^{1}H Nuclear Magnetic Resonance Study of the Association between 1,5-Dialkyl-1,5-dihydro-1,5-benzodiazepine-2,4-diones and the Shift Reagent Eu(fod)$_3$

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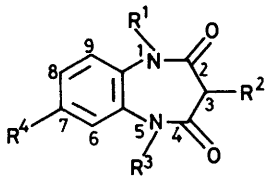
By observing the shifts of the ^{1}H n.m.r. signals of 1,5-dialkyl-1,5-dihydro-1,5-benzodiazepine-2,4-diones induced by Eu(fod)$_3$ and simulating them with the aid of the computer program TWOCEN, evidence has been found for competition in Eu co-ordination by the two carbonyl groups, involving two-site metal binding at each oxygen atom. Geometric parameters calculated for the complexes under study suggest that Eu(fod)$_3$ becomes mostly involved in a type of bidentate binding to both carbonyl groups unless a substituent is present at C-3. An electronegative group bonded to C-7, essential for optimal activity of benzodiazepine derivatives, appears to affect slightly the relative complexing ability of the two oxygen atoms. The preferred orientations of the *N*-substituents have also been deduced, by the computer-assisted LIS method.

A substrate co-ordinates to a lanthanoid shift reagent (LSR) when it contains heteroatoms which exhibit some degree of Lewis basicity.[1] Greater shifts are caused by functional groups which are most basic, although factors such as steric hindrance cannot be ignored. In order to elucidate the relationship between molecular structure and biological activity in the field of psychotherapeutic agents such as 1,5-dihydro-1,5-benzodiazepine-2,4-dione derivatives,[2] the use of Eu(fod)$_3$ co-ordination as a probe of the relative basicity of the two carbonyl groups appeared attractive. The ^{1}H n.m.r.–LIS (lanthanoid-induced shift) method[1] was applied to a representative series of 1,5-dialkyl-1,5-dihydro-1,5-benzodiazepine-2,4-diones (**1**)—(**10**), most of which [(**1**), (**4**), (**6**), and (**8**)—(**10**)] had not been previously reported, and relative LIS data were analysed by means of our computer program TWOCEN,[3] designed for LIS simulation of bifunctional substrates with two competing complexation centres. The program was conveniently extended in order to evaluate possible conformational preferences of 1- and 5-alkyl substituents, which rotate fast around the C–N bonds on the n.m.r. time-scale at room temperature.



	R^1	R^2	R^3	R^4
(**1**)	CH_2Ph	H	CH_2Ph	H
(**2**)	CH_2Ph	H	Et	H
(**3**)	CH_2Ph	H	Me	H
(**4**)	CH_2Ph	Me	Me	H
(**5**)	Me	H	Me	H
(**6**)	Me	H	Me	Cl
(**7**)	Me	H	Pr^i	H
(**8**)	Me	Me	Me	H
(**9**)	Et	H	Et	H
(**10**)	Pr^i	H	Pr^i	H

Experimental

Compounds (**3**), (**5**), and (**7**) were prepared according to the literature procedure.[4] Compounds (**1**), (**2**),[2c] (**4**), (**6**), and (**8**)—(**10**) were synthesized by similar methods. All new products gave satisfactory elemental analyses and i.r. and ^{1}H n.m.r. spectra (Tables 1 and 2). Tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium [Eu(fod)$_3$] was of commercial origin (Fluka). The usual precautions were taken to exclude impurities from the LSR and the solvent ($CDCl_3$).[5]

^{1}H N.m.r. spectra were recorded at an ambient probe temperature of 24 ± 2 °C with a Varian EM360A spectrometer. Tetramethylsilane was used as internal standard. Several spectra were acquired at fixed substrate concentration (0.57M) after adding increasing quantities of Eu(fod)$_3$ to the solution.[3,6] The LSR was added from a stock solution in $CDCl_3$ (*ca.* 300 mg ml^{-1}) with a 10 μl syringe. LIS figures corresponding to various lanthanoid–substrate molar ratios (L/S = 0.00—0.37) were measured. Limiting LIS values for the various protons (Table 3) were calculated from the slopes of the least-squares plots of Δδ(LIS) *versus* L/S.[7]

All computations were performed with an IBM 4381 computer (University of Messina). Copies of the TWOCEN program listing and the instruction manual are available from the authors.

Results and Discussion

The amides (**1**)—(**10**) were studied by the LIS method[7] with Eu(fod)$_3$ as LSR. This shift reagent was selected because of its deshielding of the signals without severe broadening. Its contact contribution to the observed shift can be neglected in our calculations. Effective axial symmetry is apparently achieved in solution through time-averaging of all possible orientations of the complex.[8] Thus the shifts induced by Eu(fod)$_3$ can be interpreted quantitatively by using the McConnell–Robertson equation in its simplified (pseudo-contact) form.[9] With regard to the stoicheiometry of the complex, evidence for the prevalence of only one kind of complex in solution and in the examined concentration range ($0 \leqslant L/S \leqslant 0.4$) comes from the straight lines which are obtained when the observed LIS values are plotted *versus* L/S: in these conditions the relative slopes

Table 1. ^{1}H N.m.r. chemical shifts (δ in p.p.m.) of compounds (**1**)—(**10**)

Compound; m.p. (°C)	3-H_2	CH_2Ph	7- and/or 8-H	6-H	9-H	CH_2Me	CH_2Me	5-Me	3-Me	3-H	1-Me	$CHMe_2$	$CHMe_2$
(**1**); 172—174	3.40	4.91		6.98—7.48									
	3.45	4.96											
(**2**); 158—160	3.29	4.76		6.83—7.50		0.84	3.58						
	3.34	5.52					4.19						
(**3**); 193—194	3.40	4.86		6.83—7.50				3.30					
	3.45	5.46											
(**4**); 105—107		4.82		6.91—7.61				3.28	1.43	3.38			
		5.53											
(**5**); 240—242	3.47		7.33	7.40	7.40			3.46			3.46		
	3.69												
(**6**); 210—212	3.30		7.21	7.23	7.21			3.28			3.27		
	3.41												
(**7**); 158—160	3.29			7.17—7.47							3.40	1.22	4.60
	3.31											1.54	
(**8**); 226—228			7.28	7.29	7.29			3.39	1.39	3.24	3.39		
(**9**); 186—188	3.27		7.41	7.42	7.42	1.11	3.67						
	3.28						4.42						
(**10**); 143—145	3.16		7.33	7.34	7.34							1.26	4.50
	3.18											1.55	

Table 2. ^{1}H N.m.r. coupling constants (Hz) of compounds (**1**)—(**10**)

Compound	J_{gem}(3-H_2)	J_{gem}(CH_2Ph)	J_{gem}(CH_2Me)	J_{vic}	$J_{6,7}$ and/or $J_{8,9}$	$J_{6,7}$ and/or $J_{7,9}$
(**1**)	−11.9	−15.5				
(**2**)	−12.1	−14.7	−14.0	7.3(Et)		
(**3**)	−12.4	−15.2				
(**4**)		−15.3		6.9(3-H, Me)		
(**5**)	−12.4				8.2	1.4
(**6**)	−12.6				8.1	1.5
(**7**)	−12.4			7.0(Pr^i)		
(**8**)				6.5(3-H, Me)	7.6	1.7
(**9**)	−11.9		−13.9	7.1(Et)	8.2	1.5
(**10**)	−11.9			6.7(Pr^i)	8.2	1.4

satisfactorily approximate to the relative limiting shifts (boundary shifts). Moreover the use of relative slopes lowers the experimental errors, especially those resulting from impurities.[6] Dimerization of the LSR can also influence the equilibrium condition, but it has been found previously that the self-association of Eu(fod)$_3$ can be neglected in $CDCl_3$.[1]

All relative limiting shifts of the 1,5-dihydro-1,5-benzodiazepine-2,4-diones (**1**)—(**10**) are listed in Table 3. At room temperature and in the absence of Eu(fod)$_3$, the 3-protons in compounds (**1**)—(**3**), (**5**)—(**7**), (**9**), and (**10**) resonate as typical AB multiplets (Tables 1 and 2). The magnetic non-equivalence of these methylene protons is interpreted in terms of an exchange between two equally populated enantiomeric forms corresponding to the limiting conformers resulting from hepta-atomic ring inversion, which occurs slowly on the n.m.r. time-scale, so that the resonances of only one conformation are actually observed.

In line with this conformational situation, the methylene protons of ethyl groups also resonate as AB systems, coupled with methyl protons [compounds (**2**) and (**9**)]; the methylene protons of benzyl substituents appear magnetically non-equivalent at room temperature [compounds (**1**)—(**4**)]; and the two methyl groups of isopropyl substituents [products (**7**) and (**10**)] show different resonances, because they are diastereotopic as a result of slow hepta-atomic ring inversion. It is assumed for the compounds under study that the *N*-side-chains undergo diffutional rotation processes: indeed it was observed[2c] in compounds (**2**) and (**3**) that the cyclic and exocyclic methylene signals collapse as a result of the same ring-inversion reaction, as do similar groups in some other benzodiazepinones.[10]

In the 3-H_2 absorption, the higher-field resonance corresponds to the axial proton, shielded by the fused benzene ring,[2a] and less shifted by Eu(fod)$_3$ than the equatorial proton. LIS computer simulation suggests that 5-Me resonates at a slightly lower field than 1-Me in compound (**6**) and that the 3-H is axial in compounds (**4**) and (**8**). The equatorial preference of 3-Me agrees with the unfavourable electronic interaction between the π-electron system of the fused benzene ring and an axial 3-substituent in the 3*H*-1,5-benzodiazepine skeleton,[11] closely related to the one under study as regards stereoelectronic characteristics.

The aromatic absorptions (A_2B_2) in compounds (**5**) and (**8**)—(**10**) were analysed by computer simulation, using the LAOCN3 program;[12] this was facilitated by the effects of LSR doping, which altered line positions and their intensities. Good agreement was reached between experimental and simulated spectra; the calculated spectral parameters are given in Tables 1 and 2. The chemical-shift attribution was based on LIS values.

In order to simulate the shifts induced by Eu(fod)$_3$ in the proton resonances of benzodiazepinediones (**1**)—(**10**), we assumed that the observed LIS of the *i*th nucleus results from a time-averaging of the shifts due to complexation at each of the oxygen atoms (centres 1 and 2) according to equation (1),

$$\Delta\nu_i = \alpha\Delta\nu_{1i} + (1 - \alpha)\Delta\nu_{2i} = K[\alpha G_{1i} + (1 - \alpha)G_{2i}] \quad (1)$$

$$(0 \leqslant \alpha \leqslant 1)$$

Table 3. Relative limiting shifts[a] induced by $Eu(fod)_3$ on proton resonances of compounds (**1**)—(**10**)

Compound	3-H_2	CH_2Ph	CH_2*Me*	CH_2Me	5-Me	3-Me	3-H	7- and/or 8-H	6-H	9-H	1-Me	CH*Me*$_2$	*C*HMe$_2$
(**1**)	100.00	55.09											
	52.58	36.28											
(**2**)	100.00	52.06	25.44	50.59									
	46.54	27.74		31.75									
(**3**)	100.00	57.64			48.97								
	46.01	30.68											
(**4**)		70.51			74.33	100.00	91.08						
		38.26											
(**5**)	100.00				57.38			9.85	20.07	20.07	57.38		
	48.58												
(**6**)	100.00				49.37			11.34	22.69	22.05	51.91		
	47.49												
(**7**)	100.00										50.21	36.59	62.71
	55.31											26.44	
(**8**)					83.53	100.00	96.72	20.77	37.72	37.72	83.53		
(**9**)	100.00		28.59	56.74				4.41	18.80	18.80			
	49.18			34.89									
(**10**)	100.00							11.23	25.65	25.65		30.30	53.58
	63.02											24.38	

[a] Slopes from plots of LIS *versus* *L*/*S*, relative to the largest slope (= 100.00).

where α is the contribution of the shift induced by Eu co-ordination at centre 1 to the total shift, $\Delta\nu_{1i}$ and $\Delta\nu_{2i}$ are the shifts induced on the same nucleus by complexation at centres 1 and 2, respectively, K is the McConnell–Robertson constant, and G_{1i} and G_{2i} are the geometric factors for the same *i*th nucleus, calculated for complexation at centres 1 and 2, respectively.[9] With the intention of evaluating the complexing ability of each competing co-ordination centre of a bifunctional substrate, a 'symmetric' compound, showing identical environments for each basic function, is compared by our TWOCEN program[5] with 'asymmetric' compounds, where one complexation centre ('symmetric' centre) may be taken as equivalent to that of the 'symmetric' compound. LIS ratios (LISR) relative to one value ('standard' nucleus) are taken to eliminate K. Then, for the 'symmetric' compound with $\alpha = 1/2$, using the two-site model (TSM) of LSR co-ordination by a carbonyl group,[3,6,10b] equation (1) becomes equation (2), where G'_1 and G'_2 are the geometric factors calculated for Eu binding to one lone pair of the two polar functions and G''_1 and G''_2 are those calculated for binding to the other lone pair; β takes into account the binding percentage to each of the lone pairs of every carbonyl oxygen atom.

For the 'asymmetric' compounds, equation (1) can be written as (3). Since the constant of the pseudo-contact equation should, to a first approximation, be a property only of the shift reagent,[13] $K_1 = K_2$, and the LISRs of the 'asymmetric' compounds are expressed by equation (4). The terms $[\beta_1 G'_{1i} + (1 - \beta_1)G''_{1i}]$ and $[\beta_1 G'_{1std} + (1 - \beta_1)G''_{1std}]$ are the geometric factors related to the complexation centre 1, equivalent to that of the 'symmetric' compound.

Table 4. TWOCEN solutions[a] for 'symmetric' compounds (**1**), (**5**), and (**8**)—(**10**)

Compound		(**1**)	(**5**)	(**8**)	(**9**)	(**10**)
Site 1	RB (°)	0	0	45	[0]	[0]
	LA (°)	75	75	75	75	60
	LB (Å)	3.1	3.1	3.1	3.1	3.1
Site 2	RB	165	180	135	[180]	[180]
	LA	45	75	15	60	15
	LB	3.4	3.4	3.4	3.4	3.4
β		0.9	0.9	0.3	0.9	0.6
d_{Eu}/Å		0.5	0.6	4.5	0.3	1.4
γ	(I)	0.4			0.4	
	(II)				0.2	0.2
	(III)					0.8
	(IV)	0.6			0.4	
R		0.0056	0.0702	0.0181	0.0854	0.0482

[a] Brackets denote values kept fixed during calculation.

In the TWOCEN program, widely described elsewhere,[3]

$$\mathrm{LISR}_i = \frac{\Delta\nu_i}{\Delta\nu_{std}} = \frac{G_{1i} + G_{2i}}{G_{1std} + G_{2std}} = \frac{\beta(G'_{1i} + G'_{2i}) + (1 - \beta)(G''_{1i} + G''_{2i})}{\beta(G'_{1std} + G'_{2std}) + (1 - \beta)(G''_{1std} + G''_{2std})} \quad (0 \leqslant \beta \leqslant 1) \tag{2}$$

$$\Delta\nu_i = \alpha K_1 G_{1i} + (1 - \alpha)K_2 G_{2i} \tag{3}$$

$$\mathrm{LISR}_i = \frac{\alpha[\beta_1 G'_{1i} + (1 - \beta_1)G''_{1i}] + (1 - \alpha)[\beta_2 G'_{2i} + (1 - \beta_2)G''_{2i}]}{\alpha[\beta_1 G'_{1std} + (1 - \beta_1)G''_{1std}] + (1 - \alpha)[\beta_2 G'_{2std} + (1 - \beta_2)G''_{2std}]} \tag{4}$$

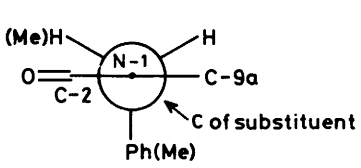
$$\mathrm{LISR}_i = \frac{\Sigma_j \gamma_j[\beta(G'_{1i,j} + G'_{2i,j}) + (1 - \beta)(G''_{1i,j} + G''_{2i,j})]}{\beta(G'_{1std} + G'_{2std}) + (1 - \beta)(G''_{1std} + G''_{2std})} \tag{5}$$

$$\mathrm{LISR}_i = \frac{\Sigma_j \gamma_j\{\alpha[\beta_1 G'_{1i,j} + (1 - \beta_1)G''_{1i,j}] + (1 - \alpha)[\beta_2 G'_{2i,j} + (1 - \beta_2)G''_{2i,j}]\}}{\alpha[\beta_1 G'_{1std} + (1 - \beta_1)G''_{1std}] + (1 - \alpha)[\beta_2 G'_{2std} + (1 - \beta_2)G''_{2std}]} \tag{6}$$

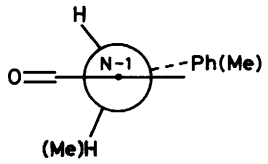
Table 5. TWOCEN solutions[a] for 'asymmetric' compounds (2)—(4), (6), and (7)

Compound			(2)	(3)	(4)	(6)	(7)
'Symmetric' centre 1			C(2)O	C(4)O	C(4)O	C(2)O	C(4)O
Centre 1	site 1	RB (°)	0	0	45	0	[0]
		LA (°)	75	75	75	75	60
		LB (Å)	3.1	3.1	3.1	3.1	3.1
	site 2	RB	165	180	135	180	[180]
		LA	45	75	15	75	15
		LB	3.4	3.4	3.4	3.4	3.4
	β_1		0.9	0.9	0.3	0.9	0.6
Centre 2	site 1	RB	345	345	0	[0]	345
		LA	75	75	30	75	75
		LB	3.1	3.1	3.1	3.1	3.1
	site 2	RB	225	195	180	[180]	225
		LA	60	60	60	15	30
		LB	2.8	3.1	3.4	3.4	3.4
	β_2		0.8	0.9	0.8	0.9	0.7
	α		0.4	0.4	0.6	0.5	0.5
	d_{Eu}/Å		0.8	0.8	5.4	0.0	1.1
	R		0.0821	0.0286	0.0185	0.0834	0.0503

[a] Brackets denote values kept fixed during calculation.



(I)



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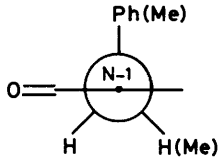

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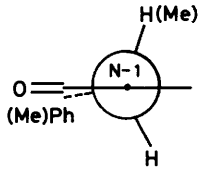
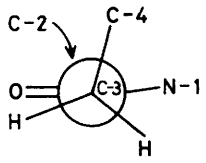


(IV)



(V)

twelve equivalent points are used to represent each methyl group.[14] Moreover, because the benzodiazepinediones under study show *N*-substituent groups (benzyl, ethyl, isopropyl) involved in free rotation processes, as well as the methyl groups, we have widened the TWOCEN program in order to evaluate the relative contributions to the total shifts by four conformational possibilities (I)—(IV) of the *N*-substituents, in fast equilibrium with each other.[10b] A further projection (V) settles the steric relationship between (I)—(IV) and the remaining part of the molecule. Then for the *i*th nucleus of a freely rotating group the equations (2) and (4) become respectively (5) and (6), where $\gamma(\Sigma_j\gamma_j = 1;\ 0 \leqslant \gamma \leqslant 1)$ gives the molar fractions of the four conformations (I)—(IV) of the complexed substrate with an accuracy of within ± 0.2. The standard nucleus must not be included in a freely rotating group.

The best TWOCEN solutions for 'symmetric' compounds are shown in Table 4, where the site 1 corresponds to the environment of the oxygen lone pair directed towards the 3-methylene group; RB is the rotatable bond angle which defines the angular relationship of the substrate with the lanthanoid atom in the complex under study;[3] LA is the Eu–O–C angle supplement, and LB is the Eu–O bond length; d_{Eu} is the calculated distance between the Eu localizations at sites 1 of both equivalent centres of co-ordination; and R is the Hamilton

agreement factor.[15] The β values are greater than 0.5 for compounds (**1**), (**5**), (**9**), and (**10**): this shows that Eu localization occurs preferentially at site 1, unless a substituent group is bonded to C-3, as in 1,5-dihydro-1,3,5-trimethyl-1,5-benzodiazepine-2,4-dione (**8**), where the 3-methyl group, equatorially situated, exerts steric hindrance to Eu co-ordination. All these observations suggest, for benzodiazepinediones unsubstituted at C-3, a europium atom located at the same distance (see small value of d_{Eu}) between the two carbonyl groups in a bidentate complex. On the other hand it is known that such lanthanoid complexes exist[16] and exhibit more important complexation constants than for single associations. The TWOCEN solutions reported in Table 4 for compounds (**9**) and (**10**) correspond to Eu localization on the carbonyl plane (RB = 0° or 180°): the best solutions obtained by incremental scanning of all facilities appear not to be completely reasonable [the related reliability factors are 0.0487 and 0.0362 for (**9**) and (**10**), respectively].

Table 5 shows the best TWOCEN solutions for the 'asymmetric' compounds (**2**)—(**4**), (**6**), and (**7**), with the related 'symmetric' centre, *i.e.* the selected reference compound. When more than one 'symmetric' reference compound (SRC) is available, as for (**2**) [SRC (**1**) and (**9**)], (**3**) [SRC (**1**) and (**5**)], and (**7**) [SRC (**5**) and (**10**)], we have explored all the possibilities, and the results agree very well with each other. The conformational preferences (γ) of freely rotating substituents are not shown in Table 5, because the optimized values for 'symmetric' compounds (Table 4) have been retained for the following calculations. The results reported in Table 5 for compounds (**2**), (**3**), (**6**), and (**7**) support the suggested Eu bidentate binding to both carbonyl groups, and implicitly the effectiveness of the TSM hypothesis.

Conclusions

We have found evidence for competition in Eu co-ordination by the two carbonyl groups in 1,5-dialkyl-1,5-dihydro-1,5-benzodiazepine-2,4-dione complexes, which involves two-site metal binding (TSM),[7] with preferred formation of a bidentate complex by means of the electronic lone pairs (one for every carbonyl group) directed towards C-3, unless a 3-substituent is present. The α values (Table 5), in the range 0.4—0.6, show the weak influence of the *N*-substituents on the relative basicity of the two carbonyl groups towards LSR. In the presence of bulky *N*-substituents, such as the isopropyl group, an increase of the Eu–O–C angle is generally observed: for instance, the optimized LA at site 2 for Eu co-ordination by (**10**) is 15°, which corresponds to an Eu–O–C angle of 165°

The α value of 0.5, calculated for the 7-chloro-1,5-dihydro-1,5-dimethyl-1,5-benzodiazepine-2,4-dione complex, indicates that an electron-attracting 7-substituent, essential for optimal activity of benzodiazepine derivatives,[17] does not notably influence the relative basicity of the carbonyl groups towards the lanthanoid atom.

Acknowledgements

This work was financially supported by C.N.R., Rome.

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Received 4*th August* 1986; *Paper* 6/1586