

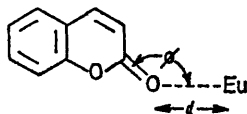
A Method for the Determination of Substitution Pattern in Coumarins using a Lanthanide Shift Reagent

By ALEXANDER I. GRAY, ROGER D. WAIGH,* and PETER G. WATERMAN

(Department of Pharmaceutical Chemistry, University of Strathclyde, Glasgow, G1 1XW)

Summary The n.m.r. shift reagent tris-(7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-octane-4,6-dionato)europium(III) [Eu(fod)₃] complexes with the carbonyl oxygen of coumarins so that all shifts can be related to a position for the europium atom in the plane of the ring and on the 3-H side of the C=O bond; relatively large shifts are produced for an 8-substituent, and information about other substituent positions can be obtained.

MANY coumarins have been isolated from plants and although modern techniques allow rapid identification of attached groups, the substitution pattern on the benzene ring may be difficult to determine. Others have attempted to correlate the substitution pattern empirically with such data as u.v. absorption¹ and chemical shift,^{1,2} and non-empirically, with long-range coupling constants² and internal nuclear Overhauser effects.³ The latter is certainly the most powerful technique but is technically more difficult and less accessible.

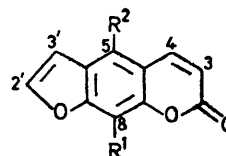


FIGURE

Normally the use of a lanthanide shift reagent to differentiate isomers requires the three-dimensional location of

where θ is the O-Eu-H bond angle and R the H-Eu distance.

The constant can be ignored since it is the same for all protons within the molecule. Calculation of values of $(3 \cos^2\theta - 1)/R^3$ for each proton then gives ratios of shifts which in many cases will fit only one likely structure. In all cases examined so far $\phi = 150 \pm 10^\circ$ and $d = 3 \pm 0.5 \text{ \AA}$.



- (1) $R^1 = \text{OMe}, R^2 = \text{H}$
(2) $R^1 = \text{H}, R^2 = \text{OMe}$

We have taken as an example the results for two isomeric methoxyfuranocoumarins, xanthotoxin (1) and bergapten (2), whose structures have been determined by synthesis.⁶ The observed and calculated shifts are given in the Table, with the values for ϕ and d obtained by trial. From u.v. spectra both must be linear. The calculated shifts for the methoxys were obtained in the maximally out-of-plane conformations, which correspond to minimum steric interactions in the stereomodels.

TABLE

Compound	ϕ	d (Å)	Shifts/p.p.m.: observed (calculated)						
			3-H	4-H	5-H	8-H	2'-H	3'-H	OMe
(1)	145	2.75	1(1)	0.25(0.26)	0.20(0.18)	—	0.10(0.10)	0.11(0.10)	0.29(0.29)
(2)	158	3.45	1(1)	0.34(0.33)	—	0.30(0.32)	0.11(0.09)	0.12(0.11)	0.14(0.13)

the lanthanide atom in the complex, a process needing a computer to achieve a 'best fit' with the observed shifts.⁴ In the present work we have striven for a simpler practical approach by reducing the problem to two dimensions, regarding the coumarin rings as planar and assuming coplanarity with the europium atom. In this way it is easy to fix the bond angle (ϕ , Figure) and O-Eu distance (d , Figure) using a field map⁵ which effectively gives lines of equal induced shift around the lanthanide atom. The coumarin 3-H is shifted most, and the shifts of the other protons are most conveniently expressed relative to shift (3H) = 1. With these ratios measured, a stereomodel of the coumarin may be placed on the (suitably scaled) field map, to give values of ϕ and d which can be used to measure θ and R for substitution in the McConnell-Robertson equation⁴

$$\Delta\nu(\text{Eu}) = \frac{3 \cos^2\theta - 1}{R^3} \times \text{constant}$$

The O-Me shift in xanthotoxin is so large that the methoxy can only be in the 8-position of the coumarin and in bergapten the shifts clearly demonstrate that the 8-position is unsubstituted.

In view of the good correlations contact shifts can be ignored, as can complexation with ether oxygens, but obviously in compounds with more powerful competing complexation sites the simple approach can only be maintained by masking the alternative electron donors. We have found, for example, that formation of the trimethylsilyl ether is an effective way of preventing interaction with the side-chain -OH groups commonly encountered in naturally occurring coumarins.

Our confidence in the generality of our method is based on experiments using Eu(fod)₃ with 6-methylcoumarin, herniarin,⁷ 4-methylherniarin, imperatorin⁷ and xanthoxyletin.⁷ Several additions of Eu(fod)₃ were used for each compound, and the relative shifts obtained graphically where possible.

We have used the method as an aid⁸ in resolving the final uncertainties concerning the structure of avicennin.⁹

Variations in ϕ and d make strict comparison between compounds difficult, but the shifts for similar substituents are always $3 \gg 4 \simeq 8 > 5 \simeq 7 > 6$.

We thank the University of Strathclyde for a grant (to A.I.G.).

(Received, 26th April 1974; Com. 470.)

¹ B. E. Nielsen, *Dansk Tidsskr. Farm.*, 1970, **44**, 111.

² W. Steck and M. Mazurek, *Lloydia*, 1972, **35**, 418.

³ T. Tomimatsu, M. Hashimoto, T. Shiugu, and K. Tori, *Chem. Comm.*, 1969, 168.

⁴ The whole field of lanthanide shift reagents has recently been reviewed: A. F. Cockerill, G. C. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, (6), 553.

⁵ R. M. Wing, T. A. Early, and J. J. Uebel, *Tetrahedron Letters*, 1972, 4153.

⁶ F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, pp. 198—208.

⁷ For structures and other data see ref. 1.

⁸ A. I. Gray, R. D. Waigh, and P. G. Waterman, in preparation.

⁹ H. R. Arthur and W. D. Ollis, *J. Chem. Soc.*, 1963, 3910.