Reductive Isomerisation in Superacidic Media. Carbon Connectivity Determination based on Natural Abundance ^{13}C–^{13}C Coupling Constants and a 2-dimensional N.M.R. Experiment

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Complete carbon connectivities have been determined for two very closely related anthrasteroids, formed in superacidic media, by natural abundance ^{13}C–^{13}C coupling constants observed *via* double quantum coherence.

The use of superacidic media provides a unique means for studying unusual isomerisations and reductions, especially in the steroid field. The reaction conditions have been shown to be of major importance for the rearrangement and reduction of steroidal enones in SbF_5–HF–hydrogen donor mixtures.[1] For example, the saturated ketone (**2**) is the major product of the reaction of the enedione (**1**) and methylcyclopentane at low SbF_5 concentration.[2] At higher SbF_5 concentration ($\geqslant 6$ M), besides ketone (**2**) (10%), two new closely-related saturated ketones (**3**) and (**4**) were isolated, each in 25% yield. These ketones ($C_{18}H_{26}O_2$), separable only by high pressure liquid chromatography, showed very similar mass, ^1H n.m.r., and ^{13}C n.m.r. spectra (Table 1), c.d. curves [(**3**)($CHCl_3$), $\Delta\epsilon_{\lambda 296}$ + 3.18; (**4**), $\Delta\epsilon_{\lambda 297}$ + 3.20], as well as close melting points and optical rotations {(**3**), m.p. 116—118 °C, $[\alpha]_D^{22}$ + 208° (*c* 1, $CHCl_3$); (**4**), m.p. 122—125 °C, $[\alpha]_D^{22}$ + 175° (*c* 1, $CHCl_3$)}. With the help of an extremely powerful new n.m.r. technique permitting the determination of the topology of the molecular framework[3,4] we establish herein the unknown structures. This is an application of the two-dimensional technique proposed by Bax *et al.*[4] for studying a compound of unknown constitution.

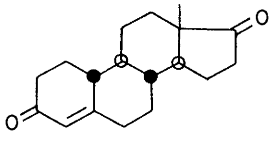
Carbon-13 n.m.r. spectral analysis of (**3**) and (**4**) was attempted at 100.62 and 62.89 MHz respectively with Bruker WM-400 and WM-250 spectrometers. The double quantum ^{13}C n.m.r. pulse sequence was used.[3] This allowed the detection of carbon–carbon coupling constants at natural abundance with suppression of the strong signals from molecules with a single carbon-13 nucleus. Solutions of (**3**) and (**4**) were prepared in [$^2H_8$]dioxan (1.2 g in 2 ml) and the 'INADEQUATE' pulse sequence[3] was optimized for $^1J_{CC}$ 35 Hz ($J\tau$ 1/4); data were accumulated for each spectrum for 12 h. The number of data points was 16 000 with a frequency range of 3600 Hz giving a digital resolution of 0.45 Hz/point.

Table 1. ^{13}C N.m.r. spectral data for the anthrasteroids (**3**) and (**4**).[a]

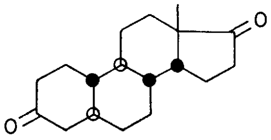
Carbon	Chemical shifts p.p.m.[b]		Coupled with carbon[c]	One-bond coupling constant for (3)
	(3) (95 °C) 100.62 MHz	(4) (70 °C) 62.89 MHz	(3)	Hz
C-1	33.61	33.77	C-5	34.0
C-2	41.55	41.54	C-1	30.8
C-3	209.30	208.83		
C-4	48.55	48.36	C-3	38.2
			C-6	31.4
C-5	42.02	43.45	C-10	34.1
			C-6	32.5
C-6	43.71	40.89	C-7	34.1
C-7	40.09	42.05	C-8	34.1
C-8	43.57	44.05	C-14	33.8
C-9	41.52	42.14	C-8	32.7
			C-10	34.3
			C-11	34.2
C-10	40.78	38.67		
C-11	31.05	30.89	C-12	33.1
C-12	32.32	32.21		
C-13	50.40	50.42	C-12	36.5
			C-14	31.3
C-14	49.88	49.86		
C-15	21.36	21.32	C-14	32.3
			C-16	34.8
C-16	33.46	33.45		
C-17	219.90	219.47		
C-18	25.52	25.44	C-13	32.4

[a] The corresponding numbering scheme is given with the structural formulae. [b] Chemical shifts were measured with respect to [$^{2}H_{8}$]-dioxan 66.5; $SiMe_4$ 0 p.p.m. [c] Coupling constants for the corresponding linkages of (3) and (4) were almost identical, they are shown for (3) and only once for all coupling pairs at that nucleus where the *J* values could be determined more precisely. One-bond carbon–carbon coupling constants for the following linkages were not measured: C-2/C-3, C-13/C-17, and C-16/C-17. Two-bond coupling constants were measured for C-2/C-4 11.3 Hz and C-13/C-16 15.2 Hz.

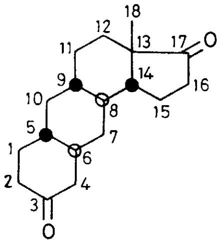
There are a number of practical problems in using the 'INADEQUATE' ^{13}C n.m.r. technique for structural analysis of steroidal molecules. The first complication arises from the similarity of most carbon–carbon coupling constants.[5]



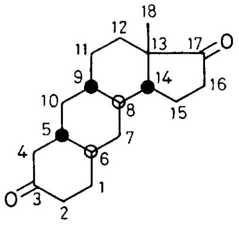
(**1**)



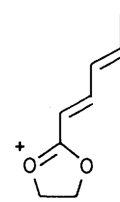
(**2**)



(**3**)

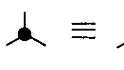


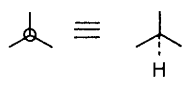
(**4**)



m/e 151

(**5**)





Furthermore, at high magnetic field the coupling carbon pairs exhibit AX or only weak AB systems. Thus, information provided by the highly unsymmetrical distribution of the satellite lines, typical for AB systems at lower magnetic field, may be partly lost especially at 100.62 MHz. The precise measurement of the coupling constants required very sharp resonance lines. Therefore, the spectra were measured for (**3**) at 95 °C and for (**4**) at 70 °C (Figure 1).

Although matching satellite pairs afforded important information concerning the carbon atom connectivities, an unambiguous determination of the complete carbon skeleton of (**3**) and (**4**) was not possible on the basis of the 1-dimensional 'INADEQUATE' experiment alone. As a consequence, a 2-dimensional Fourier transform study was undertaken of (**3**) as described by Bax *et al.*[4] The 2-dimensional spectrum was recorded on the sample used in the 1-dimensional 'INADE-

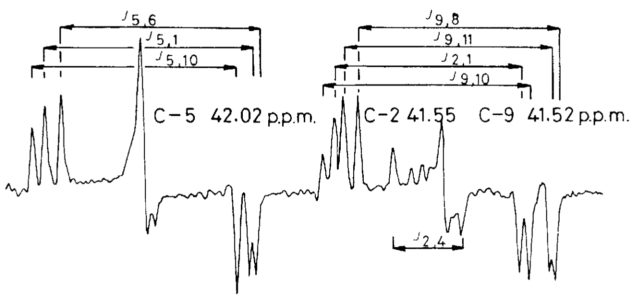


Figure 1. Section of C-9, C-2, and C-5 from the 100.62 MHz 'INADEQUATE' ^{13}C n.m.r. spectrum[3] of (**3**) recorded in [$^{2}H_{8}$]-dioxan at 95 °C. Maximum signal intensity has been selected for $^{1}J_{CC}$ 35 Hz (J_T 1/4); satellites due to the small ($^{2}J_{2,4}$ 11.3 Hz) two-bond coupling constant appear with reduced intensity; $^{1}J_{2,3}$ could not be detected.

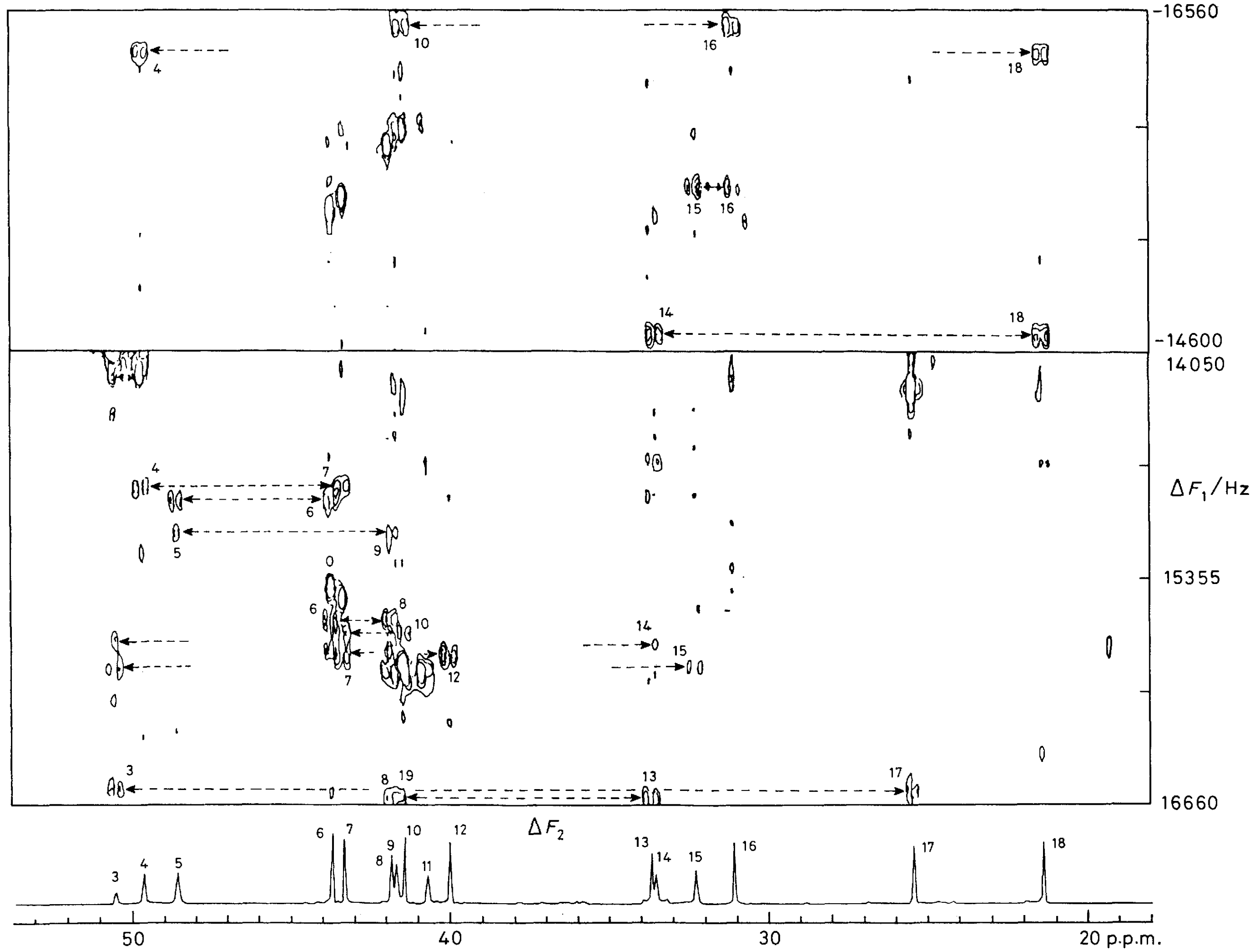


Figure 2. The high-field part of the 100.62 MHz 2-dimensional 'INADEQUATE' carbon-13 n.m.r. spectrum of (3) recorded in [$^2H_8$]-dioxan at 40 °C, represented as an intensity contour plot (absolute value representation). The F_2 dimension corresponds to the conventional ^{13}C chemical shift axis except that the strong lines from isolated nuclei (1-dimensional spectrum included also below) are suppressed leaving only the weak satellites signal in the form of four-line AX- or AB-type spectra (connectivities shown by broken lines). The F_1 dimension separates these spectra according to their individual double quantum frequencies (the sum of the chemical shifts relative to the RF pulse frequency). The signals are numbered from low to high field; this numbering system should be differentiated from standard steroid numbering.

QUATE' experiment, at 40 °C in order to shorten spin–lattice relaxation times. The data (Figure 2), optimized for maximum signal intensity with $^1J_{CC}$ 41.7 Hz, were accumulated for 16 h; quadrature detection in both dimensions was employed. A data matrix of 1000 points (F_1 dimension) by 4000 points (F_2 dimension) was used; the spectral width for F_1 was ±16 666 Hz and for F_2 was 22 000 Hz. Directly coupled carbon-13 resonances were identified by the fact that they generate the same double quantum frequency[4] and thus appear together in one row of the 2-dimensional data matrix.

This method permitted the unambiguous determination of the topology of the molecular framework as portrayed for (3) and allowed a precise carbon signal assignment to be carried out for this compound (Table 1). Thus, the 2-dimensional spectrum of (3) was of considerable help for evaluating the ^{13}C–^{13}C coupling constants from the earlier 1-dimensional 'INADEQUATE' spectrum of (3). It is important to note that a practical 2-dimensional experiment covering the full ^{13}C chemical shift range will have a digital resolution only sufficient to determine connectivities and not actual coupling constants. Knowing the ^{13}C–^{13}C coupling constants in (3) and its close structural relationship to (4), the 1-dimensional 'INADEQUATE' spectrum of the latter could also be interpreted. Consequently, the carbon skeleton of (4) was also established through the observed connectivities. The simultaneous formation of (3) and (4) during the reaction is easily explained by a common spiro-intermediate.[6] The presence of an intense signal at *m/e* 151 (5) in the mass spectrum of the A-ring ethylene acetal of (4) confirms both its anthrasteroid-type structure and the position of the carbonyl group.[6]

The C-18 chemical shift of (3) and (4) (Table 1) agrees with a C/D-*cis* ring junction,[7] the methyl group being equatorially oriented with respect to ring-C. Moreover, the chemical shift of the A-ring carbon atoms can be reconciled with an A/B-*trans* structure.[8] This peculiarity, as well as the chemical shift of the other carbon atoms of (3) and (4), imposes a 5β, 6α, 8α, 9β, 14β-stereochemistry, only compatible with calculated values[9] and with perhydroanthracene models.[10]

In the light of the structure of (**3**) and (**4**) the great similarity of their spectral characteristics could be readily rationalized.

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