

FACTORS AFFECTING THE INTERACTION OF LANTHANIDE SHIFT REAGENTS WITH SUBSTITUTED PYRIDINES

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Abstract. The complexation of five meaningful series of pyridines bearing substituents in 2,6 and other positions was investigated by ¹H-NMR with Eu(dpm)₃ and Eu(fod)₃. The former LSR leads to higher MIS values than the latter when small α-substituents are present, but the opposite effect is obtained with bulky α-substituents such as t-butyl groups.

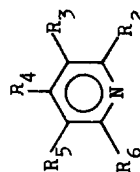
The vast literature dealing with shifts induced in NMR spectra by lanthanide shift reagents (LSR),¹ reveals that the principal aspects investigated (and still controversial) for pyridine substrates are the pseudocontact vs. contact dominant contribution, and the stoichiometry of the pyridine/LSR complexes (1 : 1 or 1 : 2). The data on 2,6-lutidine² and 2,4,6-collidine^{2,3} indicate, on one hand, that the substitution of the α-positions of the pyridine ring substantially reduces the contribution of the Fermi contact mechanism, and on the other hand that the stoichiometry of the complex is 1 : 1 even at low LSR concentration.^{3,4} Our experiments with 2,4,6-trimethylpyridine 1 in the presence of Ln(fod)₃ and Ln(dpm)₃ with Ln = Eu and Pr⁵ confirm the fact that the contribution of the contact mechanism is small and affects only the α-methyl groups. Therefore, assuming axial symmetry of the magnetic susceptibility tensors,⁶ the magnitude of the induced shifts obtained by the conventional lanthanide probe method will reflect meaningful geometrical information on the interaction between the lanthanide chelates and 2,6-disubstituted pyridines.

We prepared a series of variously substituted pyridines which possess alkyl groups in both α-positions (and in other positions of the pyridine ring as well) and present here the steric and other factors which influence the interaction with LSR's.

In continuation of previous studies on LSR-induced shifts in alkyipyridines,⁷ we converted various pyrylium salts into the corresponding substituted pyridines and studied their ¹H-NMR spectra in the presence of Eu(fod)₃ or Eu(dpm)₃ as LSR in various solvents at room temperature. Special precautions were taken to ensure anhydrous conditions; some of the polyalkylpyridines, e.g. pentamethylpyridine, are extremely hygroscopic and afford crystalline hydrates. Pyridines were distilled in dry argon under reduced pressure from LiAlH₄. The LSR's were gradually added to the pyridine solution, so that the slope from plots of induced shifts vs. molar ratio ρ (LSR/pyridine) affords molar induced shifts

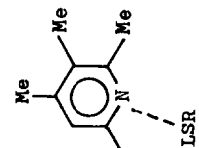
Table. Chemical shifts (δ) and MIS values (ppm) ; for Et or iPr groups the upper values refer to CH₂ or CH and lower values to CH₃.

No.	Class	Substituents						Chemical shifts						Eu(dpm) ₃ in CS ₂						Eu(fod) ₃ in CDCl ₃							
		2	3	4	5	6	2	3	4	5	6	2	3	4	5	6	2	3	4	5	6	2	3	4	5	6	
1 ^a	A-D	Me	H	Me	H	Me	2.37	6.67	2.22	6.67	2.37	18.4	8.3	5.2	8.3	18.4	5.5	2.0	1.1	2.0	5.5	5.5	2.0	1.1	2.0	5.5	
2 ^a	A, D	Me	Me	Me	H	Me	2.29	2.34	2.08	6.62	2.34	17.5	5.3	5.2	8.7	20.4	-	-	-	-	-	-	-	-	-	-	
3	A	Me	Me	Me	H	Me	2.29	2.13	6.93	2.13	2.29	18.3	5.2	6.5	5.2	18.3	10.4 ^b	2.9 ^b	3.4 ^b	2.9 ^b	10.4 ^b	10.4 ^b	2.9 ^b	3.4 ^b	2.9 ^b	10.4 ^b	
4 ^a	A	Me	Me	Me	Me	Me	2.31	2.08	2.08	2.08	2.31	16.5	4.5	4.2	4.5	16.5	7.8 ^b	1.8 ^b	1.4 ^b	1.8 ^b	7.8 ^b	7.8 ^b	1.8 ^b	1.4 ^b	1.8 ^b	7.8 ^b	
5	A	Me	(CH ₂) ₄	Me	Me	Me	2.23	2.4-2.6	2.02	2.30	2.30	20.1	5.7	5.7	5.5	20.3	-	-	-	-	-	-	-	-	-	-	-
6	A	Me	H	Ph	H	Me	2.47	6.97	7.35	6.97	2.47	17.7	8.4	4.4 ^c	8.4	17.7	6.2	2.1	1.3	2.1	6.2	6.2	2.1	1.3	2.1	6.2	
7	B	Et	H	Me	H	Me	2.62	6.58	2.17	6.58	2.33	14.9	5.7	3.7	6.2	13.8	6.0	1.9	1.0	1.9	6.0	6.0	1.9	1.0	1.9	5.3	
8	B	iPr	H	Me	H	Me	2.83	6.60	2.22	6.60	2.33	17.7	5.0	3.4	5.6	11.7	9.7	2.1	1.2	2.1	9.7	9.7	2.1	1.2	2.1	4.9	
9	B	tBu	H	Me	H	Me	1.17	6.77	2.23	6.60	2.34	0.3	0.1	0.1	0.4	2.5	2.5	1.0	0.6	1.1	2.5	2.5	1.0	0.6	1.1	3.3	
10 ^a	C	Et	H	Me	H	Et	2.62	6.60	2.19	6.60	2.62	14.1	5.6	3.6	5.6	14.1	6.0	1.5	0.8	1.5	6.0	6.0	1.5	0.8	1.5	6.0	
11 ^a	C, E	iPr	H	Me	H	iPr	1.25	6.63	2.28	6.63	1.25	3.7	0.2	0.1	0.2	0.2	1.0	1.0	0.6	1.0	1.0	1.0	0.6	1.0	1.1	4.6	
12	C	tBu	H	Me	H	tBu	1.28	6.83	2.24	6.83	1.28	0	0	0	0	0	4.6	1.1	0	0	4.6	4.6	1.1	0	0	1.1	
13	D	Me	iPr	Me	H	Me	2.42	3.29	2.27	6.57	2.27	18.5	5.3	4.9	8.3	18.8	7.3 ^e	1.5 ^e	1.0	1.5 ^e	7.3 ^e	7.3 ^e	1.5 ^e	1.0	1.5 ^e	7.6 ^e	
14	E	iPr	Me	Me	H	iPr	3.19	2.16	2.20	6.66	2.86	0	0	0	0	0	2.0	0.5	0.4	1.0	2.0	2.0	0.5	0.4	1.0	3.5	
15	E	iPr	iPr	Me	H	iPr	3.24	3.35	2.29	6.60	2.81	0	0	0	0	0	1.7	0.4	0.3	0.4	1.7	1.7	0.4	0.3	0.4	4.0	

^a Studied in ref.8.^b In CCl₄.^c o-protons^d m, p-protons^e In CS₂.

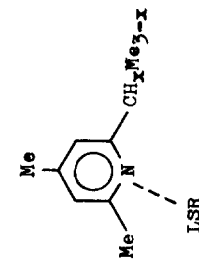
Scheme

1-15



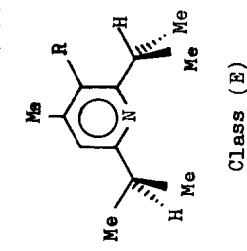
LSR

2



LSR

Class (B)



LSR

Class (E)

(MIS, ppm). The range of ρ values was 0 to 0.35 for all substrates ; reproducibility was found to be within 0.15 ppm, and the correlation factor for linear plots was at least 0.99.

Assignments for chemical shifts in 5 and 15 were carried out by selectively ⁸ deuteriating the parent pyrylium salts on refluxation in D₂O followed by treatment with NH₃ : γ -benzylic protons are deuteriated fast, α -benzylic protons more slowly ; no other protons undergo isotope exchange.

The Table presents chemical shifts and MIS values for five pyridine classes (A)-(E) :

- (A) tri-, tetra- and pentamethylpyridines (1-4), 1,3,4-trimethyl-5,6,7,8-tetrahydroisoquinoline (5) and 4-phenyl-2,6-dimethylpyridine (6) ;
- (B) 4,6-dimethylpyridines with increasingly bulkier 2-substituent : Me, Et, iPr, tBu, (1, 7-9) ;
- (C) 2,6-dialkyl-4-methylpyridines with increasingly bulkier identical α -alkyls : Me, Et, iPr, tBu, (1, 10-12) ;
- (D) 2,4,6-trimethylpyridines with increasingly bulkier 3-substituents : H, Me, iPr, (1, 2, 13) ;
- (E) 2,6-diisopropyl-4-methylpyridines with increasingly bulkier 3-substituents : H, Me, iPr (11, 14, 15).

The following trends may be observed in classes (A) - (E) depending both on the ligands in the LSR, and on the substitution pattern in the pyridines.

In class (A) with Eu(dpm)₃ in CS₂, MIS values for α -methyls are in the range 16-21 ppm. Three adjacent methyl groups in positions α , β , γ (i.e. either 2,3,4 or 4,5,6) lead to a slight but significant decrease of the MIS owing to buttressing. In 5, the tetramethylene bridge reduces the buttressing and increases thereby the MIS values. For 2 a model was proposed ⁷ with the europium atom in the plane of the aromatic ring but not on the symmetry axis of the pyridine ring (Scheme) ; this explains the higher MIS values for 6- than for 2-methyl protons, and the equal MIS values for the β - and γ -methyls. Eu(fod)₃ gives rise to lower MIS values than Eu(dpm)₃ for all class A pyridines as noted earlier for other substrates. ⁹

In class (B), a dramatic decrease of MIS values for Eu(dpm)₃ is apparent along the series 1, 7-9 ; the α -t-butyl group in 9 prevents almost entirely complex formation. Interestingly, the MIS values obtained with Eu(fod)₃ are reduced to a lesser extent by the gradual size increase of the α -substituent, thus leading to higher MIS values for 9 than with Eu(dpm)₃ (in contrast to class A pyridines). This fact can be rationalized by the lower steric requirements of Eu(fod)₃ than Eu(dpm)₃.

In class (C), a similar decrease of MIS values is observed with both Eu(dpm)₃ and Eu(fod)₃ as the bulk of two α -substituents increases. Comparing class C with class B, MIS values for one α -isopropyl and one α -methyl (8) are similar to those obtained for two α -ethyl groups (10) ; two non-buttressed α -isopropyl groups (11) lead to MIS values that are comparable with those for one α -t-butyl and one α -methyl group (9).

In class (D), the replacement of a β -H by a Me or iPr group does not influence the MIS values ; by contrast, in corresponding class (E) pyridines, with Eu(dpm)₃ the same replacement leads to the cancellation of complexation. Bearing in mind class D, this effect

in class E is too strong for a β -substituent alone and must be due to a modification involving the α -isopropyl groups; we interpret this strong effect by admitting that in 11 the isopropyl groups are freely rotating, whereas in 14 and 15 the buttressed 2-isopropyl group is forced to adopt a t-butyl-like conformation as viewed by the LSR (Scheme); with two α -isopropyl groups the MIS values in 11 are small, but an analogous larger effect is described in the accompanying paper.¹⁰ Indicative for the conformation of isopropyl groups is also the chemical shift for the CHMe_2 proton (in-plane for 2-iPr in 14 and 15, $\delta = 3.2$ ppm; out-of-plane for 6-iPr in the same compounds, $\delta = 2.8-2.9$ ppm), and the MIS ratio CH/Me_2 (in freely rotating iPr groups the ratio is 2.5-4.5, but in buttressed iPr groups it is 1.5-2). Unlike $\text{Eu}(\text{dpm})_3$, when using $\text{Eu}(\text{fod})_3$ in the same series E, there is a gradual decrease of MIS values, but the latter LSR, with smaller steric requirements than the former one, is able to afford complexes even with 14 and 15.

Some pyridines from the Table were investigated also with Pr instead of Eu chelates.⁵ Unlike $\text{Eu}(\text{dpm})_3$ which does not cause any line broadening, $\text{Ln}(\text{fod})_3$ (especially with $\text{Ln} = \text{Pr}$) leads to considerable broadening, but for α -methyl or CHMe_2 signals only; this effect may be due to a closer approach of $\text{Ln}(\text{fod})_3$ than of $\text{Ln}(\text{dpm})_3$.

In conclusion, in addition to well-known factors which affect the interaction between pyridines and LSR (nature of lanthanide metal Ln such as Eu or Pr; contact/pseudocontact mechanism; 1:1 or 1:2 stoichiometry of the complex), we present evidence for the following additional factors: (i) steric requirements of α -substituents originating either in their bulkiness or in their conformation, which in turn may be induced by buttressing due to β -substituents; (ii) steric requirements of the ligand in the LSR: $\text{Ln}(\text{fod})_3$ reagents are less sensitive to steric hindrance than $\text{Ln}(\text{dpm})_3$, but the range of MIS values for $\text{Ln}(\text{fod})_3$ is about one third from that for $\text{Ln}(\text{dpm})_3$ in the absence of steric hindrance; (iii) solvent effects are small; for the same substrate-LSR complex the MIS value decreases when changing the solvent from CS_2 or CCl_4 to CDCl_3 , as noted earlier for other substrates.¹¹

References and notes

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5. For 1 MIS ratios of 3-H and 2-Me relative to 4-Me are 1.6 and 3.6 with $\text{Eu}(\text{dpm})_3$; 2.2 and 6.0 with $\text{Pr}(\text{dpm})_3$; 1.8 and 5.0 with $\text{Eu}(\text{fod})_3$; 1.9 and 5.6 with $\text{Pr}(\text{fod})_3$.
6. However, for 2:1 complexes of α -unsubstituted pyridines this may not be valid as shown by X-Ray diffraction for $\text{Ln}(\text{dpm})_3 \cdot (4\text{-Me-pyridine})_2$, by W.DeW.Horrocks, J.P.Sipe and J.R.Luber, J.Amer.Chem.Soc., **93**, 5258 (1971); *idem*, Science, **177**, 944 (1972).
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