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^{13}C NMR SPECTROSCOPY OF SUBSTITUTED XANTHONES—II ^{13}C NMR SPECTRAL STUDY OF POLYHYDROXY XANTHONES

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Abstract—The ^{13}C NMR chemical shifts of eleven hydroxy-, two hydroxymethoxy xanthones, and xanthone-*C*-glucoside, mangiferin, are presented and analyzed. Hydroxy substituent effects depending on substituent position as well as on shielded ring carbon position have been evaluated. Hydroxy substituent increments for xanthones are proposed. Effects of hydroxylation on carbonyl carbon shift and the methylation of hydroxy group and the corresponding shift increments which are of diagnostic value have been observed and discussed.

Following our current studies dealing with ^{13}C NMR spectroscopy of polyoxygenated xanthones, we recently reported the interpretation of ^{13}C NMR spectra of a range of methoxy xanthones.[1] It was concluded that established aromatic substitution additivity rules do not hold well in this system and our extensive analysis of the data led us to propose the methoxy substituent increments for xanthones.

Since the most common type of substituent in compounds of natural origin are oxyfunctions and each type has to be examined separately for successful interpretation of the spectra, we initiated a systematic study of polyhydroxy xanthones. In the present paper, the ^{13}C NMR data of thirteen hydroxy xanthones and a xanthone-*C*-glucoside, mangiferin, are presented and analyzed. The ^{13}C NMR correlation reported here and earlier[1] by us should provide further investigators with a battery of additivity data, which can be applied to structure elucidation of naturally occurring polysubstituted xanthones[2] and especially for allocating the hydroxymethoxy substitution pattern. Since the completion of this work, several further investigations involving ^{13}C NMR of xanthones have appeared† in the literature.[3–8] However, some of the assignments reported[4,6–8] have to be revised (discussed later) in light of the data for the closely related compound presented in this and the earlier paper.[1] A paper published earlier[8] by Hostettmann *et al.* came to our notice, which dealt with interpretation of the ^{13}C NMR spectra of 1,7,8-hydroxy-3-methoxy-xanthone **13** and two corresponding glycosides with the view to locating the position of the acetyl group in the sugar moiety. However, the ^{13}C chemical shift data for the xanthone carbons have discrepancies with results of our own work. The previous assignments[8] of carbons 1 and 4a have been reversed and of carbons 4b, 5, 7, 8, 8a and 8b have been revised (Tables 2 and 3).

†Earlier work on this topic has been cited in Ref. 1.

RESULTS AND DISCUSSION

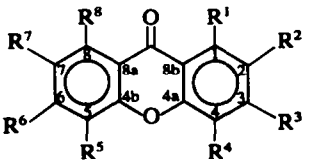
The xanthones under investigation are listed in Table 1 which covers four monohydroxy xanthones, nine 1,3-dioxygenated xanthones with or without additional hydroxy group(s) in ring A, and a xanthone-*C*-glucoside, mangiferin. All spectra were measured in DMSO-d_6 solutions. The assignments of all carbons for xanthone (1–15) are shown in Tables 2 and 3. The signals were assigned by means of single-frequency decoupling technique,[9] application of known chemical shift rules for hydroxyl substitution,[10] and from comparison of spectra from compound to compound. These correlations were confirmed by using coupled[11] nuclear overhauser enhanced spectral (gated decoupled) information in the form of signal multiplicities and coupling constants.[12] In addition the splitting simplification in gated decoupled spectra after D_2O-exchange has been applied.[13]

The effect of hydroxy groups on ^{13}C NMR shifts of aromatic carbons have been studied thoroughly.[10] However, these shift increments cannot be utilized for hydroxylated xanthones, since the π-electron frame work transmit the effect of added substituent through the whole molecule in an asymmetrical manner. Thus, increments depend both on the position of the hydroxy groups and on the position of the shifted *ortho*-, *meta*- and *para*-carbons in the ring system. From the recorded and correlated resonance frequencies (Table 2 and 3) of the single aryl carbon nuclei in mono-hydroxy-xanthones we now have derived new substituent chemical shifts, which are summarized in Table 4.

Spectra evaluation of all compounds studied has led to an additivity shift rule with a set of hydroxy substituent shifts for carbons of xanthone (Table 5), which may be applied as additive increments to the shifts of the respective carbons of the unsubstituted xanthone.

This shift rule for calculating δ-values of aryl carbon nuclei of polyhydroxy-xanthones takes into account as well their *ipso*-, *ortho*-, *meta*- or *para*-position relative to the hydroxy substituents as their position in the xanthone ring system. The C_{ipso}

Table 1. Substitution pattern of hydroxyxanthones



Compound		R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	R⁸
1	(X)	H	H	H	H	H	H	H	H
2	(1-HX)	OH	H	H	H	H	H	H	H
3	(2-HX)	H	OH	H	H	H	H	H	H
4	(3-HX)	H	H	OH	H	H	H	H	H
5	(4-HX)	H	H	H	OH	H	H	H	H
6	(1,3-DHX)	OH	H	OH	H	H	H	H	H
7	(1,3,5-THX)	OH	H	OH	H	OH	H	H	H
8	(1,3,6-THX)	OH	H	OH	H	H	OH	H	H
9	(1,3,7-THX)	OH	H	OH	H	H	H	OH	H
10	(1,3,8-THX)	OH	H	OH	H	H	H	H	OH
11	(1,3,5,6-TeHX)	OH	H	OH	H	OH	OH	H	H
12	(1,3,6,7-TeHX)	OH	H	OH	H	H	OH	OH	H
13	(1,7,8-TH-3-MX)	OH	H	OMe	H	H	H	OH	OH
14	(1,5,8-TH-3-MX)	OH	H	OMe	H	OH	H	H	OH
15	(1,3,6,7-TeH-2-GX)	OH	β-D-glucose	OH	H	H	OH	OH	H

Table 2. ^{13}C-NMR chemical shifts of hydroxyxanthones

Compound		C-1	C-2	C-3	C-4	C-4a	C-4b
1	(X)	125.92	124.28	135.44	118.10	155.55	155.55
2	(1-HX)	160.98	110.16	137.45	107.18	155.74	155.61
3	(2-HX)	108.58	153.91	124.47	119.35	149.19	155.54
4	(3-HX)	127.96	114.08	164.01	102.16	157.57	155.57
5	(4-HX)	115.25	124.12	120.21	146.64	145.23	155.38
6	(1,3-DHX)	162.91	98.16	165.90	94.10	157.39	155.35
7	(1,3,5-THX)	162.93	98.14	165.78	94.09	157.28	144.88
8	(1,3,6-THX)	162.88	97.99	165.16	93.96	157.42	157.42
9	(1,3,7-THX)	162.81	97.87	165.61	93.76	157.53	149.03
10	(1,3,8-THX)	162.18	98.56	166.55	94.35	157.44	155.47
11	(1,3,5,6-TeHX)	162.94	97.89	165.14	93.95	157.38	146.10
12	(1,3,6,7-TeHX)	162.66	97.73	164.71	93.64	157.39	150.98
13	(1,7,8-TH-3-MX)	161.94	97.17	167.09	92.75	157.71	148.01
14	(1,5,8-TH-3-MX)	161.89	97.25	166.94	92.78	157.22	143.29
15	(1,3,6,7-TeH-2-GX)	161.86	107.68	163.89	93.48	156.33	150.89

Table 3. ^{13}C-NMR chemical shifts of hydroxyxanthones

Compound		C-5	C-6	C-7	C-8	C-8a	C-8b	C=O
1	(X)	118.10	135.44	124.28	125.92	121.12	121.12	175.91
2	(1-HX)	117.98	136.39	124.53	125.36	119.83	108.28	181.69
3	(2-HX)	118.03	135.04	123.84	125.84	120.45	121.73	175.83
4	(3-HX)	117.81	134.68	124.03	125.83	121.25	114.08	174.74
5	(4-HX)	118.23	135.23	123.95	125.94	120.94	122.28	176.16
6	(1,3-DHX)	117.61	135.52	124.28	125.18	119.84	102.25	179.73
7	(1,3,5-THX)	146.15	120.61	124.06	114.60	120.95	102.20	180.17
8	(1,3,6-THX)	102.07	164.23	113.98	127.16	112.28	101.69	179.10
9	(1,3,7-THX)	118.90	124.43	153.94	108.05	120.43	101.98	179.72
10	(1,3,8-THX)	107.02	137.13	110.54	160.29	106.87	101.14	183.41
11	(1,3,5,6-TeHX)	132.48	151.92	113.09	115.93	113.09	101.48	179.69
12	(1,3,6,7-TeHX)	102.72	154.03	143.75	108.16	111.89	101.65	178.94
13	(1,7,8-TH-3-MX)	106.01	124.21	140.56	147.11	107.38	101.76	184.26
14	(1,5,8-TH-3-MX)	137.32	123.73	109.35	151.83	107.35	101.98	183.91
15†	(1,3,6,7-TeH-2-GX)	102.73	154.11	143.80	108.21	111.85	101.43	179.20

†Additional signals due to glucose carbons[20] at 81.61 (C-1), 79.07 (C-5) 73.24 (C-2), 70.72/70.45 (C-3/4) and 61.61 ppm (C-6).

Table 4. ^{13}C-Shift increments for mono-hydroxyxanthones

Substituent in position	Shift increments (in ppm) for carbon in position					
	C-1(8)	C-2(7)	C-3(6)	C-4(5)	C-4a(4b)	C-8b(8a)
1(8)	+35.1	−14.0	+2.0	−10.9	+0.2	−12.8
2(7)	−17.4	+29.6	−11.0	+1.3	−6.4	+0.6
3(6)	+2.0	−10.2	+28.6	−15.9	+2.0	−7.0
4(5)	−10.7	−0.2	−15.2	+28.5	−10.3	+1.2

Table 5. Hydroxy substituent shifts for carbons of xanthone

Carbon relative to hydroxy group	Carbon in ring position	Increment [ppm]
C-*ipso*:	1, 8	+35.5 ± 0.5
	2, 3, 4, 5, 6, 7	+29.3 ± 1.0
C-*ortho*:	1, 4, 5, 8	−16.0 ± 1.5
	8b, 4a, 4b, 8a	−11.5 ± 1.5
	2, 3, 6, 7	
	shifted by *ortho*-hydroxyat C-1, 4, 5, 8	−14.5 ± 1.0
	at C-3, 2, 7, 6	−10.5 ± 1.0
C-*meta*:	1-8	+1.0 ± 1.0
	8a, 8b	+1.0 ± 1.0
	4a, 4b	0.5 ± 1.0
C-*para*:	1, 4, 5, 8	−10.5 ± 1.0
	8b, 4a, 4b, 8a	−7.0 ± 1.0

increments (Table 5) in position 1 (8) are rather high and of about +36 ppm (downfield) in comparison with the corresponding xanthone-carbon as a result of intramolecular hydrogen bonding between the carbonyl oxygen and 1 and/or 8 hydroxy group. The C_{ipso} increments for all other positions are about 6 ppm smaller and lie between 28.5 to 29.5 ppm. Double chelation (1,8-dihydroxy) causes a downfield shift of about 6 ppm to carbonyl carbon whereas monochelation (1- or 8-hydroxy) causes about 4.5 ppm downfield shift and can be rationalized on the basis of hydrogen bonding. Additional oxygenation in position 3 or 6 causes an upfield shift of about 1.5 ppm. This change in shift can be accounted for by an increase in electron density at carbonyl carbon upon disruption of chelation. Thus CO carbon shift is a suitable probe for identifying type and number of substituents at C-1 and -8.

In the vicinity of CO group (C-1 or -8), the methylation of that hydroxy group produces an upfield shift of about 1.5 ppm in the C_{ipso} carbon. The shift observed in the signals of the ortho-related methine carbons (1, 4, 5, 8) tend to be upfield by about 2.5 ppm whereas other ortho-related non-protonated carbons (8b, 4a, 4b, 8a) suffered approximately equivalent downfield shift. It is noteworthy that methylation of hydroxy group in the position 1, 4, 5, 8 shifted the ortho-related carbons 2, 3, 6, 7 upfield which however, by methylation of hydroxy group in the position 3, 2, 7, 6 remained unaffected. The methylation of hydroxy groups causes downfield shift into the *para*-carbons (8b, 4a, 4b, 8a).

During the detailed ^{13}C NMR spectral investigation of flavonoids[14] Pelter *et al.* proposed that hydroxy- and methoxy groups exert a similar effect. But in this study we have definitely proved they exert different shift increments and can be exploited for locating hydroxy group in a hydroxy-methoxy compound, if solvent shifts have been taken into account.

Only five xanthone-*C*-glucosides are known in nature[2] and they carry glucose moiety at C-2 or C-4. Only one such compound, mangiferin **15**, was available[15] for our study. Comparison of the spectra of **12** and **15** showed that the C-*ipso* is shifted by about 10 ppm downfield whereas *ortho*- and *para*-carbons (C-1, C-3, C-4a) are shifted about 1 ppm upfield. Signals appeared due to glucose are comparable with that of β-D-*O*-glucosides,[16] however, C-1′ suffered about 20 ppm upfield shift and is due to the replacement of the C—O bond by a C—C bond. Similar observation has been reported[17] for isoorientin, a flavone-*C*-glucoside and can be taken as diagnostic of *C*-glucosides.

The spectral assignment of 2-HX, 4-HX, 1,3-DHX, and 1,3,6-THX is in agreement with a previous work[3] thus confirming the report. 1-HX has been recorded[3] earlier in $CDCl_3$. Shift values for **2** given in Tables 2 and 3 are from DMSO-d_6 solution. The downfield solvent shift of about 0.5–1 ppm for carbons 2, 3, 4 and a highfield shift of about 0.5–1 ppm for carbons 1, 4a, 8b and C=O has been observed on going from $CDCl_3$ to DMSO-d_6. Tentative correlations reported earlier[3] have been confirmed in this study. Scheinmann *et*

al.,[4] on the basis of additivity rules, assigned the carbon shifts of 1,3,6,7-tetramethoxy-, 1-hydroxy-3,6,7-trimethoxy-, 1,7-diallyoxy-3,6-dimethoxy- and 2,8-diallyl-1,7-dihydroxy-3,6-dimethoxy-xanthones and came to wrong conclusions. The assignment of carbon shifts of their first compound should be revised according to our reported data.[1] The assignment of C-1 and C-4a in the second compound need to be reversed. Accordingly, the revision of assignment of the last two compounds are warranted. Recently two papers on the ^{13}C NMR spectral study of lichen xanthones have appeared.[5,7] The published values[5] for 1,3,6,8-tetrahydroxy-xanthone correspond well with 1,3-dihydroxy-xanthone presented in this study. However, the assignments[7] of 1,3,6-trimethoxy-8-methyl-xanthone need several revision. On the basis of our earlier study,[1] the revised assignment of resonance signals are given in the parenthesis: 162.0 (C-1), 95.0 (C-2), 164.2 (C-3), 92.3 (C-4), 162.6 (C-6), 159.0 (C-4a), 158.1 (C-4b). If the premise is granted that substitution in one ring has little or no influence[1] in the other ring, the following revision at least for the chromone part of 1,3,5-trihydroxy-8-β-D-glucopyranosyl-5,6,7,8-tetrahydro-xanthone (campesteroside)[6] can be proposed and their assignment are given in parenthesis: 161.7 (C-1), 100.1 (C-2), 166.8 (C-3), 158.0 (C-4a), 104.2 (C-8b). The expected shift for the C=O carbon should be around 180 ppm.

The ^{13}C NMR data provided here and earlier[1] may be applied for the assignment of carbon signals in chromones or compounds having this chromophore, e.g. flavones. In conclusion the following points emerge: (1) The correlation of line frequencies of specific xanthone carbons can be achieved with the help of the proposed substitutent increments. (2) The shifts brought about by introduction of 1- and/or 8-hydroxy group into carbonyl carbon can be exploited to determine the substitution pattern. (3) The *ipso*-, *ortho*-, and *para*-shift increments brought about by methylation of hydroxy group(s) into xanthone carbons can be used to locate the hydroxy group in a polyoxygenated compound.

EXPERIMENTAL

Materials. All hydroxy xanthones but **13**, **14**, **15**, which are of natural origin,[2c,15,18] were obtained by demethylating corresponding methoxy xanthones prepared earlier[1] by published procedure.[19]

^{13}C NMR spectra were obtained at 20.0 MHz in Fourier transform mode using a Varian Associates CFT 20 spectrometer and were run in d_6-DMSO solutions (saturated), which also provided the deuterium locksignal. δ-Values are given in ppm downfield from TMS (δ_{TMS} = 0), measured from internal d_6-DMSO and corrected by using the equation $\delta_{TMS} = {}^{\delta}\alpha_6$-DMSO − 39.59. Measurement conditions were as follows:- Pulse width: 5 μ sec (appro. 21°); pulse delay: none; acquisition time: 1.023 sec; data points: 8192 (8K); spectra width: 4 kHz; effective resolution 0,05 ppm; probe temperature: 35°C; sample tubes: 10 mm. Accumulation of FID: (a) in ^{1}H-broad band noise decoupled mode $1-10\times10^4$ times; (b) in coupled nuclear Overhauser enhanced mode $3-30\times10^4$ times.

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