Shift Reagent ^{1}H NMR Study of Methoxycoumarins

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The complete assignment of the proton chemical shifts of coumarin (**1**), all monomethoxy derivatives and the six possible dimethoxyl substituted compounds at the aromatic ring was achieved at 60 MHz in a quantitative study utilizing Pr(fod)$_3$ as the shift reagent. It was found that in addition to the complexation at the lactone carbonyl a second interaction of the lanthanide shift reagent occurs when two methoxyl groups are found in an *ortho* distribution. The results are discussed in comparison to data published for flavones in the presence of Pr(fod)$_3$ shift reagent.

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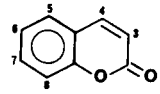
Coumarins are widely distributed in plant material [2] and extensive research on the subject has led to the application of several nmr techniques. In particular, the use of aromatic solvent induced shifts [3-4] and extensive ^{13}C nmr measurements [5] for their structural elucidation have been of great value. An alternate simple and readily available procedure, utilizing lanthanide induced shifts has been applied in a limited extent to some representatives of several types of naturally occurring coumarins [6]. However, to our knowledge no systematic study has been described for the simple representatives of this type of heterocyclic natural products.

Taking into account our efforts in the systematic study of another group of widely distributed heterocyclic aromatic natural products, *e.g.* flavones in the presence of lanthanide shift reagents [7-9] and the promising behavior outlined for some coumarins [6], we completed a detailed quantitative systematic study of all possible monomethoxy coumarins and the six possible molecules having two methoxyl groups as substituents on the aromatic ring. Our results are discussed at present in comparison to those we published for flavones [7-9]. They show the practical utility of such type of experiments even when performed in the widely distributed 60 MHz ^{1}H nmr spectrometers that also allow to ascribe the individual methoxyl resonance signals.

The chemical shifts of the individual aromatic protons, those of the lactone ring and those owing to the methoxyl groups attached to the coumarins are summarized in Table I. The values for H-3 and H-4 could in all cases be extracted directly from the spectra. These signals appear as an AB system ($J_{3,4} \cong 9.5$ Hz) in all cases in which no methoxyl group is found on the lactone ring. Their chemical shifts are indicative of the substitution pattern of methoxyl groups on the aromatic ring. Thus H-4 appears in the 7.58 to 7.70 ppm region when there is no methoxyl group at C-5, while in all 5-MeO derivatives H-4 appears

Table I

^{1}H NMR Chemical Shifts of Coumarins [a]



		3	4	5	6	7	8
1	Coumarin	6.42	7.70	7.61	7.22	7.45	7.20
2	3-MeO-	(3.93)	6.83	7.35	7.35	7.32	7.30
3	4-MeO-	5.70	(4.00)	7.80	7.48	7.38	7.18
4	5-MeO-	6.27	8.02	(3.91)	6.70	7.40	6.83
5	6-MeO-	6.42	7.67	6.85	(3.82)	7.21	7.18
6	7-MeO-	6.27	7.68	7.42	6.89	(3.89)	6.89
7	8-MeO-	6.42	7.68	7.08	7.20	7.08	(3.98)
8	5,6-(MeO)$_2$-	6.35	7.99	(3.99)	(3.90)	6.99	7.11
9	5,7-(MeO)$_2$-	6.15	7.99	(3.90)	6.30	(3.86)	6.43
10	5,8-(MeO)$_2$-	6.35	8.07	(3.89)	6.60	7.05	(3.92)
11	6,7-(MeO)$_2$-	6.27	7.65	6.89	(3.95)	(3.97)	6.83
12	6,8-(MeO)$_2$-	6.38	7.58	6.44	(3.83)	6.65	(3.91)
13	7,8-(MeO)$_2$-	6.25	7.65	7.20	6.88	(4.00)	(3.98)

[a] In ppm from internal TMS. Values in parentheses correspond to methoxyl groups.

around 8 ppm. Furthermore H-3 is also influenced but in a different way. In coumarin (**1**) and their methoxyl analogs at C-6 abnd C-8, it appears at 6.42 ppm, but when the electron releasing methoxyl group is found *ortho* or *para* to C-4a, the influence is transmitted by the C-3/C-4 double bond to C-3, which has now a slightly higher electron density thus shifting H-3 to 6.27 ppm, in agreement with calculations perfomed for methyl coumarins [10]. This effect is further evident in 5,7-dimethoxycoumarin [9] in which H-3 appears at 6.15 ppm and the effect is weaker in all remaining dimethoxy derivatives in accordance to the methoxyl group location (see Table I).

The chemical shifts of the aromatic protons in the dimethoxy derivatives were also seen dierectly in the spectra and their assignment in compounds unsubstituted at C-8 (**8, 9** and **11**) was readily adduced from the additional broadening of H-8 due to inter-ring long range coupling to H-4 [11]. For the remaining dimethoxy derivatives **10, 12** and **13**, the aromatic protons were ascribed considering the influence of the lactone hetero atom effect upon C-6 and that of the double bond upon C-5 and C-7 [12].

The situation turned more complex for those methoxycoumarins having only one substituent on the aromatic ring. From them, the signals owing to the aromatic protons in 5-methoxycoumarin (**4**) could be ascribed completely after inspection of the spectrum, as was the case for H-5 in 6-methoxy- (**5**) and in 7-methoxycoumarin (**6**). The remaining two aromatic protons in both of these compounds are overlapped as are also the three protons of 8-methoxycoumarin (**7**) in which therefore no direct assigments of the aromatic protons can be done at 60 MHz.

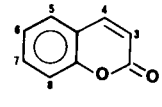
Regarding the reamining compounds **1, 2** and **3**, only H-5 in 4-methoxycoumarin (**3**) can be ascribed directly. The complete assignment of all other aromatic protons in the monosubstituted coumarins **2, 3, 5, 6** and **7** and in the parent molecule **1**, was achieved after performing the shift reagent experiments (*vide infra*).

Furthermore the assignment of the individual methoxyl resonances in the dimethoxy derivatives could be achieved in some cases from the data of the monosubstituted coumarins. This is the case for compounds **9, 10** and **12**. In the remaining three molecules, **8, 11** and **13**, it could be done after performing the shift reagent experiments.

The behavior of the coumarins in the presence of shift reagents was explored at 60 MHz. Preliminary spectra of some molecules determined in the presence of the europium and the praseodimium complexes with dipivalomethane revealed that these shift reagents do not provide highly useful spectra, since only small shifts were induced. On the other hand, with both the europium and the praseodimium complexes of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionate (fod) greater shifts were induced. However, the detailed quantitative study was performed only in the presence of $Pr(fod)_3$ since experimentally it was found that more convenient signal separations were obtained in this way and in addition it is more easy to follow shifts of aromatic protons to higher fields since thereby it is not necessary to offset the spectrometer. The results obtained for all protons of the thirteen compounds are summarized in Table II and correspond to a 1:1 molar ratio of shift reagent to coumarin. They were obtained by least-square adjustments of the straight lines provided by plotting the variation of the chemical shifts (*abscissa*) with the

Table II

Induced Chemical Shifts for a 1:1 Molar Ratio of Coumarin: $Pr(fod)_3$ [a]



		3	4	5	6	7	8
1	Coumarin	13.2	3.8	2.5	1.3	1.2	3.3
2	3-MeO-	(22.0)	13.0	4.4	2.5	2.2	5.0
3	4-MeO-	17.0	(2.2)	3.0	2.5	2.3	4.5
4	5-MeO-	13.9	4.3	(1.4)	1.7	1.7	3.7
5	6-MeO-	12.3	3.6	2.1	(1.1)	1.8	3.2
6	7-MeO-	11.2	3.5	1.9	1.3	(0.8)	3.0
7	8-MeO-	9.1	2.7	1.7	1.0	1.7	(1.9)
8	5,6-$(MeO)_2$-	13.9	5.6	(3.9)	(2.7)	3.8	2.7
9	5,7-$(MeO)_2$-	11.8	3.7	(1.2)	1.4	(0.8)	3.0
10	5,8-$(MeO)_2$-	10.8	3.4	(1.2)	1.7	2.1	(2.7)
11	6,7-$(MeO)_2$-	10.5	4.5	6.5	(9.4)	(9.1)	7.1
12	6,8-$(MeO)_2$-	11.7	3.4	2.2	(1.2)	2.1	(2.3)
13	7,8-$(MeO)_2$-	8.9	3.3	2.7	4.0	(5.3)	(7.4)

[a] In ppm. Values in parentheses correspond to methoxyl groups.

molar ratio of shift reagent to coumarin (*ordinate*), in similarity as is depicted in a work we performed on the structural elucidation of coumarins from *Perezia multiflora* [13]. The regression coefficients of the plotted data were always better than 0.988, showing that satisfactory correlations were obtained in the studied concentration range.

In general after two or three additions of 0.01 mmole of shift reagent to the deuteriochloroformic solutions containing 0.1 mmole of each coumarin, the signals could be adequately ascribed to the individual protons of the molecule. This was easily done from the multiplicities and the magnitude of the coupling constants in compounds **5, 6** and **7**, while in the case of coumarin (**1**) and their derivatives **2** and **3** the assignments were additionally secured performing double irradiation experiments at 90 MHz in which irradiation of the H-5 signal allowed the definitive distinction of the H-6 from the H-7 signals. Additions of shift reagent were continued and spectra were recorded until completion of five experiments. The extrapolated proton chemical shifts to zero shift reagent gave the chemical shift values included in Table I corresponding to those signals that could not be ascribed directly in the ^{1}H nmr spectra in the absence of shift reagent.

Inspection of the data summarized in Table II reveals that the most shifted proton is H-3 which is adjacent to the ester carbonyl at which the complexation occurs. The average value of the shift of H-3 is smaller than that found for H-3 in flavones [8] where a vinyl proton is also in *alpha* position to the carbonyl group. This difference reflects the better association occurring with the ketone carbonyl of flavones when compared to the association at the ester carbonyl in coumarins. It is also interesting to notice that in 4-methoxycoumarin (**3**) H-3 shifts more than in any other compound of the series, suggesting that the complexation is stronger due to an increase of electron density at the carbonyl oxygen caused by the methoxyl group. This better complexation is also evident from the fact that all induced shifts in 4-methoxycoumarin (**3**) are larger than those found in the parent compound **1**, although the relative magnitude of induced shifts follow the same order *e.g.* H-3 > H-8 > H-5 > H-6 > H-7. This trend is systematically observed in all monomethoxycoumarins thus showing the utility of this type of analysis. Furthermore, in coumarin (**1**) and the monosubstituted compounds, H-4 shows slightly greater induced shifts than H-8, with the exception of 3-methoxycoumarin (**2**) where the vicinity of the methoxyl and carbonyl groups modifies the electron availability at the oxygen for complexation. It has also been mentioned that in the presence of the shift reagent, the methoxyl group in 3-methoxycoumarin (**2**), although very highly shifted, remains as a sharp singlet in contrast to what happens in 3-methoxyflavone, where the methoxyl signal, while equally shifted, is severely broadened by the shift reagent due to a contact interaction in a bidentate type complexation [8].

All protons in 5,7-dimethoxycoumarin (**9**) show similarly induced shifts as those obtained for the parent molecule **1**, and their derivatives at C-5 (**4**) and at C-7 (**6**). The situation is slightly different for 5,8- (**10**) and 6,8-dimethoxycoumarin (**12**). In these two cases the methoxyl group at C-8 and H-7 are slightly more shifted than the same signals when present in 8-methoxycoumarin (**7**) and in other simple molecules of this series. A tentative plausible explanation to account for these results is to consider that a very weak second complexation occurs at the 8-methoxyl group, perhaps with some assistance of the ethereal lactone oxygen. In favor of this argument is also the fact that in those coumarins having two methoxyl groups in *ortho* distribution (**8, 11** and **13**) a second complexation at these methoxyl groups is clearly evident from the much greater shifts that are induced. This phenomenon was already observed (**6**) in an isolated case studied with Eu(fod)$_3$, although a contrasting example showing only carbonyl complexation has also been described [14] despite the presence of 6,7-dimethoxy substitution in both cases.

Thus the individual methoxyl resonance signals in compounds **8, 11** and **13** were specifically ascribed to the substituents considering the second complexation combined with the magnitudes of the shifts of all other methoxyl signals. The complexation of the lanthanide to a pair of *ortho* methoxyl groups in coumarins appears to be a pseudocontact interaction since the methoxyl signals are not broad. This is in contrast to what happens in flavones where either no second association is evident from the induced chemical shift magnitudes in cases having two *ortho* or even three *vicinal* methoxyl groups or where a strong contact interaction is evident from severe signal broadening of some methoxyl signals [9].

It can be concluded that the use of Pr(fod)$_3$ shift reagent provides sufficient simplification of the ^{1}H nmr spectra of coumarins at 60 MHz as to allow specific signal assignments that might be of further utility for other related molecules.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were determined on Varian Associates A-60 and EM-390 spectrometers in deuteriochloroform containing TMS as the internal standard. Least-square adjustments were done on a Hewlett-Packard 9100A desk computer.

Shift Reagent Study.

A solution containing 0.1 mmole of the individual coumarin in 0.3 ml of deuteriochloroform was used to record the original spectrum. After addition of 0.01 mmole of the shift reagent the spectrum was recorded again and this procedure was repeated until five shift reagent additions were completed. The chemical shifts of each individual signal in each spectrum were plotted *(abscissa) versus* the shift reagent to coumarin

molar ratio and the obtained lines were evaluated by least-square adjustments.

Coumarins.

Compounds **1**, **5**, **6**, **7**, **9**, **10**, **11** and **13** were available from a charge density-^{13}C nmr chemical shift study [15], while molecules **2** and **3** were also available from a natural products study [13]. A sample of 5-methoxycoumarin (**4**) was prepared following a known sequence of reactions [16]. Similarly in the case of 5,6-dimethoxycoumarin (**8**) a sample was prepared from 6-hydroxycoumarin [17]. To our surprise, a preparation of 6,8-dimethoxycoumarin (**12**) was not found in the literature. Therefore it was obtained as outlined below.

6,8-Dimethoxycoumarin (**12**).

Treatment of 2,4-dimethoxyacetophenone (Aldrich) with *m*-chloroperbenzoic acid followed by hydrolysis gave the known 2,4-dimethoxyphenol [18] in 65% yield. Conversion of the latter into 3,5-dimethoxy-2-hydroxybenzaldehyde was achieved by Reimer-Tiemann reaction [19] in 27% yield. The compound had mp 123-125° (from ethanol); ^{1}H nmr: 10.5 (s, hydrogen bonded hydroxyl disappearing upon addition of deuterium oxide), 9.7 (s, aldehyde), 6.78 (d, J = 2.5 Hz, H-6), 6.60 (d, J = 2.5 Hz, H-4), 3.92 and 3.81 ppm (2s, methoxyls). Knoevenagel condensation [20] of 3,5-dimethoxy-2-hydroxybenzaldehyde with malonic acid in the presence of aniline during 48 hours at room temperature, followed by decarboxylation by vigorous heating, gave the desired sample of 6,8-dimethoxycoumarin (**12**), mp 100-102° in 15% yield. The ^{1}H nmr spectral data are included in Table I.

The isolation of 6,8-dimethoxycoumarin (**12**) from a natural source has been claimed recently [21]. However the reported mp of 146-148° is in contrast to our value of 100-102° for **12**, but is in close agreement to the mp 149-150° described by us [15] and to that of 147° reported by others [22] for commercially available. (Aldrich, mp 148-150°) 5,7-dimethoxycoumarin (**9**).

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