishi, Tetrahedron Letters, this issue.

4) Part II. Idem, ibid., this issue.

5) Part III. M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, and K. Nakanishi, ibid., this issue.

6) S. Winstein, P. Carter, F. A. L. Anet and A. J. R. Bourn, J. Am. Chem. Soc., 87, 5247 (1965).

7) F. A. L. Anet, A. J. R. Bourn, J. Am. Chem. Soc., 87, 5250 (1965).