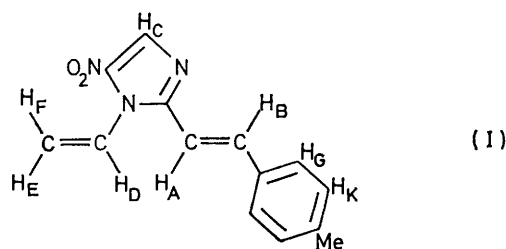


Antiparasitic Nitroimidazoles. Part V.† Interpretation of the Proton Magnetic Resonance Spectra of Olefinic Protons by Means of Additive Increments, Hammett Correlations, and the Effect of Lanthanide Shift Reagents

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A number of 2-(substituted styryl)-5-nitro-*N*-substituted imidazoles possessing antiparasitic activity have been characterised by n.m.r. spectroscopy. A full assignment of the proton resonances has been carried out by use of (i) an additive increment method for chemical shift prediction, (ii) correlations with Hammett substituent constants (σ_r , σ_m , σ_p^0), and (iii) quantitative measurements of chemical shifts induced in the title and model compounds by europium shift reagents.

THE synthesis of a series of 2-(substituted styryl)-5-nitro-*N*-substituted imidazoles has been described.¹ These compounds, particularly when the *N*-substituent



is a vinyl group, exhibit significant antiparasitic activity against *T. vaginalis* and *E. histolytica* *in vitro* and *in vivo*.¹ This paper concerns the ¹H n.m.r. spectra, from which the structures of the derivatives were mainly determined.

The ¹H n.m.r. spectrum of 1-vinyl-5-nitro-2-(4-methylstyryl)imidazole (I) in CDCl₃ is shown in Figure 1. Interpretation is straightforward and the magnitude of the coupling constant J_{AB} (16 Hz) is consistent with a *trans*- rather than a *cis*-styryl double bond, for which $J_{AB} < 12$ Hz.² The only uncertainty in the assignment concerns the relative chemical shifts of the hydrogens H_A and H_B. We have approached this problem using (i) additive increments in the estimation of chemical shifts of olefinic hydrogens, (ii) linear free-energy relationships, and (iii) europium-induced chemical shifts.

EXPERIMENTAL

Styrylimidazoles.—All the derivatives, which were prepared by Dr. W. J. Ross and Mr. W. B. Jamieson,^{1,3} had satisfactory spectral properties and microanalyses.

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³ W. J. Ross and W. B. Jamieson, *J. Medicin. Chem.*, in the press.

⁴ W. J. King and F. F. Nord, *J. Org. Chem.*, 1949, **14**, 407.

⁵ A. L. Wilds, L. W. Beck, W. J. Close, C. J. Djerassi, J. A. Johnson, T. L. Johnson, and C. H. Shunk, *J. Amer. Chem. Soc.*, 1947, **69**, 1985.

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Miscellaneous Substituted Ethylenes.—Samples of *trans*-2-thienylacrylic acid⁴ and *trans*-4- α -naphthylbut-3-en-2-one⁵ were prepared by Mr. J. P. Verge and Mrs. C. E. Smith, respectively, and had m.p.s in agreement with the literature values. 4-Hydroxymethylstyrene (n_D^{25} 1.5690, lit.,⁶ n_D^{25} 1.5725) was prepared from 4-bromostyrene.^{6,7}

¹H N.m.r. Spectra.—All spectra were recorded on an A-60A Varian n.m.r. spectrometer at 37 °C in CDCl₃. In most cases the substrate concentrations ranged from 50 to 60 mg/ml and experiments with a few derivatives showed the chemical shifts of the H_A and H_B hydrogen atoms were concentration-independent over this range.

DISCUSSION

Estimation of the Chemical Shifts of Olefinic Hydrogens by Use of the Additive Increment Method.—A number of authors have found that the approximate additivity of substituent effects can be used with considerable effect in the assignment of the chemical shifts of olefinic hydrogens.⁸⁻¹⁵ Simon and Sternhell and their co-workers¹³ expressed the chemical shift in terms of equation (1), in which the base value of δ 5.25 is assumed for ethylene and Z^i is the respective shielding increment of the substituent, for the *gem*-, *cis*-, and *trans*-orientations to the olefinic hydrogen. In our series, as all the styryl compounds are *trans*, we are concerned only with Z^i_{cis}

$$\delta = \text{base value} + \sum_i Z^i \quad (1)$$

and Z^i_{gem} and the chemical shifts of hydrogens H_A and H_B in (II) can be expressed by the relationships (2) and (3). Thus, from the observed values of δ_A and δ_B and the known shielding increments Z^x_{cis} and Z^x_{gem} , the values of the additive increments for the

⁷ J. R. Leebrick and H. E. Ramsden, *J. Org. Chem.*, 1958, **23**, 935.

⁸ L. M. Jackman and S. Sternhell, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1968, ch. 2.

⁹ E. B. Whipple, J. H. Goldstein, and G. R. McClure, *J. Amer. Chem. Soc.*, 1960, **82**, 3811.

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¹² C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, 1966, **49**, 164.

¹³ U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, 1969, **25**, 691.

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¹⁵ S. W. Tobey, *J. Org. Chem.*, 1969, **34**, 1281.

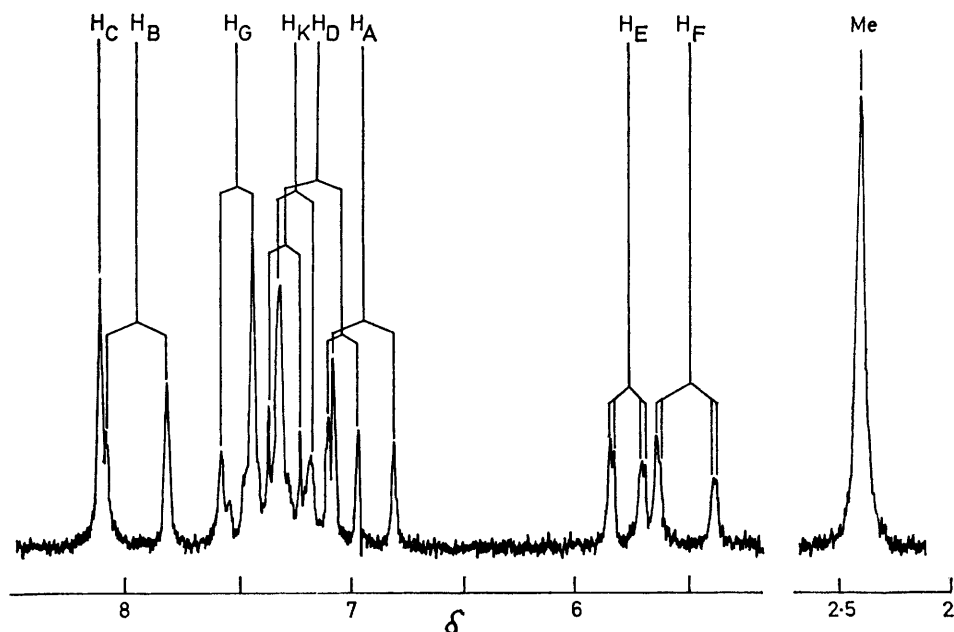


FIGURE 1 N.m.r. spectrum of compound (I)

TABLE I

Calculated additive shielding increments for olefinic hydrogens of 2-(substituted styryl)-5-nitro-*N*-substituted imidazoles

A: (II; R = vinyl)

X	Z_{gem}^x	Z_{cis}^x	δ_A	δ_B	$Z_{imid_{gem}}$	$Z_{imid_{cis}}$	δ_A	δ_B	$Z_{imid_{gem}}$	$Z_{imid_{cis}}$
Ph	1.38 ^a	0.36 ^a	7.92	6.98	2.31	0.35	6.98	7.92	1.37	1.29
<i>p</i> -ClC ₆ H ₄	1.44 ^b	0.48 ^b	7.83	6.91	2.10	0.23	6.91	7.83	1.18	1.14
<i>p</i> -MeOC ₆ H ₄	1.25 ^b	0.38 ^b	7.85	6.81	2.22	0.31	6.81	7.85	1.18	1.35
<i>p</i> -Pr ⁱ C ₆ H ₄	1.14 ^c	0.19 ^c	7.90	6.86	2.46	0.47	6.86	7.90	1.42	1.51
2-Furyl	0.94 ^d	0.21 ^d	7.60	6.87	2.14	0.68	6.87	7.60	1.41	1.41
2-Thienyl	1.25 ^e	0.08 ^e	7.95	6.89	2.62	0.39	6.89	7.95	1.56	1.45
1-Methyl-2-imidazolyl	1.37 ^f	0.84 ^f	7.66	7.38	0.76	1.57	7.38	7.66	1.04	1.29
1-Naphthyl	1.96 ^g	0.38 ^g	8.69	7.12	3.06	-0.09	7.12	8.69	1.49	1.48
			Average value		2.19	0.47			1.32	1.36
			Average deviation		± 0.40	± 0.32			± 0.14	± 0.08

B: (II; R = Me)

Ph	1.38 ^a	0.36 ^a	7.89	6.87	2.28	0.24	6.87	7.89	1.26	1.26
<i>p</i> -Pr ⁱ C ₆ H ₄	1.14 ^c	0.19 ^c	7.85	6.83	2.41	0.44	6.83	7.85	1.39	1.46
2-Pyridyl	1.50 ^f	0.97 ^f	7.90	7.57	1.68	0.82	7.57	7.90	1.35	1.15
4-Pyridyl	1.37 ^h	0.65 ^h	7.87	7.10	1.97	0.48	7.10	7.87	1.20	1.25
			Average value		2.08	0.49			1.30	1.28
			Average deviation		± 0.26	± 0.16			± 0.07	± 0.09

C: (II; R = [CH₂]₂OAc)

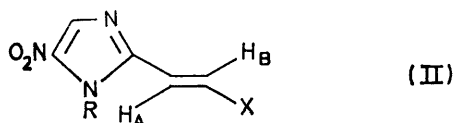
Ph	1.38 ^a	0.36 ^a	7.90	6.98	2.29	0.35	6.98	7.90	1.37	1.27
<i>p</i> -Pr ⁱ C ₆ H ₄	1.14 ^c	0.19 ^c	7.89	6.92	2.45	0.53	6.92	7.89	1.48	1.50
2-Pyridyl	1.50 ^f	0.97 ^f	7.92	7.60	1.70	0.85	7.60	7.92	1.38	1.17
			Average value		2.15	0.58			1.41	1.31
			Average deviation		± 0.30	± 0.19			± 0.04	± 0.12

^a From ref. 13. ^b Calculated from n.m.r. of corresponding styrene: Varian catalogue. ^c Calculated from n.m.r. of *trans*-*p*-PrⁱC₆H₄ CH_A=CH_BCO₂H, H_A = 7.80, H_B = 6.41, (Perkin-Elmer collected spectra) using data for CO₂H from ref. 13. ^d Calculated from n.m.r. of *trans*-2-furyl-CH=CHCHO (Varian catalogue) using data for CHO from ref. 13. ^e Calculated from n.m.r. of *trans*-2-thienyl-CH_A=CH_BCO₂H, H_A = 7.91, H_B = 6.30, using data for CO₂H from ref. 13. ^f Calculated from n.m.r. of *trans*-*N*-methylpyrrol-2-yl-CH_A=CH_B-2-pyridyl, H_A = H_B = 7.59, and 2-pyridyl-CH=CH₂ (Varian catalogue) *i.e.*, $Z^{2\text{-pyridyl}}_{gem} = 1.50$, $Z^{2\text{-pyridyl}}_{cis} = 0.97$. ^g Calculated from n.m.r. of *trans*- α -naphthyl-CH_A=CH_BCOMe, H_A = 8.31, H_B = 6.75, and data for COMe from ref. 13. ^h Calculated from n.m.r. of 4-vinylpyridine (Varian catalogue).

imidazole substituents (Z^{imid}) can be determined. Using both possible assignments for H_A and H_B we have calculated the values of $Z^{\text{imid}}_{\text{gem}}$ and $Z^{\text{imid}}_{\text{cis}}$ (Table 1).

$$\delta_A = 5.25 + Z^{\text{imid}}_{\text{gem}} + Z^x_{\text{cis}} \quad (2)$$

$$\delta_B = 5.25 + Z^{\text{imid}}_{\text{cis}} + Z^x_{\text{gem}} \quad (3)$$



Our most detailed studies concern the *N*-vinyl series and clearly the spread in the values of the shift increments is smaller if the higher-field doublet of the *trans*-double bond is assigned to H_A and the lower-field signal to H_B . Results for the *N*-methyl and *N*-2-acetoxyethyl series support this assignment. Unlike most of the substituents X used in our calculations, the 2-substituted imidazoles influence the chemical shift of the *cis*- and *gem*-olefinic hydrogens to a similar extent.

From our values of $Z^{\text{imid}}_{\text{gem}}$ and $Z^{\text{imid}}_{\text{cis}}$ for the *N*-vinyl series a number of shift increments for other substituents have been derived (Table 2). Treatment

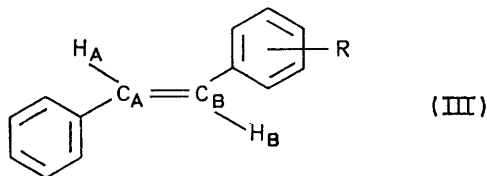
TABLE 2
New additive shielding increments for olefinic hydrogens

(II; R = vinyl) $Z^{\text{imid}}_{\text{gem}} = 1.32$ $Z^{\text{imid}}_{\text{cis}} = 1.36$

X	δ_A	δ_B	Z^x_{gem}	Z^x_{cis}
1-Naphthyl	7.32	8.28	1.67	0.75
β -Methylstyryl	6.48	7.74	1.13	-0.09
3-Pyridyl	7.03	7.91	1.30	0.46
<i>N</i> -Methyl-2-pyrrolyl	6.62	7.75	1.14	0.05
<i>N</i> -Ethylbenzimidazol-2-yl	7.86	7.86	1.25	1.29

of the substituent $-C(\text{Me})=\text{CHPh}$ as an isolated double bond¹³ gives $Z^x_{\text{gem}} = 1.24$, $Z^x_{\text{cis}} = 0.02$, values which agree closely with our experimental findings.

Correlations with Hammett Equations.—Correlation of the change in chemical shift in a series of substituted styrylimidazoles with the Hammett equation provides further support for the order of assignment of the vinylic protons in (I) and allows a dissection of the induced shifts into contributions from inductive and mesomeric effects. In compounds of type (III) H_A absorbs to high field of H_B if R is electron-withdrawing, and to low



field if R is electron-donating.^{16,17} The H_B resonance is not greatly affected by R.¹⁷

In our series of 14 2-styrylimidazole derivatives

¹⁶ C. A. Coulson and J. Jacobs, *J. Chem. Soc.*, 1949, 1983.

¹⁷ M. Güsten and M. Salzwedel, *Tetrahedron*, 1967, **23**, 173.

¹⁸ C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

(IV) (Figure 2) we find a larger variation on the high-field doublet (δ 0.29) than on the lower-field doublet (δ 0.12), supporting our assignment made in the previous section for H_A and H_B , respectively.

The chemical shifts of the H_A protons in the substituted *trans*-stilbenes correlate with a modified form (4) of the Hammett equation,¹⁷ where σ_I is the inductive

$$\delta_A = 0.15\sigma_I + 0.29\sigma_M + 7.10 \quad (r = 0.965, n = 17) \quad (4)$$

substituent constant and σ_M is the mesomeric substituent constant.^{18,19} In our series the relative weighting of the inductive and mesomeric contribution is considerably changed [equation (5)] The chemical

$$\delta_A = 0.50\sigma_I + 0.38\sigma_M + 6.98 \quad (r = 0.980, n = 10) \quad (5)$$

shifts of the H_A proton of 14 substituted styrylimidazoles correlate well with the Hammett substituent constant

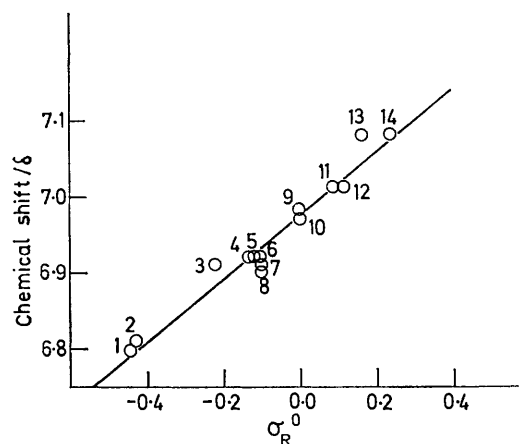


FIGURE 2 Correlation of the chemical shifts of the H_A atoms of compound (IV) with σ_R^0 : X = 1, 4-OEt; 2, 4-OMe; 3, 4-Cl; 4, 4-Bu^t; 5, 4-Bu^s; 6, 4-Prⁿ; 7, 4-Me; 8, 4-Et; 9, H; 10, 4-CH₂OH; 11, 4-CN; 12, 3-CF₃; 13, 4-CO₂Me; 14, 4-CHO

σ_R^0 (ref. 20); $\delta_A = 0.42\sigma_R^0 + 6.97$, $r = 0.974$; see Figure 2). This correlation is less satisfactory for the 17 *trans*-stilbenes ($\delta_A = 0.40\sigma_R^0 + 7.17$, $r = 0.909$). The generality of this expression is uncertain, however, as the correlation is significantly better for *para*-substituted stilbenes ($r = 0.963$, 10 points) than *meta*-derivatives ($r = 0.851$, 8 points).

As noted previously for the *trans*-stilbenes,¹⁷ the chemical shifts of the H_B protons in the styryl imidazoles do not correlate in a significant manner with any of the Hammett equations.

Europium-induced Shifts.—Addition of either of the lanthanide shift reagents, $\text{Eu}(\text{dpm})_3$ or $\text{Eu}(\text{fod})_3$, to chloroform solutions of the alcohol (V) causes downfield shifts of all protons (Figure 3), consistent with complexing at both the weakly basic 3-nitrogen of the imidazole and the hydroxy-group. In order to quantify this behaviour the model compounds (I) and (VI), which

¹⁹ M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.

²⁰ A. R. Katritzky and R. D. Topsom, *Angew. Chem. Internat. Edn.*, 1970, **9**, 87.

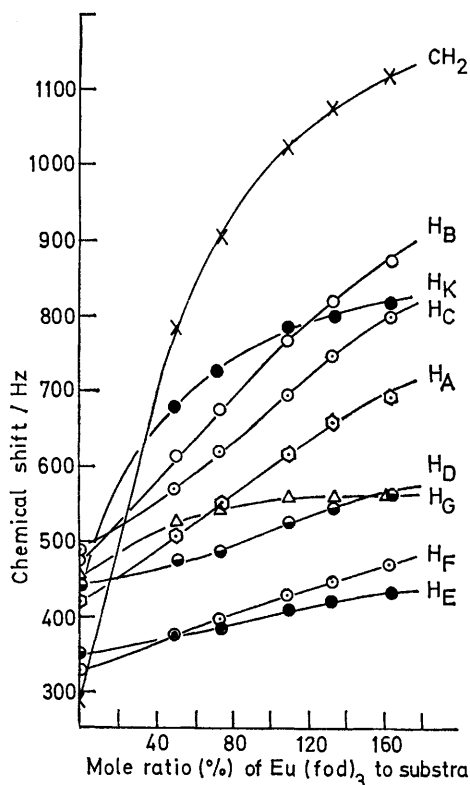
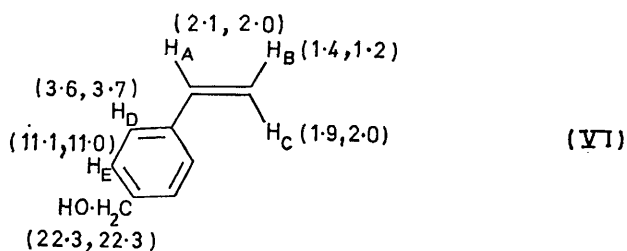
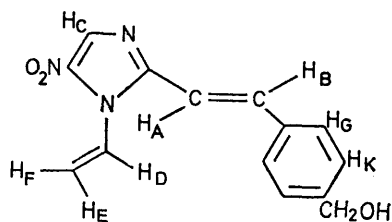
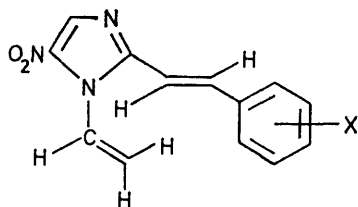


FIGURE 3 Chemical shifts of compound (V) induced by $\text{Eu}(\text{fod})_3$

each possess only one site of co-ordination, were also examined. The observed chemical shift changes for 4-hydroxymethylstyrene (VI) in the presence of $\text{Eu}(\text{fod})_3$



are illustrated in Figure 4, and are in excellent agreement with those calculated by a computer programme* with use of equation (6) to describe the pseudo-contact

$$\Delta\delta = k(3 \cos^2 \theta - 1)/r^3 \quad (6)$$

interaction.²¹ The observed chemical shift changes (including some in an upfield direction) for model compound (I) are illustrated in Figure 5. In this case, as the complexing occurs at the imidazole N(3) atom, the observed shift may reflect both contact and pseudo-contact contributions.²¹ Very poor agreement between

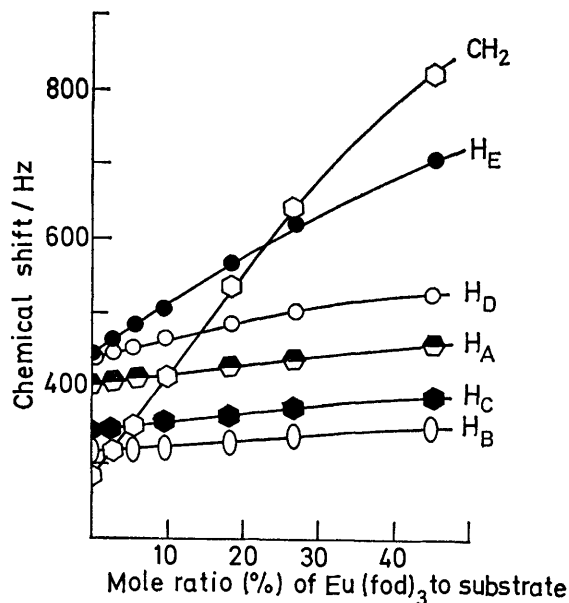


FIGURE 4 Chemical shifts of compound (VI) induced by $\text{Eu}(\text{fod})_3$. The figures in parentheses in structure (VI) refer to the observed and calculated induced shifts [equation (6)] determined from the linear portion of the graphs

observed and calculated spectra was found when it was assumed that the π system of the imidazole nucleus was coplanar with the styryl unit. However, allowance of an angle of 45° between these π systems leads to reasonable agreement between observed and predicted shifts based on pseudo-contact interaction only. To explain the observed induced shifts in compound (V), we have calculated the shift parameters, S ,²² observed for equivalent protons in model compounds (I) and (VI). These shift parameters, S , refer to the chemical shift change caused by an equivalent of lanthanide reagent [equation (5)] and are obtained from the linear portions in Figures 4 and 5. We assume the observed

* This programme optimises the position of the rare-earth atom in three dimensions with respect to the cartesian co-ordinates of this atom, the co-ordinates of the heteroatom, the co-ordinates of the substrate protons and the angle (θ) subtended by each proton with the lanthanide-heteroatom axis. We thank Dr. G. P. Moss (Queen Mary College) for supplying a copy of his programme which has been modified by Mr. G. L. O. Davies of our laboratories for this work.

²¹ H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, 1958, **29**, 1361.

²² A. F. Cockerill and D. M. Rackham, *Tetrahedron Letters*, 1970, 5149.

induced shifts for (V) arise from complexing at both the imidazole N(3) atom and the hydroxy-group. The appropriate shift parameters are related by equation (8). This approach assumes that the constant k of equation (6) is the same for all three compounds.

$$\delta_{Eu} - \delta = S[Eu(fod)_3]/[substrate] \quad (7)$$

$$S_V = aS_I + bS_{VI} + c \quad (8)$$

(a , b , and c are constants)

The very limited solubility of (V) with low concentrations of $Eu(fod)_3$ precluded measurement of quantitative proton shifts in less than 1:1 complexed forms.

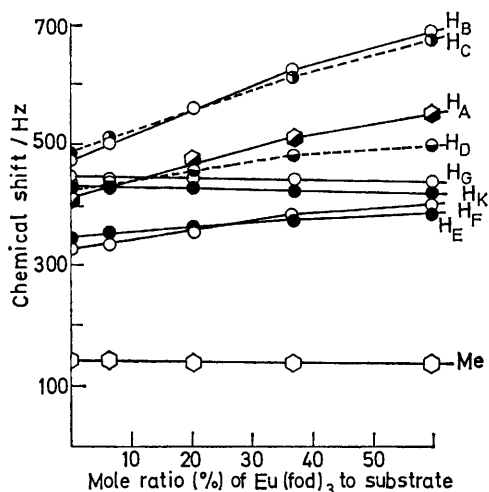


FIGURE 5 Chemical shifts of compound (I) induced by $Eu(fod)_3$

For $Eu(fod)_3$ concentrations above this level, the complex was much more chloroform-soluble. A reasonably linear relationship was found between proton shift and lanthanide concentration for $Eu(fod)_3$:substrate mole ratios of 1.1–1.8 (Figure 3). For two experiments with less than an equivalent of $Eu(fod)_3$, the solutions were filtered from undissolved solids and the position on the concentration axis estimated from interpolation of the zero and 1:1 lanthanide mole ratio readings. Reference back to the zero readings (absence of lanthanide reagent) gave a measure of the total shift experienced

owing to complexing at both sites for these estimated readings.

Trivariate computer analysis of the data (Table 3) showed that dependence on the S parameters of S_I

TABLE 3

Trivariate analysis of (V) complexing with $Eu(fod)_3$

Range of $Eu(fod)_3$: substrate concn.	% Total regression explained by regression	Test for linear effect of model †		Coefficient b/a in equation (8)
		Imidazole (I)	Alcohol (VI)	
0 to 0.70 *	99.5	207 (6)	1292 (6)	1.67
0 to 0.85 *	99.6	206 (6)	2020 (6)	1.28
0 to 1.10	99.5	69 (6)	1425 (6)	0.98
1.10 to 1.64	95.9	98 (6)	91(6)	0.25

* Estimate from Figure 3 (see text). † Figures in parentheses indicate value for 99.5% explanation of regression owing to this variable.

and S_{VI} is statistically highly significant in all cases and the computed values of b/a are a measure of the weighting of the complexation at the hydroxy (b) and imidazole (a) sites, respectively. At least 96% of the variation is accounted for by equation (8). The analysis clearly shows that the coefficient b/a (and hence the extent of complexing at the hydroxy-site) progressively decreases as the mole ratio of $Eu(fod)_3$ is increased. Concurrently, the observed variation in the chemical shift of (V) becomes statistically more dependent on the imidazole N(3) atom rather than the hydroxy-site in the molecule. In our analysis of (V) by use of equation (8) we have assumed that the shifts induced in the model compounds vary linearly with the $Eu(fod)_3$:substrate mole ratio.

Clearly from Figures 4 and 5, curvature is apparent once a ratio of greater than 40% is reached on the abscissae. Our approach is thus only satisfactory if the degree of curvature is similar for the hydrogens used in the calculation. That equation (8) explains the induced shifts of (V) over a wide range of $Eu(fod)_3$:substrate ratios bears out this assumption.

We thank Dr. W. J. Ross and Mr. W. B. Jamieson for supplying the nitroimidazoles, Mr. R. C. Harden for experimental assistance, and Mr. G. L. O. Davies for help with computation.

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