Direct Structure Determination of the Self-Condensation Product of 1-Phenylpentane-2,4-dione Using T_1 and NOE Measurements from ^{13}C NMR Spectroscopy

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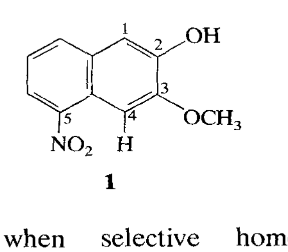
The nuclear Overhauser effect (NOE) is known to depend on molecular dynamics and structure. However, in some cases the values obtained for selective homonuclear and heteronuclear NOE are much too small, considering that the nuclei involved are located within a short distance of each other in space. A quantitative treatment of the NOE values allows a clear explanation of this apparent anomaly, and allows the possibility of using T_1 and NOE values measured with broad-band proton irradiation. The corresponding relationship is useful for solving many structural problems in organic chemistry, and has the great advantage of employing the typical high resolution of fully decoupled spectra. The method was used in this work for the structure determination of the self-condensation product of 1-phenylpentane-2,4-dione, and it was concluded that the previous assignment of the ^{13}C NMR spectrum was erroneous. An independent proof of the new assignment is given using the selective collapse of the fine structure under low-power irradiation of the methyl protons.

INTRODUCTION

The fact that NOE values depend on distances between interacting nuclei and that the dipole–dipole relaxation mechanism determines their values is well known.[1a] This knowledge has been employed in organic chemistry since the early 1970s.[1b] Nevertheless, its use has been almost entirely restricted to the homonuclear selective NOE of protons, and only a few applications of the selective heteronuclear NOE $^{13}C\{^1H\}$ have been reported.[2,3]

It is common, however, to obtain only small values of the homonuclear proton NOE for protons which are apparently close, for example, in compound **1**. Thus, when the NOE for H-4 was measured on irradiating the neighbouring methoxy group, only 7% enhancement was obtained,[4] although higher values could be predicted considering the short distance between the two interacting groups.



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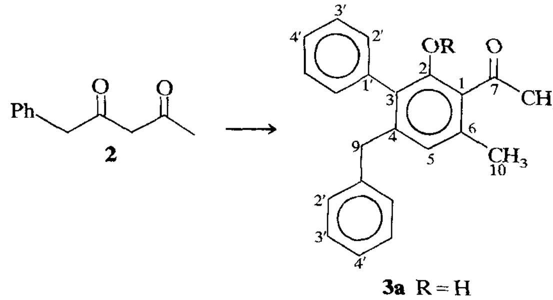
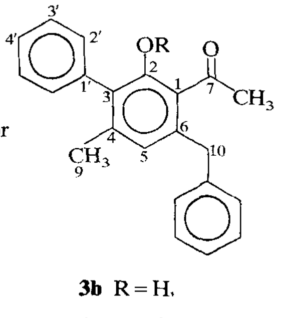
Similarly, when selective homonuclear and heteronuclear NOE values were measured in attempts to obtain structural information for the self-condensation product of dione **2**,[5] rather small values were obtained for supposedly close atoms. A mathematical treatment of the NOE values has given a satisfactory explanation of these results, and it also allows us to formulate a relationship using ^{13}C T_1 and NOE values measured under broad-band irradiation of the protons. This relationship, valid for rigid molecules, is used to distinguish between structures **3a** and **3b**, which are the two possible isomeric structures for the self-condensation product of dione **2**.[5]



3a R = H
3c R = CH$_3$

or



3b R = H.

However, the result is not in agreement with previous indirect evidence[6] for the structure of the self-condensation product of **2**. Therefore, a detailed study

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of the assignments was carried out using the selective collapse of the corresponding fine structure. A new assignment is given for C-1 and C-3 that is fully consistent with all the evidence.

RESULTS AND DISCUSSION

It has been reported that the self-condensation of 1-phenylpentane-2,4-dione (**2**) yields the hydroxyacetophenone **3a**.[5] However, the evidence presented[5] so far in favour of structure **3a** is not conclusive. On the other hand, we have studied the photoenolization of the methoxyacetophenone resulting as a self-condensation product of ketone **2** methylated at the hydroxy group, in order to distinguish between the two possible isomeric *ortho*-alkylacetophenones **3a** and **3b**. It was concluded that the structure of the product is 4-benzyl-2-hydroxy-6-methyl-3-phenylacetophenone (**3c**).[7]

Preliminary results using homonuclear proton NOE, observing the NOE for the methylene protons while irradiating the aromatic resonances at lowest field, corresponding to H-3′ and H-4′ (3-C_6H_5), in the ^{1}H NMR spectrum of the dione self-condensation product **3** gave only 10% NOE enhancement.[6] These values are usually considered too small to be conclusive.[7] Therefore, further physical evidence was necessary to distinguish between **3a** and **3b** as the self-condensation product of **2**.

Selective heteronuclear[3] NOE $^{13}C\{CH_2\}$ for several quaternary carbons of this molecule were measured, obtaining enhancement values which were too small. These results, and those obtained using homonuclear proton NOE,[6] can be explained using the mathematical expression 1 for the NOE.[1c]:

$$f_d(s) = \sum_s \gamma_s \rho_{ds}/2\gamma_d R_d - \sum_n \gamma_n \rho_{dn} f_n(s)/2\gamma_d R_d \qquad (1)$$

where $f_d(s) = (\langle I_{zd}\rangle - I_{0d})/I_{0d}$ is the NOE; in other words it is the relative increment of the magnetization of the detected nuclei (d) when the saturated nuclei (s) are irradiated. The spins not saturated, excluding d, are indicated by n. R_d, γ and ρ_{ij} are the total relaxation rate, the corresponding magnetogyric ratio, and the direct dipole–dipole relaxation between spins i and j, respectively.

Expressing ρ_{ij} as a function of the corresponding correlation time $\zeta_c(ij)$ and distance r_{ij}, eqn (1) can be written as

$$f_d(s) = \frac{\gamma_s{}^3\gamma_d\hbar^2}{2R_d}\sum_s \frac{\zeta_c(ds)}{r_{ds}{}^6} - \frac{\gamma_n{}^3\gamma_d\hbar^2}{2R_d}\sum_n \frac{\zeta_c(dn)f_n(s)}{r_{dn}{}^6} \qquad (2)$$

In the case of ^{13}C NMR, there is a high probability that the only ^{13}C atom in the molecule is the one detected, so that the second summation includes the protons neighbouring the detected carbon atom and not other ^{13}C nuclei. Further, if the molecule is rigid, all ζ_c values will be the same and eqn (2) can be rewritten as

$$f_C(H_s) = \frac{\gamma_H{}^3\gamma_C\hbar^2\zeta_c}{2R_C}\left[\frac{1}{r^6_{CH_s}} - \sum_n \frac{f_n(H_s)}{r^6_{CH_n}}\right] \qquad (3)$$

In this equation the distances r_{CH_s} or r_{CH_n} should be taken as an average when equivalent protons are considered, and the corresponding term is multiplied by the number of equivalent protons.

Using Eqn (3), it is possible to find a qualitative argument to explain the inconclusive results of the heteronuclear selective $^{13}C\{^1H\}$ technique for the molecule under consideration. For instance, if the NOE on the carbonyl carbon atom is observed on irradiating the CH_2 protons, then Eqn (3) becomes

$$f_{C=O}(CH_2) = K\left[\frac{2}{r^6_{C=O,CH_2}} - \left(\frac{3f_{C\text{-}7-Me}(CH_2)}{r^6_{C=O,C\text{-}7-Me}} + \frac{f_{OH}(CH_2)}{r^6_{C=O,OH}} + \frac{f_{C_i-C\text{-}2'H}(CH_2)}{r^6_{C=O,C_i-C\text{-}2'H}} + \frac{3f_{C_j-Me}(CH_2)}{r^6_{C=O,C_j-Me}} + \cdots\right)\right] \qquad (4)$$

$i = 9$, $j = 6$ for **3a**; $i = 10$, $j = 4$ for **3b**.

It is clear from this expression that for structure **3b** the first term is important, but the second, third and fourth could also be important and positive, depending on the homonuclear NOE values $f_{C\text{-}7-Me}(CH_2)$ and $f_{C\text{-}10-C\text{-}2'H}(CH_2)$. On the other hand, for structure **3a** the first term is very small, but the fifth term may be small and negative because CH_2—H—C-4Me are close to a linear configuration.[1]

Therefore, it cannot be concluded that the measurement of a small positive $f_{C=O}(CH_2)$ favours any of the possible structures.

Another application of Eqn (2) is obtained when all the protons are saturated (broad band irradiation); in this case Eqn (3) is simplified, for a rigid molecule, to

$$f_C(H) = \frac{\gamma_H\gamma_C\hbar^2\zeta_c}{2R_C}\sum_H \frac{1}{r^6_{C,H}} \qquad (5)$$

where the sum, as before, refers to protons which are close to the carbon atom under study.

For example, if one considers two different carbon atoms, the following ratio is obtained for carbon atoms C-1 and C-3:

$$\frac{f_{C\text{-}1}(H)}{f_{C\text{-}3}(H)} = \frac{R_{C\text{-}3}\sum_H 1/r^6_{C\text{-}1,H}}{R_{C\text{-}1}\sum_H 1/r^6_{C\text{-}3,H}} \qquad (6)$$

T_1 and NOE values were measured for every carbon atom in the spectrum and the data are presented in Table 1; the assignment of the ^{13}C NMR spectrum for this compound was reported previously.[5]

Proton—carbon distances for the two structures were obtained directly from a molecular model. More precise values of the necessary distances were also completed using geometrical calculations (see Table 2).

The application of Eqn (6) for the ratio $f_{C\text{-}1}/f_{C\text{-}3}$ gives 0.84 for structure **3a** and 1.17 for **3b** using the reported assignment.[5] Comparison of these values with the experimental NOE ratio 1.17, calculated from Table 1, suggests that structure **3b** is correct.

On the other hand, strong indirect evidence[7] supports structure **3a** for the product. Therefore, it was

Table 1. Resonance assignments,[5] spin–lattice relaxation times (T_1) and NOE values for the self-condensation product of dione 3

Carbon	δ (ppm)	T_1 (seg)	NOE
C-7	205.7 (q)[a]	50.0	0.8
C-2	160.0 (d)[a]	36.0	1.7
C-1[b]	145.9 (t)[a]	27.0	2.0
C-3[b]	140.2 (m)[a]	33.0	1.7
C-6	138.2 (q)[a]	27.0	1.0
C-5	124.6	1.7	1.2
C-4	120.5 (t)[a]	58.0	0.0
C–9	39.5	1.3	2.0
C-7—*Me*	33.3	4.1	1.7
Aromatic—Me	24.3	3.1	1.6

[a] Multiplicity of quaternary carbons in the fully coupled spectrum originating from two- and three-bond proton coupling [^2J(CH) and ^3J(CH)].
[b] The assignments[5] of these resonances are shown to be erroneous (see text). The resonances at 145.9 and 140.2 ppm are assigned to C-3 and C-1, respectively.

decided to carry out a detailed study of the assignment of all the quaternary carbon atoms of the compound. After careful observation of the fully coupled spectrum the quaternary carbons were assigned as previously reported,[5] with the exception that the resonances at 145.9 and 140.2 ppm were assigned to C-3 and C-1, respectively.

The new assignment for these resonances is based on the small differences in the multiplicity expected for C-1 and C-3, since both carbon atoms are aromatic and the three-bond coupling constant, ^3J(CH), is approximately 7 Hz for aromatic carbon atoms.[8] C-1 and C-3 have 8 and 6 protons three bonds removed, respectively, for structure **3a** and both have 7 protons for structure **3b**. The above assignment was confirmed by irradiating the methyl group at low power values. Irradiation was started at very low power values, where no change of the fine structure was observed, and the power was slowly increased until a selective change in the quaternary fine structure was observed.

Table 2. Calculated carbon–proton distances for the two possible structures for the self-condensation product of 1-phenylpentane-2,4-dione (2)

	3a		**3b**	
Carbon atom	Proton	Calculated distance[a](Å)	Proton	Calculated distance[a](Å)
C–1	C-7—*CH*$_3$	2.97[a]	C-7—*CH*$_3$	2.97[a]
	C-2—O*H*	2.51	C-2—O*H*	2.51
	C-6—*CH*$_3$	3.02[a]	C-6—C-1O*H*	2.67
			C-6—C-1O*H′*	3.37
	C-5—*H*	3.39	C-6—CH$_2$—C2′*H*	2.70[b]
	—	—	C-5—*H*	3.39
C-3	C-3—C-2′*H* C-3—C-6′*H*	2.73	C-3—C-2′*H* C-3—C-6′*H*	2.73
	C-4—C-9*H*	2.67	C-2—O*H*	3.14
	C-4—C-9*H′*	3.37		
	C-4—CH$_2$—C-6′*H*	2.69[b]	C-5—*H*	3.39
	C-2—O*H*	3.14	C-4—*CH*$_3$	3.02[a]
	C-5—*H*	3.39	—	—

[a] Average distance of the equivalent methyl protons to C-1 or C-3.
[b] Only one of the C-2′H, C-6′H protons is close enough in the most probable conformation of the corresponding structure.

When the methyl protons were irradiated the fine structure of the resonance at 140.2 ppm changed, as opposed to that of the resonance at 145.9 ppm. Further, the resonances at 205.7 and 138.2 ppm both collapsed into singlets. Therefore, the resonances at 145.9 and 140.2 ppm could undoubtedly be assigned to C-3 and C-1, respectively (see Table 1). Applications of Eqn (6) with this new assignment is shown in Table 3, and it is clear that **3a** is the actual structure of the dione **2** self-condensation product. The assignment itself is independent proof for the structure of the product.

Table 3. Calculated $f_{\text{C-1}}/f_{\text{C-3}}$ for the two possible structures, and the experimental value

NOE ratio	Structure **3a**	Structure **3b**	Experimental value
$f_{\text{C-1}}/f_{\text{C-3}}$	1.26±0.32	1.75±0.44	0.85±0.17

CONCLUSIONS

A detailed mathematical expression for the NOE values was used to support qualitatively the experimental NOE values, obtained in selective heteronuclear ^{13}C{^{1}H} experiments. Additionally, a new relationship is presented that allows the use of T_1 and NOE values measured with broad-band irradiation of protons. This was used to choose the correct structure of the self-condensation product of the dione **2**.

The method is of general application, although it is almost restricted to quaternary carbons in order to be sensitive to protons other than the first neighbour. The measurement distance errors must be as small as possible owing to their importance in the calculation. The error in the NOE measurements should be as small as in the normally used method.[9] A new assignment of the ^{13}C NMR spectrum of the product is given, which provides independent proof of the structure of the product.

EXPERIMENTAL

The self-condensation product of the dione **2** was prepared as reported previously.[5]

NMR measurements

Spectra were recorded on a Varian XL-100 (25.2 MHz) spectrometer interfaced with a pulse generator and a data system from Nicolet Technology Corp. Deuteriated chloroform was used as the solvent, lock and as an internal reference.

T_1 NOE measurements were carried out as previously reported;[9] the pulse sequence consisted of a mixture of progressive saturation experiments with gated decoupling and an additional $\pi/2$ pulse:

$$[\pi/2-(AT)_1-D1-\pi/2-(AT)_2-\pi/2-D5]_n$$

Alternate block acquisition (AT) was used to minimize temperature variation over the whole sequence. The decoupler was initially turned on (before the first $\pi/2$ pulse) and was then turned off after the second acquisition. Fitting of the magnetization at the second acquisition as a function of $(AT)_1+D1$ allowed the extraction of T_1 and M_D; fitting of the magnetization at the first acquisition as a function of $D5$ (using a double exponential) allowed the calculation of M_0. Reported NOE values are $(M_D/M_o)-1$. Power spectra, i.e. the square of the real part plus the square of the imaginary part of the Fourier transform, were used to calculate the corresponding integrals for each resonance.

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