Lanthanide-induced Shifts of Sterically Hindered Aromatic *o*-Dimethoxy Compounds: Model Compounds and *o*-Dimethoxycoumarins

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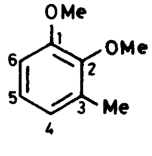
The lanthanide-induced shifts (LIS) of a series of sterically hindered *o*-dimethoxy compounds, characterized by a 3-substituted 1,2-dimethoxy unit as a structural element, were simulated in model calculations. Development of a generally suitable computational model for aromatic *o*-dimethoxy compounds allows prediction of relative LIS values for *o*-dimethoxy complexation. The model was used for several naturally occurring dimethoxycoumarins taking into account the population ratios of the two possible co-ordinating sites in these molecules (*o*-dimethoxy and lactone carbonyl).

During our studies on naturally occurring coumarin-terpenoid ethers we isolated a new coumarin derivative which turned out to be 5,6-dimethoxy-7,8-methylenedioxycoumarin (**10**).[1] One of the arguments in favour of this substitution pattern was based on lanthanide-induced shift (LIS) measurements. However, the experimental LIS values could not be interpreted in a straightforward manner. A quantitative treatment of the data is complicated by the two possible complexation sites and even qualtitative considerations seemed to disagree with the scarce literature data on other sterically hindered *o*-dimethoxy compounds.[2,3] So we found a comparatively large downfield shift for the sterically most hindered 5-methoxy group of (**10**) (in comparison with 6-OMe); however, for 10,11-dimethoxy-aporphin (**5**) the larger downfield shift was attributed[2] to the sterically less hindered methoxy group [2-OMe in (**5**)]. To clarify matters, a set of model compounds (*o*-dimethoxy compounds and coumarin itself) was used for model calculations, which in turn allowed the LIS simulation of several natural *o*-dimethoxycoumarins.

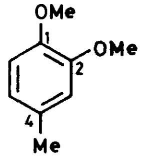
o-Dimethoxy Compounds.—Aromatic and aliphatic *o*-dimethoxy compounds co-ordinate strongly to n.m.r. shift reagents [4–6] due to a bidentate binding to the *ortho*-oxygens. This 'chelate effect'[5] is much stronger for the rigid aromatic compounds. In ref. 6 an elaborate computation of all LIS values of 1,2-dimethoxybenzene is presented using the complete expression for nonaxial symmetry of the complex including the Fermi contact contribution.

However, in numerous (much simpler) calculations of ^{1}H LIS values it was shown that the use of axial models and neglect of Fermi contact contributions for protons separated from the co-ordination site by at least three bonds usually give excellent results.[7–9] So we checked two models for *o*-dimethoxy compounds allowing the use of any one of the standard LIS programs based on the McConnell–Robertson equation. In this work the well documented PDIGM program was used.[10,11] The methoxy groups were not included in the calculations since they are prone to substantial Fermi contact contributions.

Some considerations are valid for both computational models chosen. The LIS data for the *o*-dimethoxy derivatives (**1**)—(**6**) show that the Eu^{III} position is situated symmetrically between the two oxygens, not only in the case of (**4**) and (**6**) (symmetrical substrates), but also in all other cases since comparable protons have identical relative shifts [*e.g.* 4- and 5-H in compound (**1**), see Table 1]. Moreover, comparable protons have very similar relative LIS values for all compounds studied. In the symmetrical compound (**6**) the $Eu(fod)_3$–LIS values for 4- and 5-H are 0.47 relative to 3- and 6-H = 1.00. The corresponding values for the unsymmetrical compounds (**1**) and (**3**) (with one sterically hindered OMe group) are 0.48 [for (**1**)] and 0.49 [for (**3**)]. Taking into account all data for $Eu(fod)_3$ and $Eu(dpm)_3$ (Table 1) the average value is 0.49 ± 0.04. It is interesting to note that in sterically hindered *o*-dimethoxy complexes the values for $Eu(fod)_3$ and $Eu(dpm)_3$ differ slightly, while for compounds with sterically unhindered complexation sites the LIS data are practically identical for both reagents [*e.g.* compounds (**2**), (**4**), and (**8**)]. As a consequence of the comparatively small deviations from an average value for the corresponding protons, the Eu^{III} position should deviate only slightly from an average position relative to the co-ordinating oxygens. In other words, one particular Eu^{III} position should apply to all substrate–reagent complexes of (**1**)—(**6**).



(**1**)



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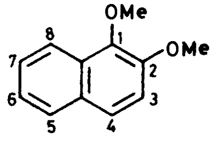
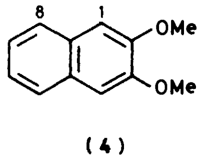
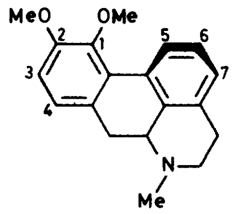


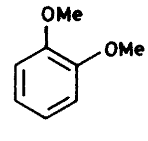
(**3**)



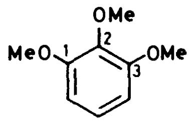
(**4**)



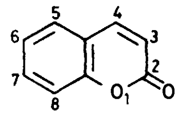
(**5**)



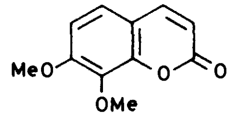
(**6**)



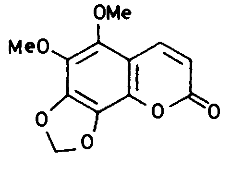
(**7**)



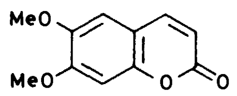
(**8**)



(**9**)



(**10**)



(**11**)

Table 1. Experimental and (calculated) LIS values for compounds (**1**)—(**11**)

		Substituent position								Calculation	
Compound	Eu(lig)$_3$	1	2	3	4	5	6	7	8	R(%)[a]	Method
(**1**)	fod	0.31 (—)	1.88 (—)	0.69 (0.64)	0.48 (0.50)	0.48 (0.50)	1.00 (1.01)			4.2	*b*
	dpm	0.36 (—)	2.09 (—)	0.68 (0.66)	0.54 (0.52)	0.54 (0.52)	1.00 (1.04)			3.7	*b*
(**2**)	fod	0.82 (—)	0.82 (—)	1.00 (0.98)	0.30 (0.33)	0.45 (0.49)	1.00 (0.98)			3.8	*b*
	dpm	0.75 (—)	0.75 (—)	1.00 (0.98)	0.30 (0.33)	0.46 (0.49)	1.00 (0.98)			3.3	*b*
(**3**)	fod	1.77 (—)	0.32 (—)	1.00 (1.04)	0.49 (0.52)	0.31 (0.31)	0.21 (0.20)	0.24 (0.24)	0.90 (0.83)	5.8	*b*
	dpm	1.86 (—)	0.43 (—)	1.00 (1.02)	0.50 (0.51)	0.30 (0.31)	0.19 (0.20)	0.19 (0.23)	0.87 (0.82)	4.7	*b*
(**4**)	fod[c]	1.00 (1.01)	0.83 (—)	0.83 (—)	1.00 (1.01)	0.36 (0.35)	0.19 (0.18)	0.19 (0.18)	0.36 (0.35)	1.6	*b*
(**5**)	fod[d]	2.00 (—)	0.19 (—)	1.00 (1.02)	0.53 (0.51)	0.61 (0.60)	−0.03 (−0.01)	0.12 (0.08)		4.2	*b,e*
(**6**)	fod[f]	0.82 (—)	0.82 (—)	1.00 (0.98)	0.47 (0.49)	0.47 (0.49)	1.00 (0.98)			2.6	*b*
(**7**)	fod[f]	0.81 (0.81)	2.84 (2.84)	0.81 (0.81)	1.46 (1.47)	0.94 (0.94)	1.46 (1.47)				*g*
		Co-ordination ratio (OMe)$_2$: C=O									
(**8**)	fod[c]			1.00 (1.00)	0.30 (0.30)	0.19 (0.18)	0.13 (0.15)	0.13 (0.15)	0.29 (0.28)	2.2	*h*
(**9**)	fod	32:68		1.00 (1.00)	0.39 (0.41)	0.38 (0.38)	0.56 (0.56)	0.35 (—)	0.80 (—)	1.5	*i*
	dpm	49:51		1.00 (1.01)	0.48 (0.48)	0.56 (0.52)	0.82 (0.84)	0.39 (—)	1.24 (—)	3.1	*i*
(**10**)	fod	11:89		1.00 (1.00)	0.38 (0.39)	0.24 (—)	0.13 (—)	0.15(0.13)		2.1	*i*
	dpm	34:66		1.00 (1.00)	0.60 (0.61)	0.84 (—)	0.40 (—)	0.24(0.20)		3.5	*i*
(**11**)	fod[j]	30:70		1.00 (1.00)	0.40 (0.40)	0.54 (0.52)	0.36 (—)	0.36 (—)	0.61 (0.63)	2.1	*i*

[a] $R(\%) = [\Sigma(\mathrm{LIS_{obs}} - \mathrm{LIS_{calc}})^2/\Sigma(\mathrm{LIS_{obs}})^2]^{\frac{1}{2}}$.[10,11] [b] Bidentate co-ordination: O · · · · Eu = 2.5 Å; Eu 35° out of the O–C=C–O plane [model (II)]. [c] For Eu(dpm)$_3$ the values were proved to be identical (±0.01). [d] Compare Ref. 2. [e] Treated as a biphenyl derivative with a torsional angle of 27°. [f] Taken from Ref. 4. [g] Additive from the experimental values of (**6**) (see Discussion). [h] Two-site model for the lactone C=O (see Figure 3). [i] Two co-ordination sites: *o*-dimethoxy parameters according to model (II) (footnote *b*); coumarin C=O parameters according to the two-site model (footnote *h*). [j] Taken from Ref. 15.

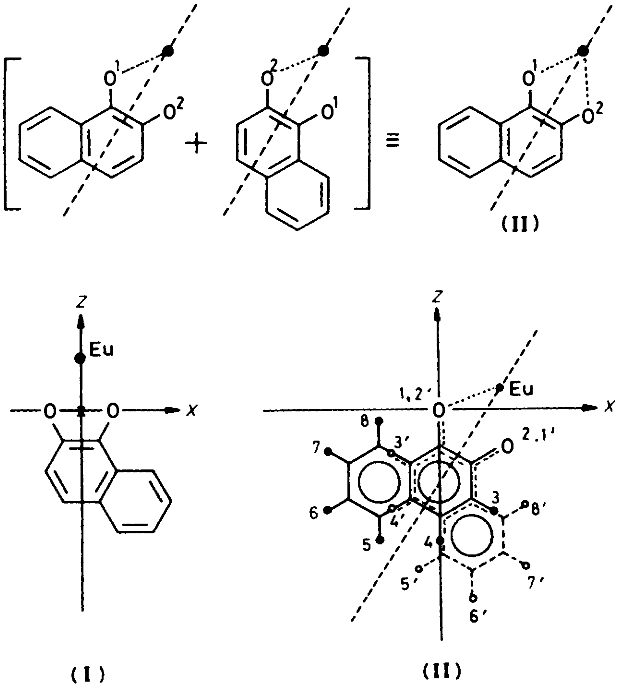


Figure 1. Models (I) and (II) for the LIS simulation of *o*-dimethoxy compounds. Model (I): hypothetical co-ordination centre between the actual ones. Model (II): superposition of two sets of molecular co-ordinates and one principal magnetic axis (equivalent to one set of co-ordinates and two magnetic axes)

Model (**I**). The simplest possible model for these experimental findings is the assumption of a hypothetical co-ordination site symmetrically between the actual ones (halfway between the two oxygens), and examination of all Eu^{III} positions equidistant to the two oxygens [model (**I**) in Figure 1]. The best possible fits for model compounds (**1**)—(**4**) were obtained for a distance of 3 Å between the Eu^{III} ion and the hypothetical co-ordination site, with an angle of 55° between the principal magnetic axis (along the line Eu–co-ordination site) and the aromatic plane (this is equivalent with the angle between the planes determined by O–Eu–O and O–C=C–O). However, the *R* factors (see footnote *a* of Table 1 and refs. 10 and 11) were not satisfactorily. Especially for compounds with protons characterized by a large angular contribution to the McConnell–Robertson equation bad *R* factors were obtained, *ca.* 8% for (**1**) and *ca.* 12% for (**3**) (fod ligand) (*R* factors < 5% indicate a good fit, *R* factors > 10% indicate a very bad model).

For the symmetrical compounds (**2**) and (**4**) with only few experimental values and all relevant protons not too far off the principal magnetic axis of the model (therefore small angular contribution) the *R* factors were smaller, 4.8% for (**2**) and 3.7% for (**4**). However, application of this model to compound (**5**) gave a very poor fit (*R* 34%). Compound (**5**) is characterized by a distorted biphenyl system reaching a rather sensitive part of the paramagnetic field in the complex (LIS values for 5-H 0.61, 6-H −0.03, and 7-H 0.12). This selective test molecule shows that model (**I**) is only suited for rather simple molecules but cannot be used generally.

Model (**II**). In model (**II**) two principal magnetic axes are presumed for the bidentate complex, along the lines connecting the two oxygen atoms with Eu^{III}. Combination of the two corresponding magnetic fields gives a new shape for the resulting magnetic field which is able to simulate the LIS values of all compounds (**1**)—(**6**) very well.

The procedure using the standard LIS program PDIGM needs some comment. The molecule is put into a Cartesian co-ordinate system with one oxygen at the origin. Figure 1 illustrates a particular example [compound (**2**)]. To account for the two magnetic axes a second molecule is defined within the co-ordinate system (dashed structure in Figure 1). The atom positions of this second molecule are symmetrical to the first one with respect to the plane bisecting the line O(1) – – – – O(2) at a right angle. In the calculations only one principal magnetic axis is necessary if the geometrical factors for corresponding positions (*e.g.* 3- and 3′-H, 8- and 8′-H, *etc.*) are averaged before scaling to the corresponding experimental data. The model (one set of co-ordinates for the substrate and two magnetic axes) is replaced by the equivalent model (two sets of co-ordinates and one magnetic axis). From Figure 1 it is evident that, for instance, the geometrical factor and therefore the calculated LIS for the arrangement O(1) - - - - Eu - - - - H(3) is identical with O(2) - - - - Eu - - - - H(3′). This is of course only valid for Eu^{III} positions equidistant from O(1) and O(2) (Eu is then within the symmetry plane).

Model (**II**) (which was already used in a similar form for 1,3-diols[12]) gave rather promising results for compounds (**1**)—(**4**) with *R* factors between 1.6 and 5.8% (see Table 1). The Eu^{III} position was off the aromatic plane by 35°, the Eu^{III} - - - - O distances were 2.5 Å (this corresponds to polar co-ordinates of r 2.5 Å, $\rho = 72°$, and $\varphi = 30°$ which may be used directly in the PDIGM program[10,11]).

The LIS values for dimethoxyaporphin as a critical and selective test molecule could be simulated with an excellent *R* factor of 4.2%. The best fit was obtained for a torsional angle of 27° between the two phenyl rings of the biphenyl moiety. The Eu^{III} position is found on the same side as the protons at positions 5 and 6 of formula (**5**). The fact that the bulky reagent is *syn* to 5- and 6-H may be surprising at first glance. However, this simply indicates that the sterically hindered methoxy group [1-OMe in formula (**5**)] points away from 5-H (*anti* to 5- and 6-H) which is a rather reasonable assumption for the substrate *and* the substrate–Eu^{III} complex; obviously the co-ordinated reagent is still less space-demanding than the directly bound methoxy group.

Model (**II**) seems to be very well suited for the LIS simulation of all aromatic dimethoxy compounds.

Methoxy-LIS. Although the LIS values for the dimethoxy groups were not used in the simulation procedure they deserve some attention. In the sterically unhindered dimethoxy derivatives (**2**), (**4**), and (**6**) the fod-LIS values are 0.82—0.83 for both methoxy groups (relative to 1.00 for the neighbouring proton). In all cases where one of the neighbouring protons was replaced by a bulky substitutent [(**1**), (**3**), (**5**)] the sterically more hindered methoxy group showed a substantial enhancement of the LIS value and the other one showed a decrease. For $Eu(fod)_3$ the corresponding values are 1.77 and 0.32 for (**3**), 1.88 and 0.31 for (**1**), and 2.00 and 0.19 for (**5**). The main reason may be a change in the conformation of the sterically hindered methoxy groups due to rotation about the C(aromatic)–O bond. However, since two lone electron pairs are available for co-ordination at each ether oxygen, the geometry in the complex seems not to be affected significantly.

The resonances (and the LIS values) of the methoxy groups were assigned by NOE experiments. For (**1**) and (**3**) the differential NOEs were measured in benzene solution because the two methoxy resonances showed much better separation in this solvent (the LIS values in $[^2H_6]$benzene are practically the same as in $CDCl_3$; see Experimental section for details). Corresponding signals in both solvents were correlated with each other by recording spectra in several mixtures of these solvents.

The LIS for (**5**) were given in the literature previously.[2] However, the larger LIS value was assigned erroneously to the sterically less hindered methoxy group. This may happen if the signals in the undoped spectra are very close; after adding the reagent it may be difficult to decide which one of the shifted OMe resonances belongs to which one of the original OMe signals of the pure substrate. The use of small amounts of reagent, thereby avoiding any abrupt changes in the lanthanide-shifted spectra, helps to overcome this difficulty.

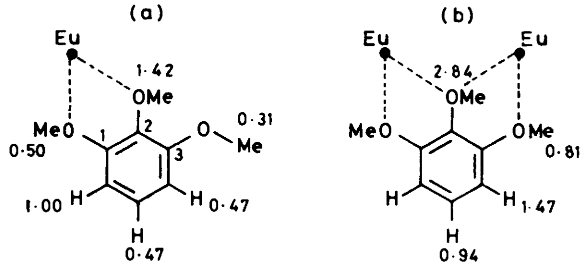


Figure 2. LIS of 1,2,3-trimethoxybenzene (**7**). (a) Hypothetical LIS values for the complex species shown: data for 4-, 5-, and 6-H taken from analogue positions of dimethoxybenzene, value for 3-OMe calculated by means of model (**II**); values for 1-OMe and 2-OMe were chosen to fit the experimental data. (b) Experimental LIS values

1,2,3-Trimethoxybenzene. A special case of a sterically hindered dimethoxy compound is 1,2,3-trimethoxybenzene (**7**). The complex of (**7**) with shift reagent may be treated formally as a mixture of two possible bidentate 1,2-dimethoxy(co-ordinated)-3-methoxy(unco-ordinated)-benzenes (Figure 2a). Using the relative values of (**6**) as a model one knows the LIS values for 4-, 5-, and 6-H. The corresponding value for the 3-OMe group may be calculated using model (**II**) for dimethoxy compounds (a planar conformation is presumed for the methoxy group;[13,14] compare Figure 2a).

Adding up symmetrical positions within the 1,2,3-trimethoxybenzene molecule gives relative LIS values of 1.47 for 4- and 6-H, and 0.94 for 5-H. Based on these relative values the experimental values[4] for the methoxy groups are: 2.84 for 2-OMe, and 0.81 for 1- and 3-OMe (see Figure 2b). The 2-OMe value is identical for both possible bidentate complexes, therefore the value for the complex species shown in Figure 2a is 2.84/2 = 1.42; the experimental value for 1- and 3-OMe (0.81) is additively composed of the uncomplexed 3-OMe contribution and the still unknown contribution of the complexed 1-OMe which must be 0.50.

The values fitting the experimental OMe-LIS (1.42 for the sterically hindered one and 0.50 for the other one) agree perfectly with the results for compounds (**1**), (**3**), and (**5**). (The assumption of equal LIS values for sterically hindered and unhindered complexed *o*-methoxy groups led to wrong conclusions concerning the third uncomplexed OMe group.[4])

Coumarins.—For coumarins, co-ordinating at the lactone carbonyl, two models for LIS calculations may be used. The simpler 'one-site model' presumes one particular (average) site for the Ln^{III} ion. This model was chosen by Gray *et al.*[15] in their extensive study on different natural coumarin derivatives.[16] To allow a simple calculation of LIS, in ref. 15 the Eu^{III} position is kept in the plane of the coumarin rings. With this restriction the best fit was obtained for an Eu^{III} position with the parameters $d = 3.0$ Å and $\rho = 24°$ (parameters defined as in Figure 3, Eu *anti* to the lactone oxygen of coumarin). Recalculation of the LIS of coumarin with newly determined experimental data (250 MHz) agree in principle completely with all results reported in ref. 15. The fit for the one-site model used in ref. 15 is characterized by *R* 4.8% (which is still good).

Nevertheless, we checked the 'two site model'[17,18] as well. In this calculation two possible complexes are assumed, according to the two non-bonded electron pairs of the (rigid) carbonyl group (for OH or OMe as co-ordinating groups an average unique lanthanide ion position is a reasonable and necessary assumption, since these groups can adopt any conformation, allowing an optimal complexation with the electron-deficient reagent).

Table 2. Bound chemical shifts for the reference protons (equal to 1.00 in Table 1), complex binding constants, and results of competition experiments for compounds (**1**)—(**4**) and (**8**)

Compound	$Eu(lig)_3$	Bound shift (reference proton)	Complex binding constant	Competition experiments		
				Equimolar mixture	Reagent	% Co-ordination
(**1**)	fod	12 ± 1	36 ± 6	(**1**):(**8**)	fod	56:44
	dpm	11 ± 1	4 ± 1		dpm	52:48
(**2**)	fod	11.5 ± 1	>100	(**2**):(**8**)	fod	94:6
	dpm	11 ± 1	55 ± 15		dpm	95:5
(**3**)	fod	12 ± 1	35 ± 8	(**3**):(**8**)	fod	54:46
	dpm	11.5 ± 1	4 ± 1		dpm	54:46
(**4**)	fod	11.5 ± 1	>100	(**4**):(**8**)	fod	84:16
	dpm	11 ± 1	26 ± 5		dpm	90:10
(**8**)	fod	13 ± 1	32 ± 6			
	dpm	12.5 ± 1	3 ± 1			

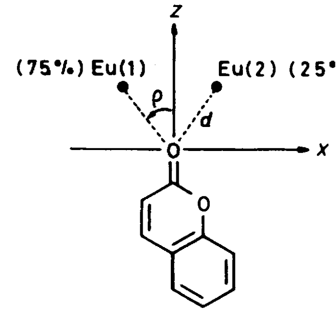


Figure 3. Two-site model for coumarins; parameters: $d = 3.0$ Å, $\rho = 35°$ for Eu(1) and Eu(2); both Eu positions are in the *xy* plane [Eu(1) *anti* to the lactone oxygen of coumarin, Eu(2) *syn*]

The parameters (*d*, ρ, φ, and the population ratio of both possible sites) were varied systematically; the arrangement with the best fit (*R* 2.2%) is shown in Figure 3 (LIS data in Table 1). A lactone carbonyl seems to behave very similarly to a ketone carbonyl group, since the site parameters are virtually the same (compare ref. 19 with a systematic study on ketones). It is interesting to note that the optimal lanthanide-ion position in the one-site model is between positions 1 and 2 of the two-site model, but closer to position 1 with the higher population ratio (75%, Figure 3). Since the fit for the two-site model is somewhat better than for the one-site model, we have used the former for all further calculations on dimethoxycoumarins (however, in principle,[20] the use of the one-site model would not change any results).

o-*Dimethoxycoumarins.*—Inspection of the LIS data for the *o*-dimethoxycoumarins (**9**)—(**11**) shows that both possible co-ordination centres, *o*-dimethoxy and carbonyl, are populated to some extent. For the determination of population ratios by additive mixing of (simulated) LIS values for *o*-dimethoxy and coumarin C=O complexes, one needs the absolute shift values ('bound' or 'limiting shifts') for the pure 1:1 complexes. The relative shift values cannot be used since they contain an unknown (and different) scaling factor for both types of complexes; the usually given extrapolated data (extrapolated to L_0:S_0 = 1:1) cannot be used either, since the extrapolated values are (only in the case of strongly binding substrates) a good approximation to the true 'bound shifts' (for weaker co-ordinating substrates the 1:1 extrapolated values are additionally a function of the substrate concentration and the binding constant of the complex formed[9,21,22]).

Limiting shifts, binding constants, competition experiments. The method of Armitage *et al.*[21,22] (a plot of S_0 *versus* $1/\Delta$ at constant L_0; S_0 and L_0 = substrate and reagent concentration, Δ = observed lanthanide-induced shift) was used to calculate the bound shifts (from the slope) and the complex binding constant (from the intercept on the S_0 axis). In Table 2 the results are summarized for the dimethoxy model compounds (**1**)—(**4**) and coumarin (**8**). The bound shifts for the reference protons next to the co-ordinating functional groups are listed [to obtain for instance the limiting shift values for other protons of (**4**)·$Eu(fod)_3$, all relative data of Table 1 have to be multiplied by 11.5]. The standard errors may be rather high using this method; however, the results are strongly supported by direct competition experiments. Equimolar mixtures of coumarin with the dimethoxy model compounds show that sterically hindered *o*-dimethoxy compounds (**1**) and (**3**) have a complexing ability comparable with the complexing ability of coumarin. In sterically unhindered compounds (**2**) and (**4**) the tendency towards complex formation is increased; complex binding constants and competition experiments agree very well (see Table 2).

LIS calculation of o-*dimethoxycoumarins* (**9**)—(**11**). The computational procedure for these compounds was as follows: (i) hypothetical values (bound chemical shifts) were calculated for a particular molecule assuming model (**II**) for dimethoxy-complexation; (ii) a set of hypothetical bound shifts for co-ordination at the lactone carbonyl (using the two-site model) was calculated; (iii) population ratios for $(OMe)_2$:>C=O were varied in steps of 1% between 0 and 100% and these mixed-complex values were scaled to the experimental data using a least-squares minimization.

The results are shown in Table 1. In all cases the carbonyl complexation site is preferred by the shift reagent. It is remarkable that for $Eu(dpm)_3$ as shift reagent the complexation at *o*-dimethoxy is increased compared with >C=O [*e.g.* for compound (**10**) 34% at $(OMe)_2$ with $Eu(dpm)_3$, only 11% with $Eu(fod)_3$; for (**9**) matters are similar]. The same effect shows up in the competition experiment of (**4**) with (**8**) (fod, 84% complexation at dimethoxy; dpm, 90% complexation at dimethoxy; see Table 2).

The relative complexing abilities of the two co-ordinating moieties in dimethoxycoumarins seem to be very sensitive to steric and electronic effects. The adjacent lactone ring decreases the tendency of co-ordination to the dimethoxy moiety: all model compounds (**1**)—(**4**) complex more strongly than coumarin (compare Table 2), for dimethoxycoumarins this is reversed (compare Table 1). Even the sterically unhindered *o*-dimethoxy of (**11**) shows a co-ordination in favour of carbonyl complexation [30:70 for $(OMe)_2$:>C=O; fod reagent]. This trend (decrease of complexing ability of the *o*-dimethoxy moiety in coumarin derivatives) leads in one sterically hindered case described in the literature to a practically negligible co-ordination of Eu(fod)$_3$ at (OMe)$_2$: for 4,6,7-trimethoxy-5-methylcoumarin[3] the population ratio (OMe)$_2$: $>$C=O is $<3\%$: $>97\%$ (using the literature data and applying the method outlined above).

The following conclusions may be drawn concerning *o*-dimethoxycoumarins. Generally both possible co-ordination centres have to be considered; however, the population ratios may differ considerably even for closely related compounds. The population ratio is usually in favour of the coumarin $>$C=O group; the use of Eu(dpm)$_3$ may increase the complexation at the *o*-dimethoxy co-ordinating site (this in turn may help to prove the *o*-dimethoxy substitution pattern and to decide between possible isomers[1]). Although the population ratios can hardly be predicted for a particular *o*-dimethoxycoumarin the lanthanide ion positions for both co-ordination centres are known and the experimental LIS can be fitted very well treating the population ratio as an additional parameter [*R* factors 1.5—3.5% for (**9**)—(**11**), see Table 1].

Experimental

The ^{1}H n.m.r. spectra were recorded on a Bruker WM-250 spectrometer equipped with an 80K Aspect 2000 computer. Compounds (**1**), (**2**), and (**4**) were prepared by methylation with diazomethane in ether–methanol from the corresponding available hydroxy compounds (reaction times up to 40 h were necessary for complete methylation). Compound (**3**) was obtained from 1,2-naphthoquinone by LiAlH$_4$ reduction, methylation, and separation from its by-product 3,3′,4,4′-tetramethoxy-1,1′-binaphthyl by t.l.c. Compound (**5**) was prepared from codeine by rearrangement in methanesulphonic acid to apocodeine, followed by methylation with diazomethane.[23] Compound (**9**) is a common natural product and (**10**) was isolated very recently from *Artemisia laciniata*.[1] Data for (**6**), (**7**), and (**11**) were taken from the literature.[4,15]

Proton chemical shifts relevant to the LIS data of Table 1 (Me$_4$Si; 250 MHz) and additional experiments to confirm the assignments of methoxy resonances are listed below; coupling constants (and multiplicities) are the usual aromatic ones and therefore omitted.

(**1**): δ(CDCl$_3$) 6.96 (5-H), 6.77 (4-H), 6.77 (6-H), 3.85 (1-OMe), 3.80 (2-OMe), and 2.28 (3-Me); δ(C$_6$D$_6$) 6.86 (5-H), 6.73 (4-H), 6.50 (6-H), 3.71 (2-H), 3.34 (1-H), and 2.26 (3-Me); irradiation at 3.34, strong differential NOE observable for the signal at δ 6.50; LIS in C$_6$D$_6$ [Eu(fod)$_3$] 0.33 (1-OMe), 1.85 (2-OMe), 0.66 (3-Me), 0.46 (4-H), 0.49 (5-H), and 1.00 (6-H).

(**2**): δ(CDCl$_3$) 6.77 (6-H), 6.70 (3-H), 6.70 (5-H), 3.87 and 3.85 (1- and 2-OMe), and 2.30 (4-Me).

(**3**): δ(CDCl$_3$) 8.12 (8-H), 7.79 (5-H), 7.62 (4-H), 7.48 (7-H), 7.36 (6-H), 7.29 (3-H), 4.00 (1- and 2-OMe); assignment of the aromatic protons either by LIS or decoupling of the doped spectra (for instance assignment of 6- and 7-H); δ(C$_6$D$_6$) 8.32 (8-H), 7.67 (5-H), 7.40 (4-H), 7.35 (7-H), 7.21 (6-H), 6.97 (3-H), 3.86 (1-OMe), and 3.47 (2-OMe); irradiation at δ 3.86, differential NOE to 8-H; irradiation at 3.47, differential NOE to 3-H; LIS in C$_6$D$_6$ [Eu(fod)$_3$] 1.74 (1-OMe), 0.40 (2-OMe), 1.00 (3-H), 0.49 (4-H), 0.29 (5-H), 0.21 (6-H), 0.23 (7-H), and 0.88 (8-H).

(**4**): δ(CDCl$_3$) 7.70 (5- and 8-H), 7.34 (6- and 7-H), 7.13 (1- and 4-H), and 4.00 (2- and 3-OMe).

(**5**): δ(CDCl$_3$) 8.23 (5-H), 7.25 (6-H), 7.10 (7-H), 7.00 (4-H), 6.83 (3-H), 3.91 (2-OMe), and 3.72 (1-OMe); for assignments see refs. 2 and 24.

(**8**): δ(CDCl$_3$) 7.74 (4-H), 7.55 (7-H), 7.51 (5-H), 7.35 (8-H), 7.30 (6-H), and 6.45 (3-H); assignments confirmed by LIS and decoupling of Eu-doped resonances.

(**9**): δ(CDCl$_3$) 7.64 (4-H), 7.18 (5-H), 6.88 (6-H), 6.27 (3-H), 4.00 (8-OMe), and 3.95 (7-OMe); assignment of the methoxy groups by aromatic-solvent-induced shifts.[25,26] The assignments of the chemical shifts of 7- and 8-OMe in CDCl$_3$ reported in ref. 26 should be reversed; the correct assignment given above was proved by a series of CDCl$_3$–C$_6$D$_6$ mixtures as solvent, adding C$_6$D$_6$ to the CDCl$_3$ solution in small incremental steps.

(**10**): δ(CDCl$_3$) 7.89 (4 H), 6.22 (3-H), 6.10 (OCH$_2$O), 3.98 (6-OMe), 3.90 (5-OMe); careful irradiation at δ 3.90, strong differential NOE for 4-H; irradiation at δ 3.98, no effect.

LIS data (Table 1) were determined by stepwise addition of Eu(fod)$_3$ or Eu(dpm)$_3$ (Merck) to *ca.* 0.05—0.15M solutions of substrate. For determination of bound shifts and complex binding constants (Table 2) substrate–reagent solutions in CDCl$_3$, 0.25M with regard to substrate and 0.015M with regard to Eu(fod)$_3$ or Eu(dpm)$_3$, were diluted in steps by known amounts of a 0.015M solution of reagent in CDCl$_3$; for the evaluation of experimental data see refs. 21 and 22. The competition experiments (Table 2) were carried out by stepwise addition of shift reagents to equimolar substrate mixtures (both 0.1M). For LIS calculations the computer program PDIGM[10,11] was used. Atom co-ordinates were calculated using the program COORD.[27] For population analysis of dimethoxycoumarins the program LIMIX was written.

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References

1 O. Hofer, G. Szabo, and H. Greger, in preparation.
2 R. V. Smith and A. W. Stocklinski, *Tetrahedron Lett.*, 1973, 1819.
3 K. K. Purushothaman, S. Vasanth, J. D. Connolly, and C. Labbe, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2594.
4 G. E. Wright and T. Y. Wei, *Tetrahedron*, 1973, **29**, 3775.
5 J. W. M. de Boer, C. W. Hilbers, and E. de Boer, *J. Magn. Reson.*, 1977, **25**, 437.
6 J. W. M. de Boer, P. J. D. Sakkers, C. W. Hilbers, and E. de Boer, *J. Magn. Reson.*, 1977, **25**, 455.
7 A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, 553.
8 F. Inagaki and T. Miyazawa, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1981, **14**, 67.
9 O. Hofer, *Top. Stereochem.*, 1976, **9**, 111.
10 M. R. Willcott, III, R. E. Lenkinski, and R. E. Davis, *J. Am. Chem. Soc.*, 1972, **94**, 1742.
11 R. E. Davis and M. R. Willcott, III, *J. Am. Chem. Soc.*, 1972, **94**, 1744.
12 O. Hofer, H. Griengl, and P. Nowak, *Monatsh. Chem.*, 1978, **109**, 21.
13 P. J. D. Park, R. A. Pethrick, and B. H. Thomas, in 'Internal Rotation in Molecules,' ed. W. J. Orville-Thomas, Wiley-Interscience, New York, 1974, p. 94; G. Allen and S. Fewster, *ibid.*, pp. 274, 275.
14 O. Hofer, *Tetrahedron Lett.*, 1975, 3415.
15 A. I. Gray, R. D. Waigh, and P. G. Waterman, *J. Chem. Soc., Perkin Trans. 2*, 1978, 391.
16 For a qualitative study on methoxycoumains see also P. Joseph-Nathan, M. Dominguez, and D. A. Ortega, *J. Heterocycl. Chem.*, 1984, **21**, 1141.
17 R. E. Lenkinski and J. Reuben, *J. Am. Chem. Soc.*, 1976, **98**, 4065.
18 B. H. S. Lienhard and A. J. Thomson, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1390.
19 O. Hofer, *Monatsh. Chem.*, 1979, **110**, 745.
20 P. Földesi and O. Hofer, *Tetrahedron Lett.*, 1980, **21**, 2137.
21 I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Commun.*, 1971, 1281.
22 I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Can. J. Chem.*, 1972, **50**, 2119.

23 F. E. Granchelli, C. N. Filer, A. H. Soloway, and J. L. Neumeyer, *J. Org. Chem.*, 1980, **45**, 2275.
24 W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, 1964, 4778.
25 R. Grigg, J. A. Knight, and P. Roffey, *Tetrahedron*, 1966, **22**, 3301.
26 F. M. Dean, A. M. B. S. R. C. S. Costa, J. B. Harborne, and D. M. Smith, *Phytochemistry*, 1978, **17**, 505.
27 QCPE Program No. 136.

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