NMR SPECTRA OF NATURAL COUMARIN DERIVATIVES

I. Coumarins

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The NMR spectra of some synthetic derivatives of coumarins were investigated for the first time by Dharmatti et al. [1]. Subsequently, with a number of coumarin derivatives containing alkyl and O-alkyl substituents, we showed [2] that the NMR spectra permit the type of substitution of the coumarin nucleus to be determined.

This paper gives the results of a consideration of the NMR spectra of a large number of coumarins. This consideration was carried out with the main structural factors determining the chemical shifts in aromatic and heteroaromatic systems being taken into account. As is well known, for such systems a good correlation between the chemical shift (CS) of the protons and the π-electron density (ED) on the carbon atom is frequently observed [3-5]. Another important factor determining the position of the proton signals in these systems is the anisotropy of the magnetic susceptibility of the aromatic ring.

We obtained the ED figures used in this paper by calculations of the molecules by the MO LCAO method in Hückel's approximation. The calculations were carried out with the same parameters as in a previous paper [6] (the program of calculation was kindly provided by A. V. Tutkevich). The effects connected with the magnetic anisotropy of the rings and other groups were considered only in qualitative form.

Table 1 gives the values of the CS and the spin-spin coupling constants of the protons found* and Table 2 gives the values of the π-electronic charges on the ring carbon atoms and also on the carbon atoms of the methoxy and acetoxy groups attached to the aromatic ring.

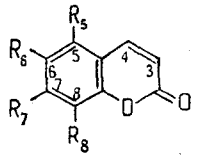
The distribution of ED in the coumarin molecule (I) permits the assumption that the signals from H_3 will appear in the strongest field and that from H_4 in the weakest field. In actual fact, the spectrum of coumarin has two doublets, at 6.44 and 7.76 ppm, with spin-spin coupling constants of 9.8 Hz, due to the protons in positions 3 and 4, respectively. Between them there is a complex multiplet relating to the protons of the benzene nucleus, forming an ABCD four-spin system. The calculation of this system for the spectrum of coumarin in tetrahydrofuran obtained on a 60 MHz instrument has been carried out by Dharmatti et al. [1].

It must be noted that the spectrum calculated from the parameters obtained for 100 MHz did not agree with the experimental spectrum in tetrahydrofuran. It is natural that these parameters did not describe the spectrum of coumarin in CCl_4 or $CDCl_3$. In view of this, we calculated the benzene part of the spectrum of coumarin taken at 100 MHz. The spectra of coumarin in CCl_4 and $CDCl_3$ are extremely similar. Because the positions of the lines the assignment of which to transitions is more or less unambiguous agree fairly well in these two solvents, we used the spectrum in CCl_4 for the calculation, since in this case there is no superposition of the bands of the $CHCl_3$ in the $CDCl_3$ on the coumarin spectrum.

The calculation was carried out by a program based on an algorithm of Swalen and Reilly [7]. The number of lines for which the frequencies and, less accurately, the intensities were determined only slightly exceeds the number

*The spectra were obtained on a JNM-4H-100/100 MHz instrument (in deuterochloroform) with the signal from tetramethylsilane being taken as 0.

Table 1. NMR Spectra of Coumarins

Compound 	Chemical shift and coupling constant (δ, ppm, multiplicity*, J Hz)								
	aromatic protons					aliphatic protons			
	3	4	5	6	8	*a*	*b*	*c*	*d*
Coumarin (I) $R_5=R_6=R_7=R_8=H$	6.44 (d; 9.8)	7.76 (d; 9.8)	—	—	—	—	—	—	—
7-Methoxycoumarin (herniarin) (II) (II) $R_5=R_6=R_8=H$; $R_7=OCH_3$ *(a)*	6.25 (d; 10.0)	7.66 (d; 10.0)	7.39 (d; 7.8)	6.86 (q; 7.8; 2.5)	6.80 (d; 2.5)	3.86 (s)	—	—	—
7-Acetoxycoumarin (III) $R_5=R_6=R_8=H$ $R_7=O-\overset{\overset{O}{\|}}{C}-CH_3$ *(a)*	6.43 (d; 10.0)	7.74 (d; 10.0)	7.53 (d; 8.0)	7.09 (q; 8.0; 2.0)	7.14 (d; 2.0)	2.41 (s)	— —	— —	— —
7-Isopentenyloxycoumarin (IV) $R_5=R_6=R_8=H$ $R_7=-O-\underset{(b)}{CH_2}-\underset{(c)}{CH}=\overset{CH_3}{\overset{\diagup}{C}}{}_{\diagdown CH_3}$ *(a)*	6.21 (d; 10.0)	7.63 (d; 10.0)	7.36 (d; 9.4)	6.82 (q; 9.4; 2.0)	6.78 (d; 2.0)	1.81 1.77 (s)	4.56 (d; 6.4)	5.46 (t; 6.4)	—
6,7-Dimethoxycoumarin (scoparone) (V) $R_5=R_8=H$ $R_6=\underset{(a)}{OCH_3}$, $R_7=\underset{(b)}{OCH_3}$	6.35 (d; 10.0)	7.70 (d; 10.0)	6.94 (s)	— —	6.90 (s)	4.01 (s)	4.04 (s)	—	—
6-Isopentenyl-7-methoxycoumarin (VI) (suberosin) $R_5=R_8=H$; $R_7=\underset{(a)}{OCH_3}$ $R_6=-\underset{(c)}{CH_2}-\underset{(d)}{CH}=\overset{CH_3}{\overset{\diagup}{C}}{}_{\diagdown CH_3}$ *(b)*	6.22 (d; 10.0)	7.63 (d; 10.0)	7.18 (s)	—	6.74 (s)	3.89 (s)	1.76 1.70 (s)	3.29 (d; 7.5)	5.27 (t; 7.5)
8-Isopentenyl-7-methoxycoumarin (osthole) (VII) $R_5=R_6=H$; $R_7=OCH_3$ *(a)* $R_8=-\underset{(c)}{CH_2}-\underset{(d)}{CH}=\overset{CH_3}{\overset{\diagup}{C}}{}_{\diagdown CH_3}$ *(b)*	6.23 (d; 10.0)	7.61 (d; 10.0)	7.30 (d; 8.2)	6.83 (d; 8.2)	—	3.91 (s)	1.84 1.66 (s)	3.48 (d; 6.3)	5.21 (t; 6.3)
6-Hydroxy-5,7-dimethoxycoumarin (fraxinol) (VIII) $R_8=H$; $R_6=OH$ *(c)* $R_5=\underset{(b)}{OCH_3}$; $R_7=\underset{(a)}{OCH_3}$	6.42 (d; 10.0)	8.11 (d; 10.0)	—	—	6.79 (s)	4.10 (s)	4.16 (s)	5.76 (s)	—
6-Acetoxy-5,7-dimethoxycoumarin (fraxinol acetate) (IX) $R_8=H$; $R_5=\underset{(b)}{OCH_3}$ $R_6=-O-\underset{\underset{O}{\|}}{\overset{(c)}{C}}-CH_3$; $R_7=\underset{(a)}{OCH_3}$	6.34 (d; 10.0)	8.00 (d; 10.0)	—	—	6.75 (s)	3.96 (s)	4.03 (s)	2.46 (s)	—

*s) singlet; d) doublet; t) triplet; q) quartet

of energy levels for a ABCD system. This leads to some ambiguity in the assignment of the lines and, consequently, to some close sets of parameters, differing from one another by not more than ~1 Hz. Table 3 gives the set of parameters for which the best agreement between the calculated and experimental spectra at 70 and 100 MHz is achieved. The values of the ED on the corresponding carbon atoms are based on the assignment proposed in Table 3.

Table 2. Calculated π-Electronic Charges on the Carbon Atoms of Some of the Compounds Studied*

Compound	q_3	q_4	q_5	q_6	q_7	q_8	q_a	q_b	q_c
Coumarin (I)	−0.065	+0.086	+0.016	−0.028	+0.019	−0.045	—	—	—
Herniarin (II)	−0.088	+0.087	+0.021	−0.073	—	−0.102	+0.105	—	—
7-Acetoxy-coumarin (III)	−0.084	+0.087	+0.020	−0.066	—	−0.093	+0.036	—	—
Scoparone (V)	−0.089	+0.085	−0.046	—	—	−0.100	+0.104	+0.104	—
Fraxinol (VIII)	−0.112	+0.090	—	—	—	−0.135	+0.104	+0.104	—
Fraxinol acetate (IX)	−0.112	+0.090	—	—	—	−0.136	+0.104	+0.104	+0.036

*The numbering of the compounds and the labelling of the atoms is the same as in Table 1.

The introduction of substituents into the benzene nucleus of coumarin simplifies the part of the spectrum due to the aromatic protons. On considering the total π-electronic charges in the molecule of 7-methoxycoumarin (II) it is seen that the proton in position 8 must undergo the greatest screening through ED. However, this proton must also undergo considerable descreening as a result of the anisotropic influence of the benzene and pyrone rings. The combined action of these two factors leads to the situation that, although the signal from H_8 is shifted in the strong-field direction as compared with the spectrum of coumarin, it nevertheless appears in the region of lower screening than the signals from H_3.

Table 3. Calculated Parameters of the Benzene Moiety in the NMR Spectrum of Coumarin

Chemical shift, ppm				Coupling constant, Hz					
σ_5	σ_6	σ_7	σ_8	J_{56}	J_{57}	J_{58}	J_{67}	J_{68}	J_{78}
7.44	7.19	7.45	7.23	7.4	1.7	0.7	7.7	1.5	8.5

The π-currents in the α-pyrone ring are weaker than in the benzene ring. Consequently, the signal from H_3 shifts in the weak-field direction under the influence of the anisotropy of the ring to a smaller extent than that from H_8. Furthermore, the differences in the anisotropic action of the carbonyl group (for H_3) and of the ethereal oxygen atoms (for H_8) may affect the positions of the signals of the protons mentioned. The assignment of the signals to the protons in positions 3 and 8 follows unambigously from a consideration of the spin-spin coupling constants. In actual fact, the signals at 6.25 ppm with a coupling constant of 10 Hz must be assigned to H_3 and the doublet at 6.80 ppm with $J = 2.5$ Hz to H_8.

A qualitative correspondence between the π-electronic charges and the CS is observed for the protons of the benzene nucleus (a decrease in the negative charge in the sequence C_8, C_6, C_5, and an increase in the chemical shift in the sequence H_8, H_6, H_5). The additional descreening of H_5 and H_8 under the influence of the π-currents of the α-pyrone ring is apparently insignificant.

The lowest ED is found for C_4, so that the signal from H_4 is found in the region of the weakest field ($\delta = 7.66$; $J = 10$ Hz). In principle, the same noncorrespondence with the ED as for H_3 and H_8 is possible for the signals from H_4 and H_5, but this does not in fact exist, probably for two reasons: in the first place, the difference in the charges on C_4 and C_5 is substantially greater than in the case of C_3 and C_8 and, in the second place, the difference in descreening due to the magnetic anisotropy of the rings is lower, since H_4 also undergoes the anisotropic influence of the benzene ring.

A similar picture is observed for other coumarins with O-alkyl substituents in position 7. In umbelliferone acetate (III), the 6- and 8- protons of the benzene ring undergo, in addition to a negative inductive influence of the

O-acetyl group, the influence of the magnetic anisotropy of this group, as a result of which their signals are displaced to a weaker field. It is apparently because of just this that the signal from H_8 has a greater CS than the signal from H_6, although the ED on C_6 is lower than that on C_8.

The positions of the signals of the aromatic protons in the spectrum of 7-isopentenyloxycoumarin (IV) are practically the same as in the case of 7-methoxycoumarin. The methylene and methine protons of IV give a doublet with $\delta = 4.56$ ($J = 6.4$ Hz) and a triplet with $\delta = 5.46$ ($J = 6.4$ Hz), respectively, from which the existence of free rotation round the C—C and C—O bonds may be inferred. At the same time, the methyl groups on the double bond are not equivalent and have somewhat differing values of the CS (1.77 and 1.81 ppm).

The spectrum of 6, 7-dimethoxycoumarin (IV) has a characteristic quadruplet of the protons of the α-pyrone ring and two closely adjacent singlets due to the protons in positions 5 and 8. The electron density on C_8 is somewhat higher than on C_5, which permits the signal in the stronger field to be ascribed to H_8 and that in the weaker field to H_5. The peaks of the protons of the methoxyl groups in positions 6 and 7 are also shifted with respect to one another, which is connected with the difference in the ED on the corresponding oxygen atoms. The π-electronic charge on the oxygen of the methoxyl group in position 6 is +0.089 and in position 7 it is +0.101. Thus, the protons of the 7-methoxy group must be descreened to a greater extent than the protons of the 6-methoxy group and their signals must be present in a weaker field.

A similar distribution of the signals of the aromatic protons is observed in the spectrum of suberosin (VI); the only difference is that the signal from H_5 is in a weaker field than the corresponding signal in V. This is due to the difference in the electron-donating properties of the isopentenyl and methoxyl groups; they are weaker in the latter. The part of the spectrum of VI due to the aliphatic protons is similar in structure to the same part of the spectrum of 7-isopentenyloxycoumarin: signals of two nonequivalent methyl groups on a double bond, a doublet of a methylene group, and a triplet with an intensity of one proton unit due to the methine proton on the double bond. The signals of the methyl groups, like the components of the triplet, are broadened somewhat because of the homoallyl interaction of the methine proton with the protons of the methyl groups. However, the position of the corresponding signals in the spectra of IV and VI differ substantially because in the first case the side chain is attached to the aromatic ring through oxygen and in the second case it is directly attached to the coumarin nucleus. This difference has the greatest effect on the position of the signals of the methylene proton and the least effect on the signals of the methyl group. Thus, two substituents widely distributed in the natural coumarins can be reliably distinguished by their NMR spectra.

The spectrum of an isomer of VI, osthole (VII), differs from that of VI only in the region of the aromatic protons. By analogy with II the doublet in the weaker field (7.30 ppm) is ascribed to H_5 and the doublet at 6.83 ppm to H_6.

In the spectra of fraxinol (VIII) and fraxinol acetate (IX) the SCs of the protons of the methoxyl groups have dissimilar values. Calculation shows that the total π-electronic charges on the oxygen atoms of the 5- and 7-methoxy groups of fraxinol are, respectively, +0.102 and +0.100, while in fraxinol acetate they are +0.103 and +0.101. Such a small difference in the π-electronic charges on the oxygen can hardly be the cause of the considerable difference in the CSs of the methoxyl protons. Provisionally, according to the results of calculation, the signal in the weaker field is ascribed to the 5-methoxy group and that in the stronger field to the methoxy group in position 7.

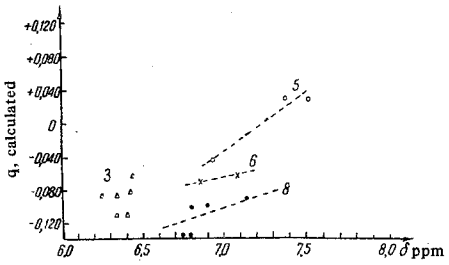
It is also interesting to consider the dependence of the chemical shifts of the protons on the magnitudes of the π-electronic charges for different molecules. In the figure, the experimental values of the CSs of the protons (δ, ppm) have been plotted along the axis of abscissas and the total electronic charges of the carbon atoms (q) along the axis of ordinates. As can be seen from the figure, no linear relationship between the chemical shifts and the π-electronic charges is observed for protons occupying different positions in the coumarin nucleus.

The deviations from linearity are due to the contribution of other factors to the magnitude of the CS and, consequently, permit an indirect judgment of the direction of the action of these factors. The main ones among them are the σ component of the electron density and the magnetic anisotropy. The contributions of each of these factors are different for different positions. An analysis of the graph permits a number of conclusions of both practical and theoretical nature.

The signals from H_3 are in the 6.25–6.45 ppm region; the values of the ED on C_3 are in the same range as for C_6 and C_8, i.e., factors exist which shift the signal from H_3 into a stronger field. We have already described one of them, the lower anisotropy of the ring. The second and third factors are the anisotropy of the C=O group and the negative induction influence of the carbonyl on the α-carbon atom, which acts in the opposite direction. The resultant action of

the first two factors prevails over the action of the third, and the signal from H_3 shifts into a stronger field. From the point of view of structural analysis, the identification of the signals from H_3 presents no difficulty: they are in the strongest field (the other signals do not come into this region, as a rule) and when there is no substituent at C_4 they are split into a 9–10 Hz doublet.

The CS from H_4 is found in the range from 7.65–8.15 ppm. The straight line passing through the points corresponding to H_4 has a very gentle slope with respect to the axis of abscissas, which shows that the SC depends only slightly on the ED on the carbon atom. The identification of the H_4 atoms from the value of the CS and the splitting constant likewise encounters no difficulties, since their signals in the spectra of the coumarins are located in the weakest field where the peaks of other protons do not appear.



Chemical shifts of the protons as functions of the π-electronic charges on the carbon atom; the figures in the diagram denote the numbers of the protons to which the given points relate (3, points of the protons at C_3; 4, points of the protons at C_4, and so on).

The signals from the C_5, C_6, and C_8 protons are present in overlapping regions and, therefore, the CS cannot be used as a basis for their reliable assignment. It can be seen from the figure that the points of the protons of different types (H_5, H_6, and H_8) are grouped about three straight lines lying one under the other, which is analogous to the displacement with respect to one another on the scale of chemical shifts.

The straight line corresponding to the protons at C_8 is shifted into the region of the strongest field. Such a systematic displacement of the signals from H_8 may be connected with the negative induction effect and influence of the magnetic anisotropy of the unshared pairs of the heterocyclic oxygen atoms and also of the oxygen atom attached in position 7.

It is interesting to note that in spite of the fact that the points of each type of proton do not lie on, but are only grouped round, the corresponding straight lines, as a rule a greater electron density on a carbon atom corresponds to a lower value of the CS of the proton. This permits the graph shown to be used for purposes of structural analysis. Such a necessity may arise where three substituents are present in the benzene ring, when the spin-spin coupling constant and the comparative position of the signals are now incapable of giving additional information, and the value of the CS of the remaining protons will have decisive value. In this case the electron density on the ring atoms of carbon may be calculated for all the alternative structures. By making use of the corresponding straight line (see figure) it is possible to determine the CS expected for a given structure. That structure for which the value of the CS of the proton found will be closest to the experimental value may be regarded as the most probable.

The solution of such problems is also possible by another method, based on the use of an additive scheme. On the basis of the experimental results for compounds I–IX the averaged contributions from the substituents most frequently encountered in the natural coumarins and the values of the CSs of the protons of the benzene moiety of the molecule were found. The chemical shift of the corresponding proton in the molecule of coumarin was taken as the initial magnitude (see Table 3). The contributions obtained in this way are given in Table 4.

In Table 5 the CS of the aromatic protons found experimentally and calculated are compared for the same compounds using the averaged increments from Table 4.

The material presented permits the use of the results of NMR spectroscopy for studying the structure of new coumarins [8, 9].

Table 4. Contributions from Various Substituents (ppm) to the Chemical Shift of the Protons of the Benzene Nucleus in the NMR of the Spectra of the Coumarins

Substituent	Ortho	Meta	Para
CH_3O-	−0.33	−0.05	−0.30
$CH_3-\overset{\overset{O}{\|\|}}{C}-O-$	−0.10	+0.09	—
$(CH_3)_2C=CH-CH_2-O-$	−0.41	−0.08	−0.15
$(CH_3)_2C=CH-CH_2-$	−0.26	−0.14	−0.15
$OH-$	—	+0.13	—

Table 5. Comparison of the Chemical Shifts of the Aromatic Protons Obtained Experimentally and Calculated by the Use of Averaged Increment

Compound	δ_3		δ_6		δ_8	
	calc.	exp.	calc.	exp.	calc.	exp.
Herniarin	7.39	7.39	6.81	6.86	6.85	6.80
7-Acetoxycoumarin	7.53	7.53	7.09	7.09	7.13	7.14
7-Isopentenyloxycoumarin	7.36	7.35	6.78	6.82	6.82	6.78
Scoparone	7.12	6.94	—	—	6.91	6.90
Suberosin	7.18	7.18	—	—	6.82	6.74
Osthole	7.30	7.30	6.78	6.83	—	—
Fraxinol	—	—	—	—	6.79	6.79
Fraxinol acetate	—	—	—	—	6.75	6.75

CONCLUSIONS

The NMR spectra of nine coumarin derivatives have been studied. The results obtained may be used for purposes of structural analysis.

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