Triazene Drug Metabolites. Part 6.[1] The Interaction of *N*-Hydroxymethyltriazenes with Lanthanide-induced Shift Reagents

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Paramagnetic induced chemical shifts were obtained for a series of 1-aryl-3-hydroxymethyl-3-methyltriazenes and related compounds by the addition of $Pr(thd)_3$ or $Eu(fod)_3$. Induced shifts were shown to be pseudo-contact in origin. Qualitative work using $Pr(thd)_3$ indicated that the N–CH_2–O proton resonances are shifted the most, followed by the N–Me resonances. Neither 1-aryl-3-methyl- nor 1-aryl-3,3-dimethyl-triazenes exhibit induced shifts of the N–Me resonances, which indicates that binding of the hydroxymethyltriazenes to the lanthanide ion occurs through the hydroxyl function. Quantitative work using $Eu(fod)_3$ allowed values of Δ_B, the paramagnetic shift of the bound hydroxymethyltriazene, and K_B, the equilibrium binding constant, to be calculated. The data are consistent with 1:1 complex formation and values of K_B, which lie between 10—60 l mol^{-1}, are little affected by the aromatic substituent. Correlation of the pseudo-contact induced shifts, Δ_B, with r^3 (where r is the distance between the resonating nucleus and the Eu^{3+} ion) occurs when the hydroxymethyltriazene is assumed to bind to Eu^{3+} through the hydroxyl oxygen atom. In contrast, 3-hydroxymethyl-3-methyl-1-(3′-pyridyl)triazene binds to both Pr^{3+} and Eu^{3+} through the pyridyl nitrogen atom.

Hydroxymethyltriazenes (**2**) are metabolites of the cancer chemotherapeutic dimethyltriazene drugs (**1**) [equation (1)].[2] The reaction outlined in equation (1) is generally considered the

$$\underset{(1)}{Ar{-}N{=}N{-}NMe_2} \xrightarrow[\text{oxidation}]{\text{enzymic}} \underset{(2)}{ArN{=}N{-}N\!\!<^{CH_2OH}_{Me}} \quad (1)$$

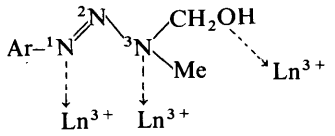
route by which dimethyltriazenes are activated and to which their therapeutic action can be ascribed.[3] The compounds (**2**) may be the possible form of the drug which is transported in the bloodstream,[3] and may undergo either direct interaction with nucleophiles[4] or loss of formaldehyde to form a monomethyltriazene which can itself react with nucleophiles[5] [equation (2)].

$$Ar{-}N{=}N{-}N\!\!<^{CH_2Nu}_{Me} \xleftarrow[-H_2O]{NuH} Ar{-}N{=}N{-}N\!\!<^{CH_2OH}_{Me} \xrightarrow{-HCHO} Ar{-}N{=}N{-}NHMe \xrightarrow{NuH} NuMe + ArNH_2 \quad (2)$$

Hydroxymethyltriazenes (HMTs) and their derivatives have consequently been receiving attention recently,[6] not least because dimethyltriazenes are poorly metabolised by humans[7] and HMTs circumvent the requirement for metabolic activation.

As part of a wider investigation of the chemistry of HMTs and their derivatives we have been interested in the decomposition reaction between HMTs and various metal ions.[8] In order to obtain a greater insight into the mode of binding between HMTs and transition metal ions prior to decomposition, we have studied the interaction of some HMTs and related compounds with two lanthanide shift reagents and herein report our results. A similar approach was used to study the decarboxylation of oxalacetic acids.[9]

The hydroxymethyltriazene functional group provides three possible sites for ligand binding: the triazene N-1 and N-3 nitrogen atoms or the hydroxyl oxygen atom, and it is feasible that, as well as functioning as monodentate ligands, HMTs may bind to the metal ion in a bidentate mode.



Experimental

All the hydroxymethyltriazenes were synthesised by known procedures[10,11] and were analytically pure. Acetate and methyl ether derivatives of the HMTs[12] were a generous gift of Dr. K. Vaughan, St. Mary's University, Halifax, Nova Scotia. Monomethyl- and dimethyl-triazenes were synthesised by standard methods.[13,14] [^{2}H]Chloroform was purified by washing with water, drying over $CaCl_2$ followed by distillation, and finally stored over 4 Å molecular seives under an atmosphere of nitrogen.

The lanthanide shift reagents $Pr(thd)_3$, $Eu(fod)_3$, and $Gd(fod)_3$ were purchased from Aldrich and were Gold Label products. They were stored in a desiccator under an atmosphere of nitrogen and used without further purification.

For the studies using $Pr(thd)_3$, a known amount of substrate and *ca.* 0.2 mol equivalents of the shift reagent were dissolved in 0.5 ml [^{2}H]chloroform. The ^{1}H n.m.r. spectra were recorded using a Perkin-Elmer R12B spectrometer and chemical shifts of the protons were compared with those of the unbound substrate.

For studies using $Eu(fod)_3$ a known amount of HMT was dissolved in 0.5 ml $CDCl_3$ and the ^{1}H n.m.r. spectrum recorded using a JEOL FX90Q spectrometer. A small, weighed quantity of $Eu(fod)_3$ was added and the n.m.r. spectrum again recorded. Finally, weighted quantities of HMT were successively added to the solution, the n.m.r. spectrum being recorded after each addition. The data were analysed by the method of Armitage and co-workers.[15]

Results and Discussion

Tris-(2,2,6,6-*tetramethyl*-3,5-*heptanedionato*)*praseodymium*-(III) [$Pr(thd)_3$].—In the presence of approximately 0.2 mol equivalents of $Pr(thd)_3$, HMTs exhibit upfield induced shifts of all the resonances in the ^{1}H n.m.r. spectrum. These shifts are

Table 1. Induced shifts Δδ/p.p.m.[a] of various HMT protons brought about by $Pr(thd)_3$ in $CDCl_3$ [HMT] = 0.06—0.2M

(2) Ar	[$Pr(thd)_3$]/[HMT]	N–CH_2–O	N–Me	Ar–N=N–N	Ar–X	Others
4-ClC_6H_4	0.2	−2.8	−1.55	−0.4	−0.27	−0.36 (4-CO_2Me)
4-$MeOC_2C_6H_4$	0.2	−2.55	−1.05	−0.4	−0.4	−0.45 (4-COMe)
4-$MeCOC_6H_4$	0.2	−2.5	−1.05	−0.5	−0.47	
4-$CF_3C_6H_4$	0.25	−2.0	−1.21	−0.4	−0.03	
2-$CF_3C_6H_4$	0.13	−1.16	−0.6	−0.15	−0.05	
4-NCC_6H_4	0.2	−2.00	−1.00	−0.35	−0.1	
4-$NO_2C_6H_4$	0.2	−2.07	−1.15	−0.47	−0.07	
3-C_5H_4N	0.2	−1.97	−1.27	−3—−1.13		

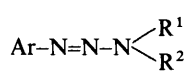
[a] $\Delta\delta = \delta_{obs} - \delta_{unbound}$.

Table 2. Induced shifts Δδ/p.p.m. of various protons in HMT-related compounds (3) brought about by $Pr(thd)_3$ in $CDCl_3$ [Substrate] = 0.094—0.263M

Ar	R^1	R^2	[$Pr(thd)_3$]/[(3)]	N–CH_2–O	N–R	Ar–N=N–N	Ar–X	Others
4-AcC_6H_4	CH_2OH	Et	0.2	−1.23	−0.5 N–CH_2C −0.12 N–C–Me	−0.2	−0.1	−0.1 (4-COMe)
4-AcC_6H_4	CH_2OH	Pr	0.2	−2.1	−1.5 N–CH_2C–C −0.73 N–C–CH_2–C −0.12 N–C–C–Me	−0.4	−0.38	−0.36 (4-COMe)
4-$MeOCOC_6H_4$	CH_2OMe	Me	0.2	−1.34	−0.8	0.72	−0.97	−1.1 (4-CO_2Me) −1.34 (Me–O–)
4-$MeOCOC_6H_4$	CH_2OAc	Me	0.2	−0.8	−0.4	−0.45	−0.75	−0.95 (4-COMe) −0.73 ($MeCO_2$–)
4-AcC_6H_4	CH_2OAc	Me	0.27	−1.3	−0.55	−0.97	−0.9	−1.62 (4-CO_2Me) 1.18 ($MeCO_2$–)
4-$NO_2C_6H_4$	CH_2OAc	Me	0.14	−0.85	−0.3	−0.06	−0.02	−0.8 ($MeCO_2$–)
4-AcC_6H_4	H	Me	0.15		−0.02	−0.18	−0.13	−0.52 (4-COMe)
4-AcC_6H_4	Me	Me	0.17		0	0	−0.1	−0.34 (4-COMe)
4-Aminoacetophenone			0.2			0.37	−0.5	−0.92 (4-COMe) −1.25 (NH_2)

collected in Table 1 and it can be seen that the size of the shift depends upon the proton environment. For the seven benzene derivatives the protons exhibiting the largest shift are those of the hydroxymethyl group, followed by the *N*-methyl protons. The least shifted are the aromatic protons and those of the substituent on the aromatic ring. The size of the shift appears to be roughly constant for equivalent protons and therefore independent of the substituent, suggesting that the mode of binding of the HMT to the lanthanide ion is similar in all cases and that the site of binding is remote from the substituent. It has been shown, for example, that the binding of anilines to tris(dipivalomethanato)europium(III) occurs *via* the aniline nitrogen atom and is sensitive to the aromatic substituent.[16] In this respect, it is worth noting that there is little difference in shift (allowing for concentration differences) between the 2-CF_3 and 4-CF_3 derivatives, which tends to indicate that the 2-CF_3 group is not exerting any steric influence on binding. Significantly, although the *N*-hydroxymethyl and *N*-methyl protons of the 3-pyridyl HMT exhibit shifts similar to those of the benzene series the aromatic protons also undergo large shifts, in some cases exceeding those of the *N*-hydroxymethyl shifts.

We further examined the effect of $Pr(thd)_3$ on the proton resonances in some compounds related to the HMTs (2), *viz.* compounds of structure (3). These compounds were chosen to gauge the contribution of the various structural features present in HMTs on their induced chemical shifts brought about by the lanthanide shift reagent. The data are given in Table 2, and from these several observations can be made. First, the higher *N*-alkyl HMT homologues (3; R^1 = CH_2OH, R^2 = Et or Pr) follow a similar pattern to that for the *N*-methyl HMTs described above. Again, the *N*-hydroxymethyl protons are those shifted by the largest amount, and the induced shift of the *N*-alkyl protons decreases with their distance from the N-3 nitrogen atom. The aromatic and substituent protons are shifted only a small amount. Second, the methyl ether derivative (3; Ar = 4-$MeOCOC_6H_4$, R^1 = CH_2OMe, R^2 = Me) exhibits relatively large induced shifts for all protons including those on the aromatic ring. Both the ether methyl and methylene proton resonances are shifted the most and by the same amount. The substituent methyl ester proton resonances are shifted by almost the same amount as the ether proton resonances, an effect not seen in the corresponding HMT (see Table 1). Third, the three acetate derivatives also exhibit significant shifts of the N–CH_2–O proton resonances, and these are larger than those for the N–Me proton resonances, but the acetate methyl signals are also shifted by a similar amount. Moreover, for the 4-$MeOCOC_6H_4$- and 4-AcC_6H_4-acetate derivatives the proton resonances of the substituent are shifted more than the N–CH_2–O protons. Further, for these two compounds, but not the 4-NO_2 derivative, the aromatic proton resonances are shifted by almost the same amount as the N–Me resonances. Fourth, the monomethyl- and dimethyl-triazenes (3; R^1 = H, R^2 = Me, and R^1 = R^2 = Me) exhibit essentially no shift of the triazene methyl signals and only a small shift of the aromatic proton signals. By far the most shifted resonances are those of the acetyl substituent on the aromatic ring. It has been noted previously that the structurally similar azobenzenes do not



(3)

exhibit induced proton shifts in the presence of lanthanide shift reagents.[17]

In contrast, 4-aminoacetophenone exhibits significant shifts of the NH_2 and acetyl proton resonances and also relatively large shifts for the signals of the aromatic protons. In fact, the protons *ortho-* to the amino group exhibit downfield shifts, whereas all of the other observed shifts are upfield. Unfortunately, a quantitative analysis of HMT–lanthanide ion binding proved impracticable using $Pr(thd)_3$ due to the small shifts observed at the low concentrations of lanthanide ion required for such a study. We therefore carried out quantitative studies using $Eu(fod)_3$.

Tris-(1,1,1,2,2,3,3-*heptafluoro*-7,7-*dimethyl*-4,6-*octanedionato*)*europium*(III) [$Eu(fod)_3$].—In the presence of $Eu(fod)_3$, the HMT proton resonances display a downfield shift characteristic of binding to Eu(III) (Table 3). Qualitatively, the magnitude of these proton shifts parallel those for Pr(III). This is good evidence that the HMTs bind to each lanthanide ion through the same atom. In order to probe further by which atom the HMTs bind to the metal ion, and also the equilibrium binding constant, K_B, for this process [equation (3)] we adopted

$$Ln(lig)_3 + HMT \overset{K_B}{\rightleftharpoons} Ln(lig)_3(HMT) \qquad (3)$$

the approach of Armitage *et al.*[15] and measured the observed shift $\Delta\delta$, (where $\Delta\delta = \delta_{obs} - \delta_{free\ substrate}$) in the proton resonances of the HMT for varying concentrations of substrate $[S]_0$, at a fixed concentration of $Eu(fod)_3$,$[L]_0$. From these data, provided that there is fast exchange between the bound and complexed HMT, it is possible to determine the stoicheiometry of the binding process, and to calculate the values of the chemical shifts Δ_B, and K_B for the bound HMT. For all the data reported here we observed only one signal for each proton in the ^1H n.m.r. spectrum, the chemical shift of which varied with $[S]_0/[L]_0$ which is good evidence for a fast exchange process.

Armitage *et al.* have shown that linear plots of $[S]_0$ *versus* $1/\delta_{obs}$ are evidence for 1:1 stoicheiometry between the lanthanide and complexing ligand,[15] in this case the HMT. Such a plot is shown for the HMT (**2**; Ar = 4-ClC_6H_4) in Figure 1. The straight lines for all types of protons passing through a common intercept is good evidence that HMT–Eu(III) binding has a 1:1 stoicheiometry with a common equilibrium binding constant and therefore a common site of attachment to the lanthanide ion. Similar plots were obtained for other HMTs. An alternative procedure is to plot log [S] *versus* log[LS]/[L][18] where [S], [L], and [LS] are the concentrations of the free substrate, free lanthanide ion, and the lanthanide–substrate complex respectively. The slope of such a plot is equal to $1/n$, where n is the number of moles of HMT which combine with one mole of the lanthanide shift reagent. Figure 2 is such a plot for (**2**; Ar = 4-ClC_6H_4). The slope is 0.99, from which it can be deduced that the HMT–$Eu(fod)_3$ complex has 1:1 stoicheiometry.

While it is possible to obtain values of Δ_B and K_B from plots such as those in Figure 1, we preferred to fit the data to equations (4) and (5) where [LS] is the concentration of Eu(III)–

$$\Delta\delta = \frac{[LS]}{[S]_0}\Delta_B \qquad (4)$$

and

$$K_B = \frac{[LS]}{([L]_0 - [LS])([S]_0 - [LS])} \qquad (5)$$

HMT complex. Solving for [LS] in equation (5) and substituting this value into equation (6) allows K_B and Δ_B to be determined by the iterative procedure discussed by Armitage *et al.*[15] Values of K_B and Δ_B determined in this way are recorded in Table 3. Since the NCH_2O resonances exhibit the largest values of $\Delta\delta$, and hence Δ_B, values of K_B calculated from the experimental data obtained from these protons should contain the smallest errors. Therefore, we chose this value of K_B to recalculate Δ_B for all of the other protons in each HMT. These recalculated values of Δ_B are in excellent agreement with those obtained directly from the ^1H n.m.r. spectra except for a few exceptional cases (Table 3). A significant observation that can be made from the data in Table 3 is that the values of K_B, determined from different protons within an HMT, are in fairly good agreement suggesting a common equilibrium binding process gives rise to the observed induced shifts of all protons. A further observation that can be made from the K_B values is that they have remarkably similar magnitudes despite the range of Hammet σ-values that the substituents span (0.23—0.78). This suggests that the substituent is remote from the site of binding to the lanthanide ion and is not in conjugation with it.

Site of Binding between the HMT and Ln(III).—Lanthanide induced shifts arise through two types of interaction between a

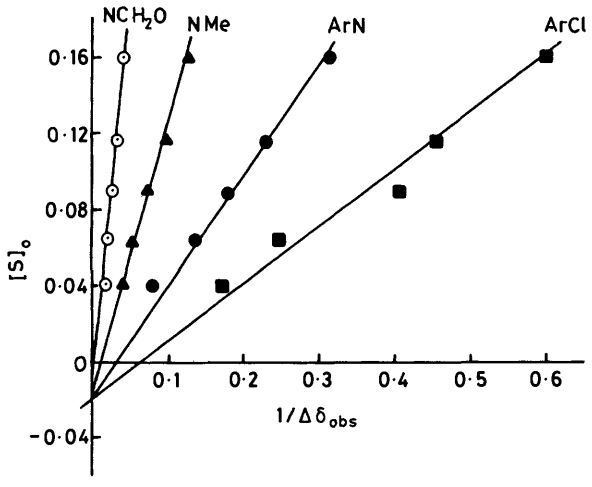


Figure 1. Plot of $[S]_0$ *versus* $1/\Delta\delta$ for the protons of the HMT (**2**; Ar = 4-ClC_6H_4)

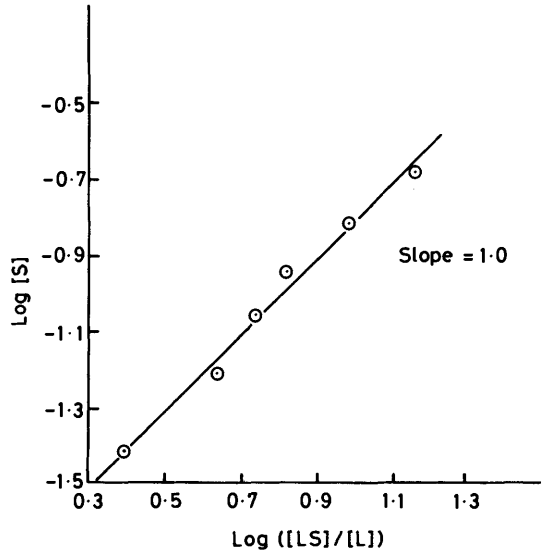


Figure 2. Plot of log[S] *versus* log[LS]/[L] for the HMT (**2**; Ar = 4-ClC_6H_4)

Table 3. $Eu(fod)_3$ bound shifts, Δ_B/p.p.m.,[a] for HMT protons resonances and equilibrium constants, K (l mol^{-1}), for HMT–$Eu(fod)_3$ complexes in $CDCl_3$ at 25 °C

	N–CH_2–O		N–Me		Ar–N=N		Ar–X		Others	
	Δ_B	K_B	Δ_B	K_B	Δ_B	K_B	Δ_B	K_B	Δ_B	K_B
4-ClC_6H_4	17.61	65	6.25	59	2.67	53	1.42	33		
	(17.61)		(6.11)		(2.55)		(1.27)			
4-$MeOCOC_6H_4$	9.65	13	3.68	10	1.81	10	3.17	14	3.63	12
	(9.65)		(3.25)		(1.60)		(3.28)		(3.50)	
4-AcC_6H_4	17.75	10	7.59	8	7.20	9	7.42	13	5.32	15
	(17.75)		(6.75)		(5.05)		(8.12)		(9.13)	
4-$CF_3C_6H_4$	27.91	20	10.15	21	2.78[b]	20	2.78[b]	20		
	(27.91)		(10.35)		(2.78)		(2.78)			
4-NCC_6H_4	15.77	22	7.00	26	2.50	45	1.13	8		
	(15.77)		(7.00)		(2.79)		(1.13)			
4-$NO_2C_6H_4$	22.55	17	8.38	15	3.41	3	0.92	19		
	(22.55)		(7.87)		(4.40)		(0.92)			

[a] Values in parentheses are calculated using equations (5) and (6) using the K_B value for the NCH_2O protons. [b] The aromatic protons for this compound appear as a singlet at all concentrations of HMT.

ligand and the lanthanide ion, namely a Fermi-contact interaction and a dipolar (or pseudo-contact) interaction.[19] The Fermi-contact contribution is a through-bond effect which falls off rapidly through σ-bonds. The pseudo-contact term is a through-space effect and its size depends largely, though not exclusively, on the distance of the resonating nucleus from the lanthanide ion. In general, for ^1H n.m.r. the induced chemical shifts arise predominantly from pseudo-contact processes. A number of methods for demonstrating this have been outlined previously.[19]

A pseudo-contact mechanism for induced shifts is indicated if the ratios of the gradients, G(Ln), of all the protons in the molecule for two different lanthanides are constant (G is the slope of the linear portion of a plot of Δδ *versus* $[Ln^{3+}]$/[substrate]).[20] We were able to determine the ratio $G(Eu^{3+})/G(Pr^{3+})$ for the HMT (**2**; Ar = 4-ClC_6H_4) and found them to be: NCH_2O, −4.0 ± 0.5; Me, −3.7 ± 0.5; Ar–N, −4.2 ± 0.5; Ar–Cl −3.9 ± 0.5; the negative sign indicating the different direction of the induced shift. Further evidence that the induced shifts are pseudo-contact in origin is given below.

The magnitude of the induced pseudo-contact shift is related to the distance of the resonating nucleus from the lanthanide ion, r, and the angle, θ, between the vector joining the resonating nucleus to the metal atom and the principle magnetic axis of the complex, usually chosen as the bond between the lanthanide ion and the ligating atom [equation (6)].[19] However, it has been

$$\Delta_B = K(3\cos^2\theta - 1)/r^3 \quad (6)$$

found experimentally that many systems conform to a 'distance only' equation, such as equation (7), although correlations

$$\Delta_B = K'/r^3 \quad (7)$$

between Δ_B and r are improved on inclusion of the $3\cos^2\theta - 1$ term. Clearly, the smaller the distance r the larger Δ_B. Using the data in Table 2 this model indicates that the N–CH_2O resonances are closest to the europium ion and that they are closer than the N–Me protons. These data probably rule out the triazene function as the site of binding and point to the hydroxy oxygen atom of the hydroxymethyl group as the point of binding to the lanthanide. This is corroborated by the earlier findings with $Pr(thd)_3$ in which we observed essentially no shift of the *N*-methyl resonances for either *N*-methyl- or *N*,*N*-dimethyl-triazenes. Moreover, complex formation through

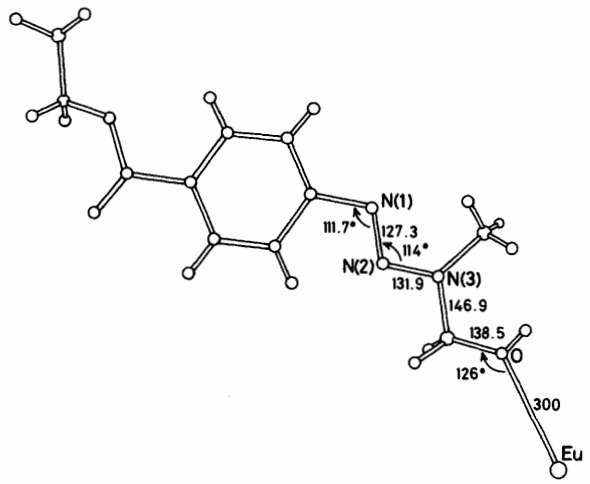


Figure 3. General structure of the HMT–Eu(III) complex

binding of the HMT hydroxy function is consistent with a lack of variation of K_B with the aromatic substituent.

If equation (7) applies to HMT–Eu(III) complex formation, then a plot of log Δ_B *versus* log r for the protons of a particular triazene should yield straight lines with slope −3. Such plots require a knowledge of the hydroxymethyltriazene structure. As far as we are aware only one crystal structure, that for (**2**; Ar = 4-$EtOCOC_6H_4$),* is known. Using these data as the basic structure for all 1-aryl-3-hydroxymethyl-3-methyltriazenes, and the assumption that the europium–oxygen bond length is 300 pm and the Eu–O–C bond angle is 126°,[21] we constructed a molecular model of the HMT–Eu complex (Figure 3) which enabled us to make log Δ_B − log r plots which are shown in Figure 4. The range of possible distances r is indicated by the length of the bars in the diagram. Only those conformations which did not have severe steric interactions with the fod ligands were considered. It is clear that, for those derivatives in which the substituent is unable to compete as an alternative binding site to Eu^{3+} (*i.e.* Cl, CN, CF_3, NO_2), the relationship expressed

* We are grateful to Dr. R. J. Simmonds, University College, Aberystwyth for providing us with the molecular structure of this compound prior to publication.

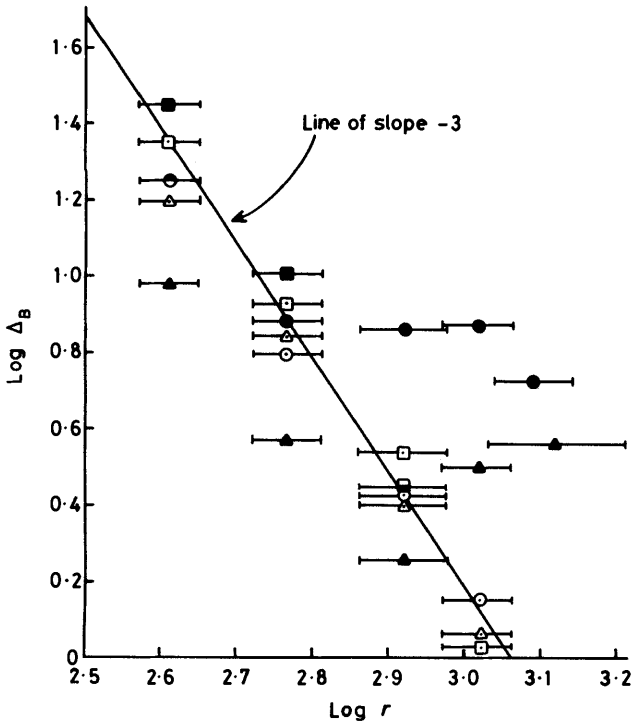


Figure 4. Plots of log Δ_B *versus* log *r* for some HMTs: ⊙, 4-ClC_6H_4; Δ, 4-NCC_6H_4; ⊡, 4-$NO_2C_6H_4$; ■, 4-$CF_3C_6H_4$; ●, 4-AcC_6H_4; ▲, 4-$MeOCOC_6H_4$. The line is of slope −3

by equation (7) holds for HMT–Eu(fod)$_3$ complexes. While the correlations would probably improve on inclusion of the angle term, such improvement is unwarranted here given the rotational freedom of the HMT system. Two observations are worth reinforcing. First, such correlations are impossible to make if the Eu^{3+} ion is attached to any other ligating atom and second, the values of log Δ_B for the N–CH_2–O proton resonances fall on the lines of log Δ_B *versus* log *r*. Deviation away from such lines of log Δ_B for protons close to the site of binding is taken as evidence of the existence of a Fermi-contact contribution to the induced shift. This is further evidence that the shifts observed in the present work are pseudo-contact in origin. The lack of a linear correlation for the 4-MeOCO and 4-MeCO derivatives is probably a result of competitive binding of the europium(III) ion by the substituent. Similar effects have been observed in other systems, and we did not pursue this further. However, it can be seen from Figure 4 that the N–CH_2–O and N–Me proton resonances correlate quite well with the line of slope −3, poor correlation being observed for the aromatic and substituent protons.

In contrast to the results for HMTs containing a substituted benzene nucleus, the heteroaromatic HMT (**2**; Ar = 3′-pyridyl) displays large shifts for the aromatic protons (Table 4). In particular, those protons next to the pyridine nitrogen atom exhibit the largest proton shifts of all. We interpret this as evidence for the HMT binding to Eu^{3+} *via* the pyridine nitrogen atom. Significantly, the binding constant, K_B, for this complex is calculated to be 485 l mol^{-1} which is in an order of magnitude larger than for binding through the hydroxyl oxygen atom.

If one assumes that the structure of the 3-pyridyl HMT is a combination of pyridine itself and of the hydroxymethyltriazene function, then it is possible to construct a log Δ_B *versus* log *r* plot for the HMT–Eu(III) complex in which the HMT binds to the Eu^{3+} ion *via* the pyridyl nitrogen atom. The Eu–N bond distance in such a complex should be close to 265 pm, the

Table 4. Bound shifts, Δ_B, for the HMT protons in the HMT–Eu(fod)$_3$ complex of (**2**; Ar = 3′-pyridyl)

	N–CH_2–O	N–Me	2–H	4–H	5–H	6–H
Δ_B/p.p.m.	13.52	7.02	33.27	12.07	9.52	35.22

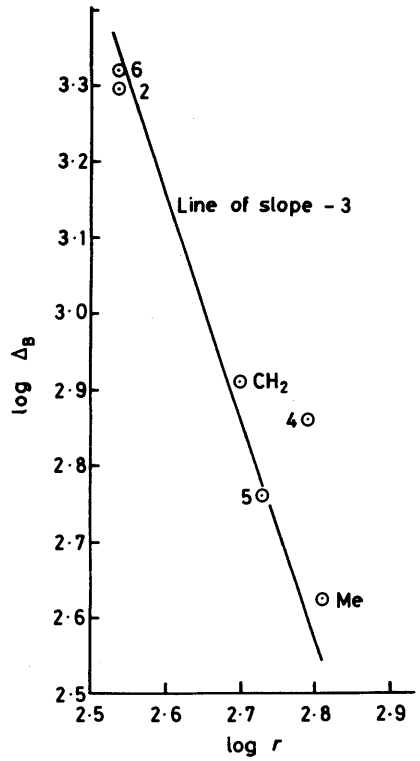


Figure 5. Plot of log Δ_B *versus* log *r* for (**2**; Ar = 3′-pyridyl). The line is of slope −3

distance in the Eu(dpm)$_3$(pyr)$_2$ complex.[22] Such a plot can be seen in Figure 5, in which a line of slope −3 (not the best line through the data) is indicated. Clearly there is sufficient correlation to indicate that (**2**; Ar = 3′-pyridyl) does indeed bind to Eu^{3+} through the pyridyl nitrogen atom.

Acknowledgements

We would like to thank Dr. K. Vaughan for the generous gift of compounds and Dr. R. J. Simmonds for crystallographic data. One of us (S. C. C.) thanks the Open University for the award of a studentship. J. I. thanks N.A.T.O. for the award of collaborative grant number 853/83.

References

1 Part 5, J. Iley, E. Rosa, and L. Fernandes, *J. Chem. Res.*, 1987, (*S*) 264; (*M*) 2216.
2 G. F. Kolar, M. Maurer, and M. Wildschutte, *Cancer Lett.*, 1980, **10**, 235.
3 K. Vaughan, Y. Tang, G. Llanos, J. K. Horton, R. J. Simmonds, J. A. Hickman, and M. F. G. Stevens, *J. Med. Chem.*, 1984, **27**, 357.
4 A. H. Soloway, R. J. Brumbaugh, and D. T. Witiak, *J. Theor. Biol.*, 1983, **102**, 361.
5 T. A. Connors, P. M. Goddard, K. Merai, W. J. C. Ross, and D. E. V. Wilman, *Biochem. Pharmacol.*, 1976, **25**, 241.

6 See, for example, C. M. Hemens and K. Vaughan, *J. Chem. Soc., Perkin Trans. 2*, 1986, 11 and references therein.
7 C. J. Rutty, D. R. Newell, R. B. Vincent, G. Abel, P. M. Goddard, S. J. Harland, and A. H. Calvert, *Br. J. Cancer*, 1983, **48**, 140.
8 S. C. Cheng, Ph.D. Thesis, The Open University, 1984.
9 C. Reyes-Zamora and C. S. Tsai, *J. Chem. Soc., Chem. Commun.*, 1971, 1047.
10 S. C. Cheng, M. L. de S. Fernandes, J. Iley, and E. Rosa, *J. Chem. Res.*, 1983, (*S*) 108; (*M*) 1101.
11 A. Gescher, J. A. Hickman, R. J. Simmonds, M. F. G. Stevens, and K. Vaughan, *Tetrahedron Lett.*, 1978, 5041.
12 C. M. Hemens, H. W. Manning, K. Vaughan, R. J. LaFrance, and Y. Tang, *Can. J. Chem.*, 1984, **62**, 741.
13 S. C. Cheng and J. Iley, *J. Chem. Res.*, 1983, (*S*) 320.
14 Y. F. Shealy, C. A. Krauth, C. E. Opliger, H. W. Guin, and W. R. Laster, Jnr., *J. Pharm. Sci.*, 1977, **60**, 1192.
15 I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Can. J. Chem.*, 1972, **50**, 2119.
16 L. Ernst and A. Mannschreck, *Tetrahedron Lett.*, 1971, 3023.
17 C. Beaute, Z. W. Wolkowski, and N. Thoai, *Chem. Commun.*, 1971, 700.
18 I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Ind. (London)*, 1972, 79.
19 A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, 553.
20 J. K. M. Sanders and D. H. Williams, *Nature*, 1972, **240**, 385.
21 B. C. Mayo, *Chem. Soc. Rev.*, 1973, **2**, 49.
22 R. E. Cramer and K. Seff, *J. Chem. Soc., Chem. Commun.*, 1972, 400.

Received 30*th January* 1987; *Paper* 7/165