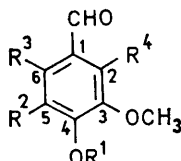# 13C Nuclear Magnetic Resonance Spectroscopy of Vanillin Derivatives

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13C Chemical shifts of vanillin and its chloro-, nitro-, O-acetyl, and O-methyl derivatives are reported. Carbon shifts together with carbon–proton and proton–proton coupling constants provide unambiguous structural determination.

IN the course of work designed to provide compounds related structurally to sporidesmin, the toxin responsible for causing facial eczema of sheep and cattle in Australia and New Zealand,[1] compounds (1)—(16) have been prepared and their 13C n.m.r. spectra recorded. The carbon shifts are presented in Tables 1—3.

CHO

Compound	R¹	R²	R³	R⁴
(1)	H	H	H	H
(2) [a]	H	Cl	H	H
(3) [b,c]	H	H	H	NO₂
(4) [a]	H	Cl	H	NO₂
(5) [c]	H	Cl	NO₂	H
(6) [c]	H	H	NO₂	H
(7)	CH₃	H	H	H
(8) [d]	CH₃	Cl	H	H
(9) [e]	CH₃	H	H	NO₂
(10) [d]	CH₃	Cl	H	NO₂
(11) [d]	CH₃	Cl	NO₂	H
(12) [f]	CH₃	H	NO₂	H
(13) [b]	COCH₃	H	H	H
(14) [a]	COCH₃	Cl	H	H
(15) [b]	COCH₃	H	H	NO₂
(16) [a]	COCH₃	Cl	H	NO₂

[a] L. C. Raiford and J. G. Lichty, *J. Amer. Chem. Soc.*, 1930, **52**, 4576. [b] R. Pschorr and C. Sumuleanu, *Chem. Ber.*, 1899, **32**, 3405. [c] L. C. Raiford and W. C. Stoesser, *J. Amer. Chem. Soc.*, 1928, **50**, 2556. [d] L. C. Raiford and D. E. Floyd, *J. Org. Chem.*, 1943, **8**, 358. [e] F. Hayduck, *Chem. Ber.*, 1903, **36**, 3528; F. B. Whittmer and L. C. Raiford, *J. Org. Chem.*, 1945, **10**, 527. [f] C. A. Fletscher, *Org. Synth.*, Coll. Vol. IV, 1963, p. 735.

TABLE 1
13C Chemical shifts of substituted vanillins [a]

	(1)	(2)	(3)	(4)	(5)	(6)
C(1)	128.7	128.0	118.3	118.3	118.4	123.2
C(2)	110.6	109.1	143.1	140.9	113.5	110.5
C(3)	148.0	148.6 [b]	139.3	141.9	149.0	151.6
C(4)	152.9	148.7 [b]	157.2	153.7	149.0	150.8
C(5)	115.3	120.0	117.9	123.3	112.8	110.9
C(6)	126.0	125.4	130.6	130.6	141.8	143.5
CHO	190.7	190.0	187.6	187.2	187.1	187.9
C(3)OMe	55.6	56.3	61.5	62.7	56.8	56.3

[a] δ Values, in p.p.m. downfield from Me₄Si [δ(Me₄Si) = δ[(CD₃)₂SO] + 39.5 p.p.m.]. [b] Assignments may be reversed.

Signal assignment was attempted initially by the use of additive substituent parameters [2] in relation to the basic

[1] A. Taylor, *Microbial Toxins*, 1971, **7**, 337; S. Safe and A. Taylor, *J.C.S. Perkin I*, 1972, 472 and earlier papers in this series; Y. Kishi, S. Nakatuka, T. Fukuyama, and M. Havel, *J. Amer. Chem. Soc.*, 1973, **95**, 6493; J. W. Ronaldson, *Austral. J. Chem.*, 1975, **28**, 2043.

[2] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972, p. 81.

3,4-dioxybenzaldehyde skeleton, *e.g.* compounds (1), (7), and (13), but in many instances ambiguities arose due

TABLE 2
13C Chemical shifts of substituted vanillin methyl ethers [a]

	(7)	(8)	(9)	(10)	(11)	(12)
C(1)	129.8	132.1	120.1	122.9	123.4	125.2
C(2)	108.7	109.4	144.2	142.6	110.2	109.5
C(3)	149.2	154.0	140.8	146.0	154.4	152.8
C(4)	154.1	150.4	158.2	155.0	150.4	152.0
C(5)	110.1	128.5	112.7	131.0	121.0	106.9
C(6)	126.4	125.4	128.2	126.6	144.2	143.5
CHO	190.4	189.6	185.6	184.4	184.7	187.2
C(3)OMe	55.9 [b]	56.0	62.8	62.6 [c]	56.6	56.6
C(4)OMe	55.7 [b]	60.7	56.6	61.3 [c]	61.3	56.6

[a] δ Values in p.p.m. downfield from Me₄Si; δ(Me₄Si) = δ(CDCl₃) + 76.9 p.p.m. [b,c] Assignments designated in any vertical column may be reversed.

TABLE 3
13C Chemical shifts of substituted vanillin acetates [a]

	(13)	(14)	(15)	(16)
C(1)	134.8	134.5	125.1	125.4
C(2)	110.6	109.2	144.7	143.3
C(3)	151.5	153.0	144.1	146.0 [b]
C(4)	144.5	141.4	148.8	145.9 [b]
C(5)	123.0	128.8	125.9	131.8
C(6)	124.1	124.3	126.4	126.1
CHO	190.5	189.5	185.7	184.4
C(3)OMe	55.7	56.3	62.8	63.0
CH₃CO	167.8	166.9	167.3	166.2
CH₃CO	20.3	20.1	20.6	20.0

[a] See foonote a, Table 2. [b] Assignments may be reversed.

to large deviations from additivity (see later), and the proximity of resonances. These obstacles could be overcome by the use of two- and three-bond carbon–hydrogen coupling information, most easily obtained by decoupling regions of the proton spectrum. Thus, characteristically large *meta*-coupling, ³J_CH, and the interaction of C(3) and, where appropriate, C(4) with their methoxy-substituent protons could be observed.[3] In all cases C(1) showed *ca.* 25 Hz coupling with the aldehydic proton.[4] The signal of a methine carbon atom *ortho* to another methine could be recognized by the appearance of extra, second-order lines in the single-frequency off-resonance decoupled spectrum.[3,5] Analysis of the J values thus proved to be not only an assignment technique, but also a method of corroboration of structures previously assigned.

[3] E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gašić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, ' Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances,' in ' Topics in Carbon-13 NMR Spectroscopy,' ed. G. C. Levy, Wiley–Interscience, New York, 1976.

[4] J. B. Stothers, ' Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972.

[5] E. W. Hagaman. *Org. Magnetic Resonance*, 1976, **8**, 389.

The coupling constants of the aromatic protons led to identification of the tetrasubstituted compounds (see Table 4), and carbon shifts and coupling data (see above)

TABLE 4
Aromatic ring proton–proton couplings

Compound	Relationship	J/Hz
(3)	ortho	8
(9)	ortho	8.5
(15)	ortho	8
(2)	meta	2
(8)	meta	1.5
(14)	meta	2
(6)	para	<1
(12)	para	<1

TABLE 5
Effect of an oxy-substituent on an aromatic ring [a]

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
Phenol [b]	26.3	−13.1	1.3	−7.4	1.3	−13.1
2-Methylphenol [b]	24.1	−13.9	1.6	−7.2	2.0	−12.7
2,6-Dimethylphenol [b]	22.1	−14.0	2.3	−7.8	2.3	−14.0
Anisole [c]	29.8	−15.9	−0.4	−9.3	−0.4	−15.9
2-Methylanisole [c]	27.0	−13.1	−0.2	−9.0	0.3	−19.7
2,6-Dimethylanisole [c]	25.7	−8.6	0.8	−6.1	0.8	−8.6

[a] δ(phenol or anisole) − δ(corresponding hydrocarbon); hydrocarbon shifts from ref. 4. [b] Ref. 6. [c] Ref. 7.

provided additional evidence. In several cases the substituent parameters of the chloro- and nitro-groups, derived from the monosubstituted compounds,[2] show large deviations, many of which can be traced to the effects of methoxy-groups on ortho-substituted aromatic rings. Table 5 shows the differences in chemical shifts of ring carbon atoms of a few phenols [6] and anisoles,[7] and the corresponding δ values for the related hydrocarbons.[4] Whereas the substituent parameters of the hydroxy-group

carbon atoms. This phenomenon constitutes steric inhibition to resonance and has been reported before.[7-10] The two effects combine to produce an absolute 20.1 p.p.m. downfield shift difference for C(6) of 2-methyl-anisole on C(6) methylation, i.e. 11.0 p.p.m. more than the effect in the case of toluene and benzene.[4]

Analogously, the introduction of a chlorine atom at C(5) causes deshielding of this carbon atom by ca. 5 p.p.m., when the C(4) substituent is a hydroxy-group (6.2 p.p.m. for chlorobenzene [2]), but 18.4 p.p.m. in the presence of a 4-methoxy-function. The shielding is only 5.9 p.p.m. for the acetylated compounds, and their C(1) and C(3) shifts are unaffected, indicating only small inhibition of resonance of an ortho,ortho'-disubstituted acetoxy-group. Similar arguments can be used to explain the extremely large perturbation of the α-effect on C(2)-nitration (33.5 ± 2 p.p.m.), and the α-effect at C(6) (17.5 ± 1 p.p.m.) is reminiscent of that in nitrobenzene (20.0 p.p.m.).[2]

In accordance with Lauterbur's results for simple nitrobenzenes,[9] introduction of a nitro-group into a 3,4-dioxybenzaldehyde nucleus at C(2) shields (C1) by 9.8 ± 0.7 p.p.m. and C(3) by 7.7 ± 1 p.p.m. and, likewise, a nitro-group at C(6), flanked by a formyl at C(1) and a chlorine at C(5), shields these positions by ca. 9 and 7.5 p.p.m., respectively. However, a 6-nitro-group substituted only at one ortho-position shields its ortho-carbon atoms by only 4.3 ± 1.1 p.p.m.

The recognition of these empirical observations allows the prediction of the shifts of the pentasubstituted chloro-nitro-compounds (4), (5), (10), (11), and (16), which were all made by nitration of 5-chlorovanillin derivatives and thus have the nitro-groups at position 2 or 6. In Table 6

TABLE 6
Absolute discrepancies (|Δ|) and mean discrepancy per carbon atom (Σ|Δ|/6) between calculated and observed chemical shifts for the ring carbon atoms of the pentasubstituted benzenes

Compound	Calc. for formula	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	Σ|Δ|/6
(4)	(4)	0.7	1.1	2.0	0.7	0.7	0.6	0.9
(4)	(5)	3.9	31.1	10.3	7.1	8.1	12.3	12.1
(5)	(5)	4.1	3.7	3.2	2.4	2.4	1.1	2.8
(5)	(4)	4.2	31.7	10.3	7.1	8.1	12.3	12.3
(10)	(10)	0.5	1.6	0.4	0.5	0.1	0.6	0.8
(10)	(11)	1.4	34.0	9.9	4.1	10.1	17.2	12.8
(11)	(11)	4.1	0	3.2	1.9	4.3	1.7	2.5
(11)	(10)	4.6	32.4	11.6	6.5	5.7	1.3	10.3
(16)	(16)	0.6	0	0.6	0.2	0.1	0.5	0.3

are largely unaffected by ortho-substituents, those of a methoxy-group change in magnitude for ortho-carbon atoms when one ortho-substituent is introduced, but not for para-carbon atoms (cf. the shift differences of 2-methylanisole and anisole). This is interpretable in terms of a γ-shielding effect of the O-methyl group acting on C(6) but not on C(2).[8] The introduction of a second ortho-methyl group to give a compound with three large substituents on contiguous carbon atoms, however, decreases the shielding of the para- as well as the ortho-

the observed chemical shifts of the ring carbon atoms are compared with those calculated for the appropriate 5-chloro-2-nitro- and 5-chloro-6-nitro-compounds. The calculations involved the use of the shifts of the vanillins (1), (7), and (13) and the appropriate increments for the introduction of individual chloro- and nitro-groups at each position, based on shifts of the tetrasubstituted compounds. Thereby the validity of the proposed structures is demonstrated.

The same result can be obtained independently from the chemical shifts of the methoxy-carbon atoms. Tables

[6] P. C. Lauterbur, J. Amer. Chem. Soc., 1961, 83, 1846.

[7] K. S. Dhami and J. B. Stothers, Canad. J. Chem., 1966, 44, 2855.

[8] G. W. Buchanan, G. Montaudo, and P. Finocchiaro, Canad. J. Chem., 1974, 52, 767.

[9] P. C. Lauterbur, J. Chem. Phys., 1963, 38, 1415, 1432.

[10] K. S. Dhami and J. B. Stothers, Canad. J. Chem., 1965, 43, 479, 498.

1—3 show that they fall into two ranges, **61—63** and **55—57** p.p.m. The analogy with alkyl-substituted anisoles [7] indicates that the former group correponds to *ortho, ortho'*-disubstituted methoxybenzenes and the latter to all others. Since the diethers (7)—(12) were prepared by the methylation of the phenols (1)—(6), a simple analysis of the methoxy-carbon atom shifts for each compound pair [(1) and (7), (2) and (8), *etc.*] is sufficient for unambiguous determination of the location of the substituents on the 3,4-dioxybenzaldehyde skeleton.

EXPERIMENTAL

The carbon shifts in Tables 1—3 were recorded with a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode.

Known compounds were prepared according to the methods employed in the cited references, except where noted below.

5-*Chloro-*6-*nitrovanillin* (5).—4-O-Acetyl-5-chlorovanillin (300 g in batches of 40 g) was nitrated according to the method of Raiford and Lichty.[11] Recrystallization of the product from ethanol gave the expected 2-nitro-compound (16) (200 g) and, on concentration of the mother liquor, an oil which was redissolved in ethanol (100 ml). Aqueous sodium hydroxide (20%; 200 ml) was added, and when the mixture had cooled an orange solid was removed. Acidi-

fication of the filtrate gave 4-chloro-2-nitrovanillin (50 g). The orange precipitate (5 g) was washed with ethanol and dissolved in dimethyl sulphoxide (10 ml); acidification and dilution with water gave the colourless 5-*chloro-*6-*nitrovanillin,* m.p. 192—193° (from ethanol) (Found: C, 41.5; H, 2.7; Cl, 15.4; N, 6.1. $C_8H_7ClNO_5$ requires C, 41.5; H, 2.6; Cl, 15.3; N, 6.1%).

Methylations of Substituted Vanillins.—Methylation methods described in the literature which involve aqueous solvents were found to be less satisfactory than modifications using aprotic solvents. For example 2-nitrovanillin (16 g) was suspended in acetonitrile (50 ml) and dimethyl sulphate (10 ml), then anhydrous potassium carbonate (21 g) was added. T.l.c. showed that methylation was complete after heating under reflux for 10 min. Pouring the cooled mixture into water caused precipitation of the dimethyl ether (17.1 g, 99%), m.p. 63—65° (from ethanol) (lit.,[12] 55—56° and 63°)

[11] See footnote *a* to formulae.
[12] See footnote *e* to formulae.