Conformational analysis. Part 30.[1] The conformational analysis of some lactones by the lanthanide induced shift (LIS) technique

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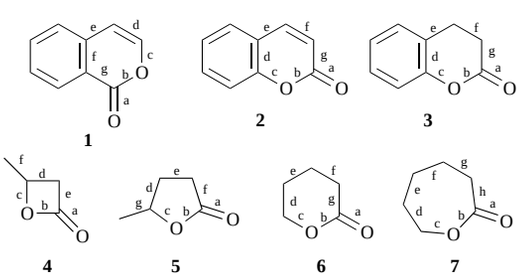
An improved LIS technique, using Yb(fod)$_3$† to obtain the paramagnetic induced shifts of all the spin 1/2 nuclei in the molecule, together with complexation shifts obtained by the use of Lu(fod)$_3$, has been used to investigate the conformations of several lactones. The appropriate complexation model was obtained by investigations on the planar well-defined structures of isocoumarin (1) and coumarin (2). This complexation model was then used to investigate the conformations and conformational equilibria in 3,4-dihydrocoumarin (3), β-butyrolactone (4), γ-valerolactone (5), δ-valerolactone (6) and ε-caprolactone (7).

3,4-Dihydrocoumarin is puckered with both C2 and C3 displaced from the benzene ring plane. β-Butyrolactone is planar. γ-Valerolactone interconverts between the two envelope conformations with C4 out of the plane of the other ring atoms with 70% of the conformer with a pseudo-equatorial methyl group. For δ-valerolactone the two interconverting conformations are the half-chair and the boat form and analysis of the data suggests that there is *ca*. 20% of the boat form. In ε-caprolactone the LIS data gives a well-defined minimum for 100% of the chair form with no other significantly populated conformer. The LIS results agree with both the *ab initio* and MM optimised geometries and the observed and calculated conformer energies are in reasonable agreement to give ΔG (ax–eq) 0.6 kcal mol^{-1} for γ-valerolactone, ΔG (boat–half-chair) 0.9 kcal mol^{-1} for δ-valerolactone and ΔG (boat–chair) > 3.5 kcal mol^{-1} for ε-caprolactone.

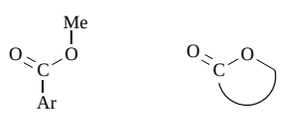
Introduction

The lactone group is a constituent of a large number of naturally occurring metabolites[2] and the synthesis and configuration of substituted lactones is of considerable chemical importance. Despite this there have been relatively few investigations into their structures, conformations and conformer energies. The simple lactones are liquid and not suitable for X-ray analysis and their structures are too complex and unsymmetric for microwave (MW) and electron diffraction studies. Thus Wiberg and Waldron in a recent investigation[3] had to use structures generated by *ab initio* and molecular mechanics (MM) calculations without recourse to experimental data. We now report a LIS and theoretical analysis of the basic lactones, isocoumarin (**1**), coumarin (**2**), 3,4-dihydrocoumarin (**3**), β-butyrolactone (**4**), γ-valerolactone (**5**), δ-valerolactone (**6**) and ε-caprolactone (**7**), of which **3** and **5**–**7** may exhibit conformational flexibility.



1 **2** **3** **4** **5** **6** **7**

Lactones are esters constrained by their cyclic nature to adopt the less stable[4] (*E*)-conformation, as evidenced by their much lower dipole moments (1.9 D *vs*. 4.5 D), enhanced reactivity towards hydrolysis and enhanced basicity[3,5] compared with acyclic esters.



's-*cis*' or '*Z*' 's-*trans*' or '*E*'

Also lactones have a partial double bond, the O–CO bond in the ring and their ring conformations resemble those of the corresponding cycloalkenes rather than cycloalkanes, with four sequential ring atoms in the same plane. Thus isocoumarin (**1**) and coumarin (**2**) are planar, whilst 3,4-dihydrocoumarin (**3**) would be expected to be non-planar, analogous to 3,4-dihydronaphthalene.[4] Similarly the saturated lactones with four-, five-, six- and seven-membered rings would be expected to have conformations analogous to their olefinic analogues.

β-Butyrolactone (**4**) has been reported to be planar on the basis of MW spectra and *ab initio* (3-21G) calculations,[6] but recent MM3 calculations have given very different geometrical parameters.[7] A Kerr constants study suggested that γ-valerolactone (**5**) exists in an envelope conformation,[8] but the calculated (3-21G) energies for the envelope and twist conformations were very similar.[9] Jaime *et al*.[10] showed that the substituted γ-butyrolactones they studied by NMR existed in two (often degenerate) envelope conformations with C4 out of the plane of the other four atoms and their results were consistent with *ab initio* and MM calculations.

Six-membered ring lactones have been found to be slightly less stable than five-membered ring ones,[11] and analogous to cyclohexene,[4,12] both half-chair[13] and boat[14] conformations have been suggested for δ-valerolactones. Wiberg and Waldron[3] reported some geometrical parameters of δ-valerolactone (**6**)

† fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione.

from *ab-initio* MP2/6-31G* calculations but no conformer energies were given. A Raman and MW study determined the half-chair to be more stable by *ca*. 0.6 kcal mol^{-1} in agreement with MM calculations[15] and Lambert[16] from the temperature dependence of vicinal H–H couplings obtained 1.0 kcal mol^{-1} energy difference in favour of the half-chair form. Neither of these determinations are definitive as few resonances from the boat form were observed in ref. 16 and three parameter fits of the temperature dependence of vicinal couplings in terms of the unknown conformer couplings and the conformer energy difference are notoriously poorly determined.[17]

The observed vicinal proton couplings of some *gem*-dimethylphenyl-δ-valerolactones were indicative of the half-chair conformation,[18] *e.g.* in 2,2-dimethyl-4-phenylvalerolactone the H3–H4 and H4–H5 couplings are 5.0 and 11.0, and 12.8 and 3.5 Hz, respectively, confirming the staggered arrangement of the CH_2–CHPh–CH_2 fragment. In contrast the H4–H5 couplings in the CH_2–CH_2 fragment of 3,3-dimethyl-2-phenylvalerolactone are 5.6, 5.4, 5.5 and 9.0 Hz and these were interpreted as arising from more than one equilibrating conformation.

Molecular mechanics calculations on ε-caprolactone (**7**) predicted the chair conformation as the most stable form, the boat and half-chair being 2.7 and 4.2 kcal mol^{-1} higher in energy.[19] The conformation with a *trans* lactone ring was even higher in energy (5.3 kcal mol^{-1}). In agreement with these calculations a MW study could detect only the chair conformation.[20]

Gray *et al.*[21] performed a comprehensive LIS study on 22 substituted coumarins, mainly to determine the substitution pattern and found that the lanthanide appears to preferentially bind the carbonyl oxygen *anti* to the heterocyclic oxygen. Previous LIS investigations in our laboratories have demonstrated the importance and utility of the LIS method in determining the structures and conformations of a variety of molecules in solution[1,22–28] and the essential conditions necessary for successful LIS studies have been given. Amongst these are the determination of only one or two molecular parameters (*e.g.* a torsional angle or conformer ratio) and both the quality and the comprehensiveness of the experimental data. In particular, (*i*) Yb(fod)$_3$-induced shifts (ΔM_i) are collected for all the ^{1}H and ^{13}C nuclei of the substrate, (*ii*) Lu(fod)$_3$ is used[1,23] to evaluate diamagnetic complexation contributions (ΔD_i), and (*iii*) pseudocontact contributions $(\Delta M - \Delta D)_i$ are simulated according to the McConnell–Robertson equation[29] and a chemically reasonable two- or four-site complexation model is used.[27] Recent very accurate *ab initio* calculations[30] on carbonyl complexes in which the C=O · · · M (M = H, B *etc*.) angle is *ca*. 120° strongly supports the use of multisite models.

Excellent results with the crystallographic agreement factor R_{cryst} < 0.5% were obtained for unhindered aromatic ketones when reliable starting geometries were available.[23] It was shown recently[22] using this refined LIS technique that simple aromatic ester structures (*e.g.* methyl benzoate) obtained from geometry optimisation using the recommended GAUSSIAN 6-31G* basis set[31,32] did not give good agreement factors when applied to the LIS data whereas the experimental crystal structures gave much better agreement factors. Thus the refined LIS method given in preceding parts of this series is now a sensitive method of testing molecular structures in solution.

Experimental

All samples were obtained commercially (Aldrich and Fluka), except isocoumarin (**1**) and 3,4-dihydrocoumarin (**3**). **1** was prepared from *N*-methylbenzamide *via* 1-hydroxy-2-methyl-3-oxo-1,3-dihydroisoindole following the procedure of Narasimhan and Mali[33] and **3** was obtained as a gift from Professor Ranise (Genoa University). **3**–**6** were purified by distillation and chromatography prior to use, the others were used directly for the LIS experiments. The solutions were made up to 0.5 M in deuteriochloroform which had been stored for at least 24 h over molecular sieves prior to use. The shift reagent Yb(fod)$_3$ is available commercially and Lu(fod)$_3$ was prepared following the method of Springer *et al.*[34] The shift reagents were dried *in vacuo* over P_2O_5 at *ca*. 35 °C for 24 h, and maintained *in vacuo* over P_2O_5 between successive additions to the sample. Three additions of shift reagent (*ca*. 15–20 mg) were weighed directly in the NMR tube. The plots of chemical shift *vs.* ρ the ligand : substrate ratio were checked for linearity (all correlation coefficients >0.999) and for the intercept at the origin (a good test for any impurities). The slopes obtained are the Δ*M* values recorded. The diamagnetic shifts (Δ*D*) were obtained from identical experiments using Lu(fod)$_3$.

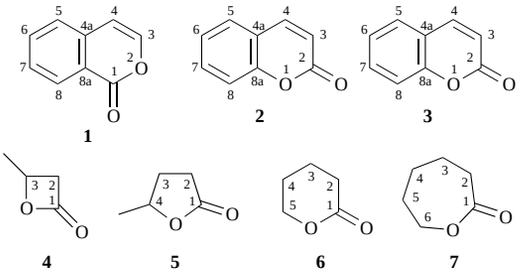


Fig. 1 Numbering of compounds **1**–**7** used in Tables 1 and 2

For compounds **3**–**7** the LIS measurements were recorded on a Varian Gemini 200 spectrometer operating on ^{1}H and ^{13}C nuclei at 22 °C. Digital resolution was better than 0.09 Hz for the proton spectra and 0.36 Hz for the carbon spectra, a 4 s pulse delay was used for the accumulation of the carbon spectra. Compounds **1** and **2** were recorded on a Bruker AMX-400 spectrometer. Typical proton spectral widths were 6000 Hz with 128 K transform, carbon spectral widths were typically 23 000 Hz with 128 K transform using a line broadening of 2.0 Hz.

Spectral assignments

The spectral assignments for all the compounds except **5** and **7** were straightforward utilising previous literature assignments for **1**,[33,35] **2**,[36–39] **3**,[36] **4**,[40,41] **5**[40] and **6**,[40,42] additive substituent chemical shifts[43] and the size of the Δ*M* values obtained. Note that in **4** and **5** in which the methylene protons vicinal to the methyl groups are well separated, the assignment given is supported by the general rule that methyl SCS are negative (*i.e.* upfield) for the *cis* proton and positive (*i.e.* downfield) for the *trans* proton.[44] In caprolactone **7**, COSY and HETCOR correlations were needed to assign the proton and carbon spectra. Full details of all the spectral assignments are given elsewhere.[45] The observed chemical shifts (δ), diamagnetic shifts (Δ*D*), LIS values (Δ*M*) and pseudo-contact shifts [$\Delta M(PC) = \Delta M - \Delta D$] are given in Tables 1 and 2 for the compounds measured here. The numbering used is consistent but as it is not the standard numbering for all the molecules this is given explicitly in Fig. 1.

The initial molecular geometries were taken from either experimental (*i.e.* X-ray or microwave) data or molecular mechanics (PCMODEL,[46] NEMESIS[47]) and *ab initio* optimisations (GAUSSIAN92/94[31] with the recommended 6-31G* basis set)[32] and the ring geometries for the stable conformers of all the compounds studied are given in Table 3. Further details of all these geometries and of those of the less stable conformers are given in ref. 45.

Results

The lanthanide complexation model

It is first necessary to determine the most appropriate complexation model for the lactones and following our previous procedure the conformationally rigid planar molecules of coumarin and isocoumarin were selected as suitable substrates. For

Table 1 Observed carbon and proton chemical shifts (δ), LIS values (ΔM), diamagnetic shifts (ΔD) and pseudo-contact shifts ΔM(PC) for isocoumarin (**1**), Coumarin (**2**) and 3,4-dihydrocoumarin (**3**)

Compound		CO	C_3	C_4	C_{4a}	C_5	C_6	C_7	C_8	C_{8a}	H_3	H_4	H_5	H_6	H_7	H_8
1	δ	162.197	144.722	107.011	136.470	125.560	134.787	128.582	129.613	121.884	7.276	6.505	7.432	7.717	7.520	8.286
	ΔM	152.75	28.61	25.52	30.22	16.73	15.40	18.32	44.70	61.66	15.09	13.91	11.31	8.38	9.09	49.46
	ΔD	4.27	−0.59	1.96	0.85	0.35	1.71	0.92	1.22	−0.92	—	0.17	—	—	—	0.17
	$\Delta M - \Delta D$	148.48	29.11	23.56	29.37	16.38	13.69	17.40	43.48	62.58	15.09	13.74	11.26	8.30	9.09	49.29
2	δ	160.767	116.664	143.480	118.843	127.904	124.444	131.836	116.852	154.047	7.705	6.406	7.502	7.290	7.502	7.290
	ΔM	121.68	51.07	24.54	19.19	9.93	8.07	8.19	13.05	24.57	36.70	12.06	6.89	4.65	4.98	10.05
	ΔD	5.11	−0.13	2.66	0.72	0.60	1.54	1.21	0.71	−0.26	0.35	0.11	—	—	—	—
	$\Delta M - \Delta D$	116.57	51.20	21.88	18.47	9.33	6.53	6.97	12.33	24.83	36.35	11.95	6.89	4.65	4.98	10.05
3	δ	168.399	29.190	23.677	122.562	127.931	124.288	128.144	116.812	151.882	2.785	2.993	7.198	7.127	7.250	7.036
	ΔM	166.50	65.75	28.37	24.60	12.93	10.75	10.38	17.12	32.10	47.90	20.39	9.35	6.26	6.73	13.50
	ΔD	7.84	—	−0.83	0.12	0.41	1.49	0.53	0.44	—	0.35	—	—	—	—	—
	$\Delta M - \Delta D$	158.66	65.73	29.30	24.48	12.52	9.26	9.85	16.68	32.62	47.55	20.39	9.35	6.26	6.73	13.50

1a Yb(fod)$_3$ S_0 = 0.55 mM. ρ = 3.64, 8.93, 13.89 × 10^{-2}, corr. coef. >0.9998. **1b** Lu(fod)$_3$ S_0 = 0.55 mM. ρ = 2.90, 5.97, 9.44 × 10^{-2}, corr. coef. >0.9946. **2a** Yb(fod)$_3$ S_0 = 0.53 mM. ρ = 4.03, 8.01, 12.15 × 10^{-2}, corr. coef. >0.9998. **2b** Lu(fod)$_3$ S_0 = 0.53 mM. ρ = 2.86, 8.25, 11.96 × 10^{-2}, corr. coef. >0.9911. **3a** Yb(fod)$_3$ S_0 = 0.53 mM. ρ = 5.43, 8.56, 13.97 × 10^{-2}, corr. coef. >0.9998. **3b** Lu(fod)$_3$ S_0 = 0.55 mM. ρ = 3.33, 7.27, 12.54 × 10^{-2}, corr. coef. >0.9970.

Table 2 Carbon and proton chemical shifts (δ), LIS values (ΔM), diamagnetic shifts (ΔD) and pseudo-contact shifts ΔM(PC) for β-butyrolactone (**4**), γ valerolactone (**5**), δ-valerolactone (**6**) and ε-caprolactone (**7**)[a]

		CO	C_2	C_3	C_4	C_5	C_6	C_{Me}	H_2	*	H_3	*	H_4	H_5	H_{Me}
4	δ	167.892	44.377	67.858	—	—	—	20.639	3.068(*c*)[b]	3.576(*t*)[b]	4.703	—	—	—	1.576
	ΔM	152.22	52.57	38.50	—	—	—	18.03	32.59(*c*)[b]	32.44(*t*)[b]	24.64	—	—	—	15.48
	ΔD	7.82	−0.69	3.83	—	—	—	−0.57	—	—	—	—	—	—	—
	$\Delta M - \Delta D$	144.40	53.26	34.68	—	—	—	18.60	32.59(*c*)[b]	32.44(*t*)[b]	24.64	—	—	—	15.48
5	δ	177.129	29.092	29.710	77.226	—	—	21.063	2.558	—	1.837(*c*)[b]	2.387(*t*)[b]	4.653	—	1.418
	ΔM	150.36	57.87	26.96	33.63	—	—	16.31	38.42	—	18.73(*c*)[b]	16.63(*t*)[b]	22.24	—	13.67
	ΔD	8.29	0.87	−0.36	4.18	—	—	−0.49	0.28	—	—	—	—	—	—
	$\Delta M - \Delta D$	142.07	57.00	27.32	29.45	—	—	16.80	38.14	—	18.73(*c*)[b]	16.63(*t*)[b]	22.24	—	13.67
6	δ	171.283	29.859	19.115	22.328	69.433	—	—	2.561	—	1.891	—	1.891	4.352	—
	ΔM	172.73	66.35	27.95	24.33	34.99	—	—	49.68	—	19.64	—	17.81	22.74	—
	ΔD	8.12	−0.16	−0.71	−0.30	2.37	—	—	0.17	—	—	—	—	0.07	—
	$\Delta M - \Delta D$	164.61	66.51	28.66	24.62	32.62	—	—	49.51	—	19.64	—	17.81	22.67	—
7	δ	175.984	34.580	22.994	28.963	29.345	69.245	—	2.646	—	1.776	—	1.776	1.817	—
	ΔM	157.21	58.88	28.15	18.26	19.20	32.67	—	44.99	—	22.37	—	13.13	15.41	—
	ΔD	7.12	−0.20	−0.53	0.10	−0.68	2.35	—	0.10	—	—	—	—	—	—
	$\Delta M - \Delta D$	150.09	59.08	28.68	18.16	19.88	30.32	—	44.89	—	22.37	—	13.13	15.41	—

[a] H6 Compound (**7**), δ 4.234, ΔM 21.76, ΔD 0.0. **4a** Yb(fod)$_3$ $S_0 = 0.50$ mM. $\rho = 3.19, 6.89, 10.92 \times 10^{-2}$, corr. coef. >0.9972. **4b** Lu(fod)$_3$ $S_0 = 0.50$ mM. $\rho = 2.57, 7.26, 10.49 \times 10^{-2}$, corr. coef. >0.9914. **5a** Yb(fod)$_3$ $S_0 = 0.60$ mM. $\rho = 2.81, 6.46, 9.95 \times 10^{-2}$, corr. coef. >0.9989. **5b** Lu(fod)$_3$ $S_0 = 0.52$ mM. $\rho = 3.42, 7.22, 11.18 \times 10^{-2}$, corr. coef. >0.9985. **6a** Yb(fod)$_3$ $S_0 = 0.61$ mM. $\rho = 2.87, 6.33, 10.14 \times 10^{-2}$, corr. coef. >0.9999. **6b** Lu(fod)$_3$ $S_0 = 0.59$ mM. $\rho = 4.43, 7.59, 12.40 \times 10^{-2}$, corr. coef. >0.9994. **7a** Yb(fod)$_3$ $S_0 = 0.50$ mM. $\rho = 4.53, 11.62, 14.52 \times 10^{-2}$, corr. coef. >0.9999. **7b** Lu(fod)$_3$ $S_0 = 0.54$ mM. $\rho = 3.02, 8.76, 13.12 \times 10^{-2}$, corr. coef. >0.9992. [b] *c* = *cis*, *t* = *trans* to the methyl group.

Table 3 Experimental and optimised lactone geometries[a,b,c]

		a	b	c	d	e	f	g	ab	bc	cd	de	ef	fg	ga
1	G92	1.184	1.352	1.351	1.321	1.456	1.395	1.477	118.63	122.95	123.68	118.99	117.81	120.28	125.06
	PCMOD	1.225	1.347	1.357	1.355	1.463	1.413	1.475	119.70	123.68	121.03	120.04	118.42	118.06	121.54
	NEM	1.221	1.371	1.369	1.339	1.342	1.349	1.344	116.65	119.42	119.74	120.41	120.74	120.00	123.66
2	Expt 1	1.204	1.368	1.374	1.389	1.435	1.357	1.451	117.12	121.85	121.40	118.18	120.18	120.99	125.48
	Expt 2	1.205	1.366	1.378	1.395	1.432	1.344	1.448	117.30	121.63	121.59	117.69	119.98	121.96	125.55
	G92	1.184	1.353	1.354	1.388	1.453	1.330	1.468	118.89	123.73	121.20	117.15	120.52	121.06	124.77
	PCMOD	1.225	1.347	1.361	1.411	1.463	1.358	1.469	120.28	122.69	120.15	118.81	119.37	119.48	120.21
	NEM	1.238	1.351	1.370	1.410	1.441	1.363	1.434	118.17	121.52	120.45	118.51	119.40	120.18	121.89
3	G92	1.180	1.344	1.373	1.385	1.508	1.502	1.510	119.22	122.63	121.46	117.88	109.59	113.15	124.48
	PCMOD	1.223	1.342	1.373	1.405	1.506	1.487	1.518	120.45	122.99	120.11	119.13	112.29	112.95	120.52
4	Expt	1.169	1.430	1.430	1.520	1.521	1.520	—	133.80	91.00	92.40	84.25	—	—	—
	G92	1.173	1.342	1.446	1.536	1.517	1.510	—	128.38	93.24	89.33	83.24	—	—	—
	PCMOD	1.205	1.353	1.412	1.521	1.511	1.528	—	129.89	91.26	92.27	81.38	—	—	—
5	G92	1.181	1.334	1.427	1.532	1.526	1.517	1.514	123.10	112.35	104.36	101.02	102.89	—	—
	PCMOD	1.221	1.335	1.414	1.541	1.539	1.513	1.530	123.28	111.77	104.21	104.29	99.93	—	—
6	G92	1.184	1.334	1.420	1.517	1.525	1.528	1.518	119.65	123.34	113.15	109.01	108.98	114.91	121.98
	PCMOD	1.224	1.341	1.414	1.531	1.533	1.533	1.520	119.57	124.04	110.48	108.76	109.77	113.10	118.92
7	G92	1.185	1.333	1.416	1.523	1.529	1.529	1.515	118.99	124.07	113.57	114.48	114.67	114.32	—
	PDMOD	1.224	1.340	1.414	1.533	1.536	1.536	1.520	119.14	124.84	110.44	113.40	114.63	113.63	—

[a] Bond lengths in Å and bond and dihedral angles in degrees. [b] Other bond lengths and bond angles: **7** h 1.515, **4** ea 137.43°, fd 118.43°, fc 111.82°; **5** fa 127.78°, gd 115.83°, gc 109.00°; **7** gh 113.66°, ha 122.16°. [c] Torsional angles: **3** bcd −19.7°, def 31.6°, gfe −48.8°; **4** bcf −120.4°, fde 114.5°; **5** bcd 20.9°, cde −31.8°, def 30.9°, efa 159.5°, bcg 145.2°, gde −151.6°; **6** abc −162.6°, bcd −36.5°, cde 53.8°, def −58.0°, efg 44.8°, fga 158.5°; **7** abc −175.9°, bcd −71.2°, cde 79.7°, def −58.2°, efg 59.7°, fgh −79.8°, gha −115.3°, all others 0° or 180°.

Table 4 LIRAS3/4 analysis of isocoumarin (**1**) and coumarin (**2**)

Method	No. of sites	R_{cryst} (%)	r/Å	φ/°	ψ/°	Pop (%)[a]
Isocoumarin (**1**)						
GAUSS	2	0.623	2.75	61	148	17
	3	0.674	2.80	45	—	6
PCMOD	2	0.809	2.63	53	162	0
	3	1.225	2.53	54	—	0
NEMESIS	2	1.512	2.25	64	167	0
	3	1.552	2.21	63	—	0
Coumarin (**2**)						
EXPTL[b]	2	0.633	2.85	55	146	68
	3	0.665	2.83	43	—	16
EXPTL[c]	2	0.651	2.85	57	144	68
	3	0.769	2.80	44	—	17
GAUSS	2	0.830	2.83	66	140	68
	3	0.730	2.87	43	—	
PCMOD	2	0.614	2.68	55	154	69
	3					
NEMESIS	2	0.549	2.68	55	154	69
	3	0.580	2.61	49	—	17

[a] In the two-site model the % population is *anti* to the heterocyclic oxygen; in the three-site model the % population is for the *anti* lone pair in **1** and for the eclipsed lone pair in **2** (see text). [b] Ref. 48. [c] Ref. 49.

coumarin two reliable crystal structures were available[48,49] and in addition optimised geometries were generated. For isocoumarin we were unable to find a suitable crystal structure in the literature and thus used optimised geometries (Table 3).

These geometries were used with the pseudo-contact shifts (Table 1) to determine the appropriate lanthanide complexation model. The two possible complexation models for the lactone carbonyl group are the two-site model of LIRAS3 in which the lanthanide geometries expressed in the polar coordinates (r, φ, ψ) are symmetrical with respect to the π plane of the carbonyl, any asymmetry being reflected solely in the lanthanide populations and the three site model of LIRAS4 modelling sp^3 type complexation in which the lanthanide complexes to three oxygen lone-pairs with 120° dihedrals. Full details of these programmes have been given.[25,26]

The results of this analysis are given in Table 4 and are of some interest. The lanthanide complexation positions are all similar for the various molecular geometries, as expected, and agree well with those deduced by previous investigations.[21,35] In coumarin the lanthanide prefers the position *anti* to the ether oxygen as in the methyl esters, probably due to the greater nucleophilicity of this lone pair. In isocoumarin, owing to the steric hindrance of the perihydrogen, this tendency is reversed. The best fit for the three-site model in coumarin has the three oxygen sp^3 lone-pairs arranged so that one eclipses the ether oxygen and this lone pair has the minor population. In isocoumarin this lone pair is *anti* (*trans*) to the ether oxygen and again has the minor population (see Table 4).

For coumarin the crystal structures give very good agreement factors (AF), slightly better for the two-site model and similar AF are given for the MM geometries of PCMODEL and NEMESIS. The *ab initio* geometry of GAUSSIAN92 gives a slightly poorer AF which is still acceptable. (Note, any AF less than 1.0% is considered acceptable though many solutions have AF less than 0.5%.) For isocoumarin the results are quite different in that the GAUSSIAN geometry gives the best AF and again the two-site model is slightly better than the three-site. The PCMODEL geometry gives an acceptable AF for the two-site model but not for the three-site model, but the NEMESIS geometry does not give an acceptable AF with either complexation model. There are substantial differences between the NEMESIS geometry and the other optimised geometries (*cf.* bonds e, f and g which are much shorter than for the other geometries) and this suggests that this force field may not be adequately parametrised for this type of molecule. Thus we will restrict further consideration to the geometries given by PCMODEL and GAUSSIAN92. These results also show that the two-site model is to be preferred to the three-site for these systems and we will consider henceforth only the two-site model. For more detailed discussion see ref. 45.

Conformational analysis

The LIS data in Tables 1 and 2 may now be used to investigate the conformational equilibria in these compounds. It is important to restate the caveat mentioned earlier, that due to the small number of LIS only one or two unknowns can be investigated in any given system. Here we will attempt to determine the conformations and conformational equilibria in these compounds and also one key geometric parameter, the ring torsional angle which of course may differ in the different conformers. From the above results the analysis of the observed LIS was carried out using the LIRAS3 programme incorporat-

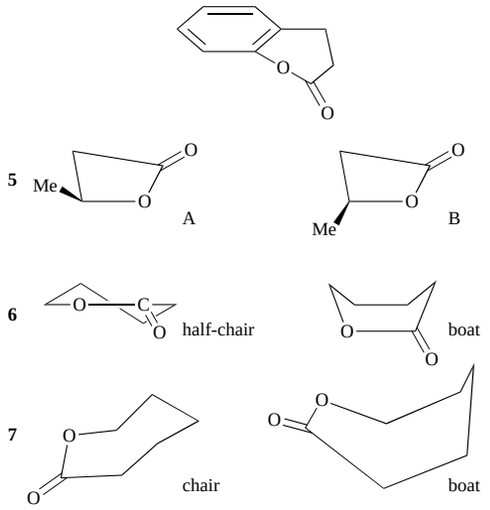


Fig. 2 Possible lactone conformations

ing the four-site complexation model. Following from ref. 1 we may regard any solution (observed minus calculated shifts) with an agreement factor (AF) <1.0% (*i.e.* 0.01) and with all calculated LIS within 1.0 ppm of the observed shifts as an acceptable solution

Dihydrocoumarin (3). Owing to the CH_2–CH_2 fragment, the lactone ring of hydrocoumarin is not planar but puckered and it is of interest to see whether the LIS method can determine the extent of this pucker. No suitable crystal geometry for this compound was available thus the starting geometries were obtained from MM and *ab initio* calculations. They are very similar (see Table 3) and in both geometries the benzene ring and atoms O1 and C4 are coplanar. The conformation of the lactone ring is however not an envelope conformation with only C3 out of the plane, but a puckered conformation with both C2 and C3 appreciably displaced from the aromatic ring plane even though the fragment C–O–C=O–C is still planar. The conformation may be defined by the angle α between the aromatic ring plane and that defined by the atoms O1–C2–C3–C4 which is calculated to be *ca.* 155° by both PCMODEL and GAUSSIAN. These geometries were input with the observed pseudo-contact shifts into LIRAS3 and the angle of pucker α searched for the best solution. A well defined minimum in the plot of AF *vs.* α was found with excellent AF values of 0.30 and 0.46, respectively, for both geometries with values of α corresponding to those of the initial geometries. Thus the LIS method provides strong support for the conformation of this lactone as predicted by the optimised geometries.

β-Butyrolactone (4). The four-membered ring of β-butyrolactone is constrained by strain energy to be planar and both experiment[6] and theory (PCMODEL and G92, see Table 3) agree that both the ring and the carbonyl oxygen are coplanar. Thus the conformation of this molecule is not in question, but it is of some interest to see whether the two-site model can adequately reproduce the observed pseudo-contact shifts in this highly strained molecule. The observed and calculated geometries are again very similar (Table 3) and these geometries when input into LIRAS3 with the observed pseudo-contact shifts (Table 2) all gave good AF values (Table 5), that for the PCMODEL geometry being slightly larger than those for the MW and G92 geometries. The results thus confirm unequivocally the applicability of the LIS method to even highly strained molecules such as **4**.

γ-Valerolactone (5). Again in the absence of an experimental structure for this molecule we used optimised geometries. Both PCMODEL and GAUSSIAN gave optimised geometries (Table 3) which were for the envelope conformation with C4 out of the plane formed by the other four atoms and no other optimised geometry could be found. Owing to the methyl substitu-

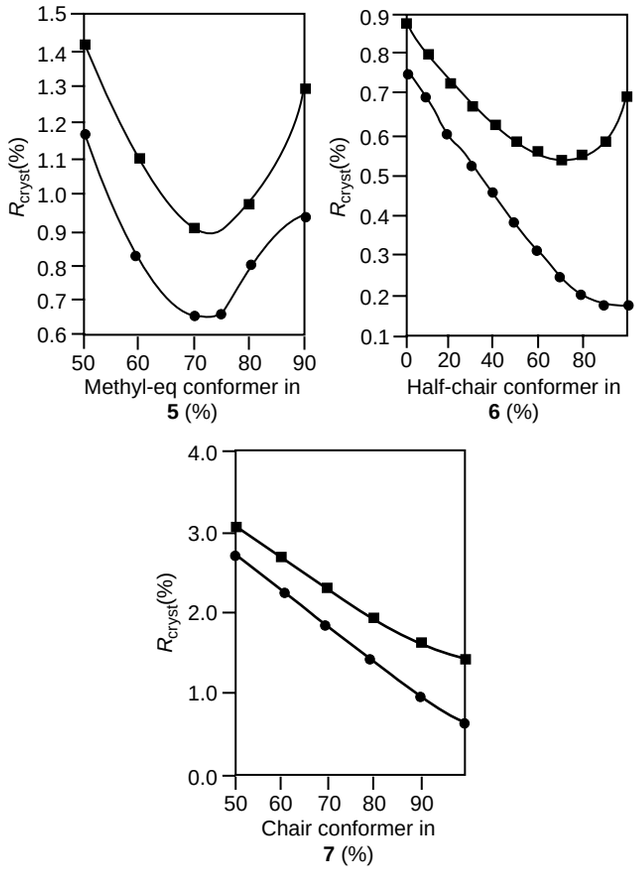


Fig. 3 Agreement factor (R_{cryst}) *vs.* (*a*) the % methyl-eq conformer in **5**, (*b*) the % half-chair conformer in **6** and (*c*) the % chair conformer in **7**; ■ PCMODEL and ● GAUSSIAN92 geometry

ent there are however two possible conformations for this molecule with the methyl pseudo-equatorial (A) and pseudo-axial (B) (Fig. 2, A and B). Apart from the calculated energies (see later) there is no experimental evidence relating to the proportions of these conformers. The NMR chemical shifts and coupling constants are not useful in this case as the proton spectrum is a complex second-order spin system with the H2 prochiral methylene protons not resolved at 200 MHz. Also the barrier to interconversion of the two conformers would be expected to be too low to observe the individual conformers by low temperature NMR spectroscopy.

The LIS data can now be used to determine the percentage of the two forms present. A combined Z-matrix consisting of both conformers was created and used as input into the LIRAS3 programme, varying the proportions of the two conformers. Both the GAUSSIAN and PCMODEL geometries gave well defined minima in these plots of R_{cryst} *vs.* % for 72% of the pseudo-equatorial conformer with AF values of 0.66 and 0.91, respectively [Fig. 3(*a*)]. The angle of pucker of the envelope was also varied from that of the optimised geometries (165 and 153°) but this did not give any better solution. Finally, as the assignment of H3a and H3b in Table 2 was based on general chemical shift considerations this assignment was reversed and the LIRAS3 programme again searched for the minumum AF. In this case the AF values were much worse (*ca.* 1.3%) and this result provides strong supporting evidence for the correctness of the assignment given in Table 2.

δ-Valerolactone (6). The conformational analysis of the six-membered ring of δ-valerolactone for which again there was no experimental geometry available, proceeded in a similar fashion to the above. There are a number of possible conformations for the six-membered ring. Eliel *et al.*[4] describes five theoretically possible conformers, the chair, boat, twist, envelope (sofa) and half-chair. However the only optimised geometries, *i.e.* geom-

Table 5 LIRAS3 analysis of 3,4-dihydrocoumarin (**3**), β-butyrolactone (**4**), γ-valerolactone (**5**), δ-valerolactone (**6**) and ε-caprolactone (**7**)

Compound	Geometry	R_{cryst} (%)	r/Å	φ/°	ψ/°	Pop (%)[a]
3	G92	0.457	2.72	66	144	63
	PCMOD	0.304	2.53	55	166	69
4	MW	0.838	2.52	69	152	92
	G92	0.662	2.70	91	137	76
	PCMOD	0.959	2.60	65	146	87
5[b]	G92	0.661	2.80	60	141	77
	PCMOD	0.906	2.63	50	162	100
6	G92[c]	0.175	2.57	62	151	60
	PCMOD[d]	0.549	2.52	51	176	100
7[e]	G92	0.654	2.22	73	177	30
	PCMOD	1.426	2.21	69	178	13

[a] For the 4-site model the % population is *anti* to the heterocyclic oxygen. [b] 72% methyl equatorial conformer. [c] 96% half-chair. [d] 70% half-chair. [e] 100% chair.

Table 6 Observed and calculated conformer energies (kcal mol^{-1}) for **5**–**7**

	Conformer	Observed LIS	Calculated HF/6-31G*	Calculated PCMODEL
5	Me (ax)–Me (eq)	0.59	0.76	0.16
6	Boat–chair	0.9	1.16	0.41
7	Twist–chair	>3.0	5.60	4.31
	Boat–chair	>3.0	3.60	3.51

etries with a minimum energy on the potential surface obtained by both PCMODEL and GAUSSIAN were the half-chair and the boat conformations (Fig. 2). All the other possible conformers relaxed to these conformers when optimised. Thus the LIS analysis considered only these two conformers. The geometries for these forms are given in Table 3 and the results obtained by combining these two forms in one Z-matrix and varying their populations are shown schematically in Fig. 3(*b*). All the geometries give acceptable agreement factors (*i.e.* R_{cryst} <1%) and this is very probably due to the general spatial similarity of the boat and half-chair conformers together with the not very over-determined nature of this system (nine equations in five unknowns). Nevertheless the LIS analysis does lead to some useful conclusions. The PCMODEL geometry gives a well-defined minimum with *ca*. 23% of the boat form with an acceptable AF of 0.55%.The GAUSSIAN geometry gives the best solution with R_{cryst} 0.18% for 100% of the half-chair form but excellent solutions (R_{cryst} < 0.2%) for up to 20% of the boat form. At this point the AF increases rapidly. Thus for this geometry any solution with <20% of the boat form is fully acceptable with the LIS data. Thus for this compound the LIS analysis is not as definitive but we may conclude that the half-chair conformation is the stable conformer with up to *ca*. 20% of the boat form.

ε-Caprolactone (7). The seven-membered ring of ε-caprolactone has even more flexibility than those previously considered and as a consequence both PCMODEL and G92 optimised to three distinct conformations, the chair, boat and twist conformation (Fig. 2), with the boat and particularly the twist conformation calculated to be considerably higher in energy than the chair. The conformational analysis proceeded as previously though in this case for simplicity we assumed a mixture of (i) the chair and boat and (ii) the chair and twist form as the introduction of more than two interconverting conformers would give a much more complex input and analysis. In this case this approach was amply justified as both plots of R_{cryst} *vs*. the % composition gave the best AF for 100% chair form with no indication of any appreciable amount of the boat or twist conformer. The plot of the chair and boat conformations is shown in Fig. 3(*c*), that of the chair and twist conformations is very similar and is given in ref. 45. The G92 geometry gave a very acceptable AF (0.65%), but that for the PCMODEL geometry (1.43%) was only moderately acceptable. Thus the result of the LIS analysis in this case is that ε-caprolactone exists completely in the chair conformation with no significant amount of any other form.

Discussion

The lanthanide complexation geometries and crystallographic agreement factors R_{cryst} for the best solutions for compounds **4**–**7** are given in Table 5. It is instructive also to compare the results obtained here for the conformer energies with those of other investigations and with the *ab initio* and modelling calculations and these are collected in Table 6.

The lanthanide complexation geometries are unremarkable. In all cases except one the lanthanide prefers to coordinate with the lone pair *anti* to the heterocyclic oxygen atom exactly as found previously for the methyl esters[22] and for coumarin.[21] This is very probably due to the greater basicity of this lone pair which has been noted also in protonation studies. In caprolactone (**7**) this tendency is not observed, but in this case for both the G92 and PCMODEL geometries the lanthanide complexes essentially along the C=O axis (note ψ ≈ 180°, Table 5) and thus the % population in the lone pairs is not well-defined. It is also possible that in the seven-membered ring steric hindrance between the lanthanide and the α protons of the ring is greater than in the six- or five-membered ring (note that one O=C–C–H dihedral angle is *ca*. 0° for the seven-membered ring compared with *ca*. 30 and 60° for the six- and five-membered rings).

The observed and calculated conformer energies are given in Table 6 and are of some interest. In general the conformer energies calculated from the GAUSSIAN and PCMODEL are in very reasonable agreement with those obtained from the LIS analyses, though the PCMODEL calculated energies are rather low for **5** and **6**, whereas the G92 energies are almost identical with the LIS data. The methyl group pseudo-axial *vs*. pseudo-equatorial energy in **5** may be compared with the analogous value in cyclohexane (1.9 kcal mol^{-1})[4] and may be considered an appropriate model for the ax–eq difference in the cyclopentane ring.

The boat *vs*. chair energy difference obtained for **6** which is not as definitive as the result for **5** is also in good agreement with the earlier estimates of 0.6 kcal mol^{-1} obtained previously by Allinger[15] and by Lambert.[16] Thus considering all the observed and calculated values the general conclusion would support the value of 0.9 kcal mol^{-1} as the boat minus half-chair energy difference in **6**.

In caprolactone (**7**) the LIS results agree entirely with both the calculated energy differences and also with the previous microwave data[17] thus we can conclude that in **7** no significant amount of any conformer except the chair form is present in condensed media. This result could be of some significance in the conformational analysis of seven-membered ring systems.

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References

1 Part 29, R. J. Abraham, S. Angiolini, M. Edgar and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1997, 41.
2 S. Omura, *Macrolide Antibiotics, Chemistry, Biology and Practice*, Academic Press, New York, 1984.

3 K. B. Wiberg and R. F. Waldron, *J. Am. Chem. Soc.*, 1991, **113**, 7697, 7705.
4 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of organic compounds*, Wiley, New York, 1994 and refs. therein.
5 R. Huisgen and H. Ott, *Tetrahedron*, 1959, **6**, 253.
6 R. Gonzalez, J. C. Lopez and J. L. Alonso, *J. Mol. Struct.*, 1990, **223**, 365.
7 N. L. Allinger, Z. S. Zhu and K. Chen, *J. Am. Chem. Soc.*, 1992, **114**, 6120.
8 L. H. L. Chia, H. H. Huang and Y. F. Wong, *J. Chem. Soc.* (*B*), 1970, 1138.
9 N. V. Riggs, *Aust. J. Chem.*, 1985, **38**, 1575.
10 C. Jaime, R. M. Ortuna and J. Font, *J. Org. Chem.*, 1986, **51**, 3946.
11 J. M. Brown, A. D. Conn, G. Pilcher, M. L. P. Leitao and Y. Meng-Yan, *J. Chem. Soc., Chem. Commun.*, 1989, 1817.
12 F. A. L. Anet, in *Conformational analysis of cyclohexenes, cyclohexadienes and related hydroaromatic compounds*, ed. P. W. Rabideau, VCH, New York, 1989.
13 A. McL. Mathieson, *Tetrahedron Lett.*, 1963, 81.
14 K. K. Cheung, K. H. Overton and G. A. Sim, *Chem. Commun.*, 1965, 634.
15 T. Philip, R. L. Cook, T. B. Malloy, Jr., N. L. Allinger, S. Chang and Y. Yuh, *J. Am. Chem. Soc.*, 1981, **103**, 2151.
16 J. D. Lambert and M. L. E. TeVrucht, *Org. Magn. Reson.*, 1984, **22**, 613.
17 R. J. Abraham, P. Leonard, T. A. D. Smith and W. A. Thomas, *Magn. Reson. Chem.*, 1996, **34**, 71.
18 R. N. Johnson and N. V. Riggs, *Tetrahedron Lett.*, 1967, 5119.
19 N. L. Allinger, *Pure Appl. Chem.*, 1982, **54**, 2515.
20 C. D. Cogley, *J. Phys. Chem.*, 1987, **91**, 4235.
21 A. I. Gray, R. D. Waigh and P. G. Waterman, *J. Chem. Soc., Perkin Trans. 2*, 1978, 391.
22 R. J. Abraham, S. Angiolini, M. Edgar and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1973.
23 F. Sancassan, G. Petrillo and R. J. Abraham, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1965.
24 R. J. Abraham, L. Pollock and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2329.
25 R. J. Abraham and I. S. Haworth, *Magn. Reson. Chem.*, 1988, **26**, 252.
26 R. J. Abraham, H. A. Bergen and D. J. Chadwick, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1161.
27 R. J. Abraham, D. J. Chadwick and F. Sancassan, *Tetrahedron*, 1982, **38**, 1485; 3245.
28 R. J. Abraham, D. J. Chadwick and F. Sancassan, *Tetrahedron*, 1981, **37**, 1081.
29 H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, 1958, **29**, 1361.
30 K. B. Wiberg, M. Marquez and H. Castejon, *J. Org. Chem.*, 1994, **59**, 6817.
31 Gaussian 94, (Revision B2), Gaussian 92, (Revision F.4), M. J. Frisch, G. W. Trucks, M. Head-Gordon, J. R. Cheeseman, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. P. Stewart and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1995.
32 W. J. Hehre, L. Radom, P. V. R. Schleyer and J. A. Pople, *Ab-Initio Molecular Orbital Theory*, Wiley, New York, 1988.
33 N. S. Narasimhan and R. S. Mali, *Synthesis*, 1975, 797.
34 C. S. Springer, Jr., D. W. Meek and R. E. Sievers, *Inorg. Chem.*, 1967, **6**, 1105.
35 H. Duddeck and M. Kaiser, *Spectrochimica Acta, Part A*, 1985, **41**, 913.
36 H. Duddeck and M. Kaiser, *Org. Magn. Reson.*, 1982, **20**, 55.
37 H. E. Gottlieb, R. A. De Lima, F. Delle Monache, *J. Chem. Soc., Perkin Trans. 2*, 1979, 435.
38 K. K. Chan, D. D. Giannini, A. H. Cain, J. D. Roberts, W. Porter and W. F Trager, *Tetrahedron*, 1977, **33**, 899.
39 C. Chang, H. G. Floss and W. Steck, *J. Org. Chem.*, 1977, **42**, 1337.
40 R. J. Abraham, *J. Chem. Soc. B*, 1968, 173.
41 E. Pretsch, J. Seibl, T. Clerc and W. Simon, *Tables of Spectral data for Structure Determination of Organic Compounds*, Springer-Verlag, Berlin, 2nd edn., 1989.
42 P. Deslongchamps, R. Chenevert, R. J. Taillefer, C. Moreau and J. K. Saunders, *Can. J. Chem.*, 1975, **53**, 1601.
43 R. J. Abraham, J. Fisher and P. Loftus, *Introduction to NMR Spectroscopy*, Wiley, Chichester, 1988.
44 R. J. Abraham, M. A. Warne and L. Griffiths, *J. Chem. Soc., Perkin Trans. 2*, 1997, 31.
45 A. Ghersi, Tesi di Laurea, University of Genoa, 1996.
46 PCMODEL, Serena Software, PO Box 3076, Bloomington, IN.
47 NEMESIS, Version 1.1, Oxford Molecular Ltd., Oxford, OX4 4GA.
48 E. Gavuzzo, F. Mazza and E. Giglio, *Acta Crystallogr., Sect. B*, 1974, **30**, 1351.
49 I. Csoregh, *Chem. Commun., Univ. Stockholm*, 1976, 1.

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