Determination of the Structure of a Trimer of Biacetyl by Carbon-13 Autocorrelation Nuclear Magnetic Resonance Spectroscopy

By **John Hudec** and **David L. Turner,*** Department of Chemistry, The University, Southampton SO9 5NH

The structure of one of the trimers of biacetyl (butane-2,3-dione) has been determined unambiguously using a novel n.m.r. technique: a new molecular structure (5) is proposed and discussed in terms of its latent symmetry properties.

THERE are a variety of instrumental methods currently available to organic chemists for structural elucidation, varying from *X*-ray crystallography, which can provide absolute structures, to various spectroscopic methods (i.r., u.v., mass spectroscopy, n.m.r. *etc.*) which can only provide information on separate chromophoric segments within a molecule. Thus complete structural determinations at present rely only on the method of *X*-ray diffraction and are limited to compounds which form suitable crystals.

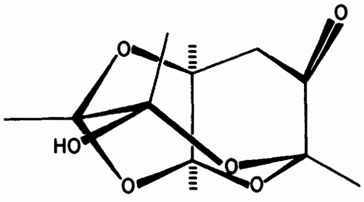
In this article, we demonstrate a novel method using the principles of two-dimensional n.m.r. to correlate the resonance lines of directly bonded carbon atoms and so obtain a complete molecular structure for a compound in solution.

The compound chosen was a trimer of biacetyl (butane-2,3-dione) m.p. 104 °C, which was prepared originally by Diels and Jost[1] by treatment of biacetyl with concentrated hydrochloric acid. The structure originally proposed was subsequently found to be incompatible with i.r. and ^{1}H n.m.r. evidence and a new structure (1) was proposed.[2] It was suggested that this structure arose from the open chain trimer (2A) by the stepwise cyclisation shown by the arrows; there is another structure (3) which can arise from the alternative cyclisation shown by the arrows (2B). However, neither structure (1) nor (3) is fully compatible with the n.m.r. evidence, principally the magnitude of the geminal coupling constant of the methylene protons next to the carbonyl group. Its magnitude of $^{2}J_{HH}$ *ca.* (—)10.0 Hz is inconsistent with the models of (1) and (3) which indicate that the conformation of the CH_2–C=O fragment is the same as that in a chair cyclohexanone, for which a geminal coupling constant of *ca.* —12.5 Hz would be expected.[3]

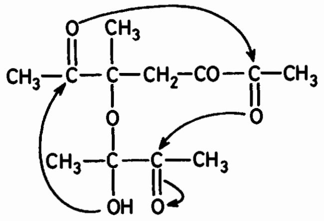
In order to discount any unusual effects of hybridisation (decrease in the tetrahedral angle)[3] due to strain, the ketone was reduced ($NaBH_4$ in methanol) and the mixture of alcohols (*ca.* 10 : 1) acetylated. The major acetate showed an AB quartet with $^{2}J_{HH}$ (—)14.5 Hz, a much larger change than one might expect from the conformations of the structures (1) or (3).

Such spectroscopic inconsistencies suggest that the structure previously reported may be incorrect and a complete determination of structure is therefore desirable.

The Autocorrelation Experiment.—The normal proton-coupled ^{13}C n.m.r. spectrum of the trimer clearly indicates the presence of five methyl groups and one methylene. A single carbonyl group is distinguished by its large chemical shift. The ^{1}H n.m.r. spectrum shows in addition a single hydroxy proton. However, n.m.r. spectroscopy has a great deal more information to offer than these unconnected signals and this can be obtained by correlating transitions using two-dimensional techniques.[4]



(1)



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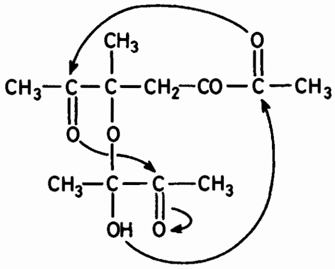

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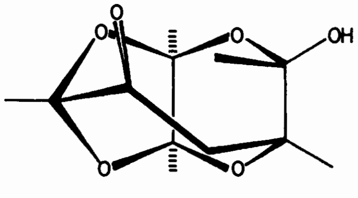


(3)

The essence of such experiments is the transfer of magnetisation from one transition to another by a sequence of radiofrequency pulses which can, in principle, be designed to utilise any interaction between magnetic particles to reveal correlations. The relationship between transitions is then analysed by means of a two-dimensional Fourier transform, giving a spectral *surface* in which peaks represent correlations between frequencies present during two time intervals in the pulse sequence. The close relationship between dipolar couplings and molecular structure has been used to assign deuterium spectra from such correlations;[5] in the present case, the relative constancy of scalar couplings between directly bonded carbon-13 nuclei provides a more useful criterion for correlation, allowing the framework of carbon–carbon bonds to be determined.[6]

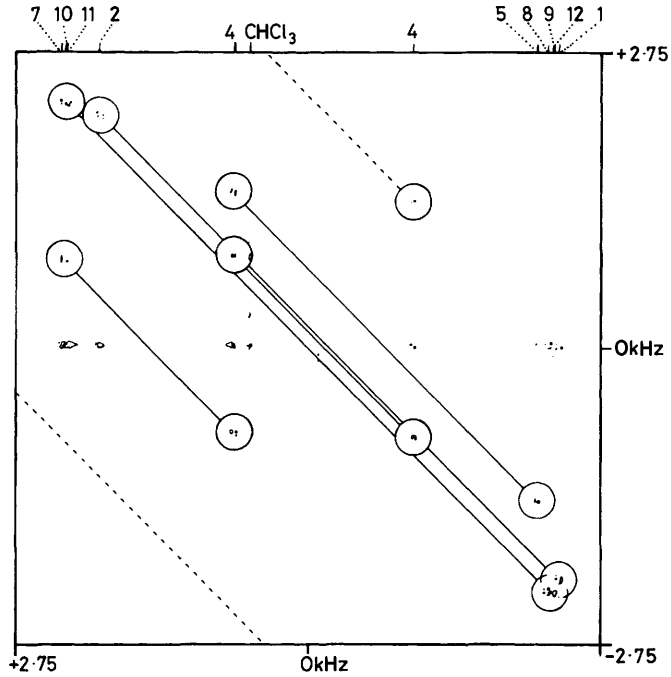


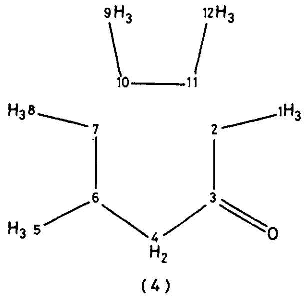
FIGURE 1 The two-dimensional carbon-13 n.m.r. autocorrelation spectrum of the trimer obtained according to method B of ref. 6. Carbon-13 chemical shifts appear in the horizontal dimension with the differences of these frequencies in the second, vertical dimension. Peaks appearing in this contour plot represent correlations between carbon-13 satellites in the natural abundance carbon-13 spectrum and, since all signals other than those from doublets with splittings of *ca.* 40 Hz have been suppressed, such correlations directly represent carbon–carbon bonds

Observation of the natural abundance carbon-13 satellites in the proton-decoupled carbon-13 spectrum is facilitated by suppressing the intense singlets arising from molecules containing isolated carbon-13 nuclei since the weak satellites might otherwise be obscured. The method of singlet suppression used is that proposed by Bodenhausen[7] which has the additional advantage of being tunable to leave only doublets with a predetermined splitting; for this purpose we choose splittings of the order of 40 Hz which are typical of directly bonded carbon atoms.

Figure 1 shows a contour plot of the two-dimensional carbon-13 autocorrelation spectrum obtained by method B of ref. 6. The autocorrelation is produced by a Hahn echo following the pulse sequence for singlet suppression so that the frequencies in the first dimension, shown horizontally, are conventional chemical shifts and the frequencies of the second dimension are chemical shift differences and therefore have linewidths which are independent of inhomogeneities in the static magnetic field to first order.

The sample used was a saturated solution of the compound in chloroform contained in a 10 mm o.d. tube, and the spectrum was obtained using a Bruker CXP 200 spectrometer with a double-tuned solenoid for carbon observation at 50.3 MHz and proton decoupling at 200 MHz. A spectral width of 5.5 kHz was used in the chemical shift dimension with 1 024 points acquired for each free induction decay. The resonance of the carbonyl carbon was folded into this region, but suppressed by a low pass filter. In the second dimension, a spectral width of ±2.75 kHz was defined by 256 increments in the pulse spacing. For each increment, the signal was time averaged over four 32-step cycles to suppress carbon-13 singlets and sum frequencies. Thus a total of 32 768 signals were accumulated in *ca.* 60 h, giving a signal to noise ratio of *ca.* 5 : 1 for the satellite correlation peaks in the two-dimensional spectrum.

The sequence of carbon–carbon bonds may be determined by inspection of the spectrum or from the two-dimensional frequencies reported in the Table. Each pair of chemical shift frequencies in the first dimension showing responses at a common absolute frequency in the second dimension represents those molecules which contain a pair of carbon-13 nuclei bonded together. The sequence of bonds determined in this way is shown in (4) with the exception of C(10)–C(11) which would produce correlation peaks close to zero frequency in the second dimension because of the small chemical shift difference and might therefore be obscured by the signals at $\pm{}^1J_{\mathrm{CC}}/2$ and zero in this dimension. These nuclei form a tight AB group (δ/J *ca.* 0.3) which have been shown to give very weak responses in related one-dimensional experiments.[8] A second experiment using method A of ref. 6 which shows correlations between bonded carbon atoms at frequencies in the second dimension which are *sums* of chemical shift frequencies with respect to the



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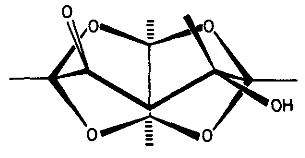
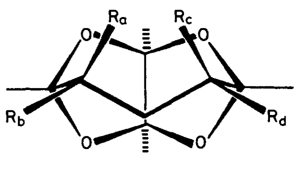


(5)



(6) R$_a$ = R$_c$ = OH, R$_b$ = CH$_3$, R$_d$ = H
(7) R$_a$ = R$_d$ = OH, R$_b$ = R$_c$ = CH$_3$
(8) R$_a$ = R$_c$ = OH, R$_b$ = R$_d$ = CH$_3$

Assignment [a]	C-3	C-7	C-10(11)	C-11(10)	C-2	C-6	C-4	C-5	C-8	C-9(12)	C-12(9)	C-1
Unit	C:O	C	C	C	C	C	CH_2	CH_3	CH_3	CH_3	CH_3	CH_3
Chemical shift in chloroform (p.p.m. from Me_4Si)	211.0	112.6	111.8	111.5	105.9	80.7	47.2	23.8	22.0	21.1	20.9	20.1
Shift difference in pyridine	−1.4	1.2	−0.1	0.0	0.2	−1.0	1.1	0.4	0.2	0.5	−0.1	0.5
^{13}C T_1/s [b]	8.3	10.8	10.8	10.8	12.1	6.1	0.4	0.8	0.9	0.7	0.7	0.9
Autocorrelation frequencies (Hz) [c]												
1	(7 276)	2 324	2 282	2 271	1 985	721	−966	−2 144	−2 235	−2 277	−2 290	−2 329
2		2 276	2 283	2 283	2 160	1 435	−841	−1 435	−2 276	−2 283	−2 283	−2 160
		800			−2 645	841	(−4 121)					
						−800						

[a] Alternative assignments are given in parentheses. [b] Measured by inversion–recovery, ±5%. [c] Frequencies ±2 Hz in the first dimension, ±5 Hz in the second. Folded lines are indicated by parentheses.

transmitter, confirmed the information from method B with similar sensitivity and also failed to show the correlation between C(10) and C(11), but the presence of a bond is clearly indicated by the observable correlations.

Completion of the three-dimensional structure then required the inclusion of four oxygen bridges according to the empirical formula. This could be achieved by repeating the autocorrelation experiment with the singlet suppression tuned to leave only two-bond carbon–carbon couplings, but it is sufficient to locate the position of the hydroxy proton. Dissolving the compound in pyridine led to the shift changes shown in the Table and moved the resonance of the hydroxy proton sufficiently far down field to make a selective nuclear Overhauser enhancement experiment possible. Coherent on-resonance irradiation for one second, using 0.2 W attentuated by 10 dB, had no effect on the nearby methylene protons and a carbon-13 n.O.e. difference spectrum then showed a single weak response at 79.7 p.p.m.

Thus C(6) bears the hydroxy-group and the complete molecular structure is that shown in (5).

DISCUSSION

The revised structure (5) accounts for all the spectroscopic properties very well. The unusually positive deviation of the methylene $^2J_{HH}$ is explained by the relative orientation of the π orbital of the carbonyl group with respect to the methylene, which is bisected by it.[3,9] The negative change of 4.5 Hz on conversion of the ketone into the major acetylated alcohol is easily accounted for by the effect of the β-s-acetoxy-group and the β-t-hydroxy-group (6), given the change in conformation.[10]

The structure of the trimeric ketone (5) was also confirmed by its reaction with methyl-lithium to give a bistertiary alcohol which revealed its latent symmetry properties. An attack by MeLi on the CO group from the *cis*-side with respect to the hydroxy would give rise to a DL-diol (7) with C_2 symmetry which would be reflected in the n.m.r. spectra as three pairs of equivalent methyl groups with the methylene protons also becoming magnetically equivalent. An attack from the *trans*-side with respect to the hydroxy-group should yield a *meso*-diol (8) with C_s symmetry and only two pairs of equivalent methyl groups, two methyl groups being non-equivalent.

The symmetry of the sole isolated product is not obvious from the carbon-13 spectrum at room temperature as shown in Figure 2 because of slow conformational exchange, but at elevated temperatures the 2 : 2 : 1 : 1 ratio of the integrated intensities of the methyl resonances clearly indicates a plane of symmetry.

Molecular models show that in both the keto-alcohol (5) and the symmetrical diol (8) the three-carbon bridge that spans the [3.3.0]bicyclic system is part of a virtually strainless eight-membered ring in a crown conformation. The interconversion of conformers appears to have a higher energy barrier in the diol (8) than the keto-alcohol (5) and this is confirmed by the observation of exchange broadening in proton n.m.r. at reduced temperatures. The models also suggest that the conformers with axial methyl groups are likely to be the more stable at low temperatures because of steric interactions, with the dihedral angles decreased between vicinal equatorial bonds in crown formations of the cyclo-octane type.

The apparently exclusive formation of the *meso*-diol (8) with C_s symmetry on reaction with methyl-lithium is surprising, as one might expect attack from the less hindered equatorial side, *cis* to the hydroxy, which would give the product with C_2 symmetry. However, the evolution of methane indicates that methyl-lithium reacts much faster with the tertiary alcohol. The lithium alkoxide, being much larger than a methyl group, would then favour an axial position where the lithium cation can be solvated by the acetal oxygen atoms of the bicyclic[3.3.0] system. A subsequent attack by MeLi on the ketone from the less hindered equatorial side and *anti* to the lithium alkoxide could then only lead to the *meso*-diol observed.

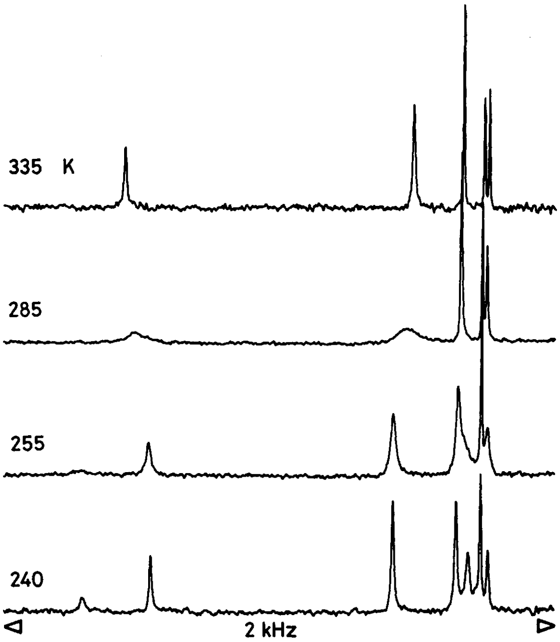


FIGURE 2 Proton-decoupled ^{13}C n.m.r. spectra of the diol formed by methylating the carbonyl group of the trimer. The conformers interconvert slowly at room temperature, but at higher temperatures the 2 : 2 : 1 : 1 ratio of the integrated intensities of the methyl resonances show this to be the stereoisomer with C_s symmetry (*meso*-form)

The stereochemical aspects of this reaction in the local environment of (5) is being investigated computationally.[11]

Conclusions.—The three-dimensional structure of this fascinating trimer of biacetyl has been determined unequivocally using n.m.r. methods alone and this structure has been confirmed physicochemically by means of its latent symmetry.

A by-product of this method of structural determination is a complete assignment of the ^{13}C n.m.r. spectrum, limited only by the resolution of lines, and the method can be applied to compounds of known structure for that purpose.[12]

Despite its ready availability and high solubility, this trimer of biacetyl is far from ideal for such techniques since several of the carbon-13 longitudinal relaxation times exceed 10 s, and the structure is not completely determined by the carbon framework. The successful outcome of this study therefore provides an impressive demonstration of the utility of carbon-13 autocorrelation spectroscopy.

EXPERIMENTAL

To the biacetyl trimer (5) (520 mg) dissolved in dry ether (40 ml) was added methyl-lithium in ether (11 ml, 0.9M) with concomitant evolution of gas which was shown to be methane by mass spectrometry. A small portion of the reaction mixture was worked up by addition of water, extraction with more ether, drying (Na_2SO_4), and evaporation of ether. The residual oily solid showed strong i.r. bands at 1 720, 3 400—3 500, 980, and 1 080—1 160 cm^{-1}. The remainder of the mixture was refluxed for 4 h and worked up as above. The oily residue, which had no band at 1 720 cm^{-1}, was crystallised from light petroleum (b.p. 40—60 °C), m.p. 109—111 °C.

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Note added in proof: A single-crystal *X*-ray study by Dr. D. J. Williams, Imperial College, London, has confirmed structure (5). Full details will be published separately.

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