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Determination of the *Z*/*E*-Configuration of 3-Phenyl-3-pyridylallylamines Related to Zimelidine by means of Lanthanide-induced Shifts in Proton Magnetic Resonance

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The effect of $Eu(fod)_3$ on the ^1H NMR spectra of a series of 3-(4-bromophenyl)-3-pyridylallylamines in $CDCl_3$ was investigated. The lanthanide shift reagent (LSR) was found to complex preferentially with the pyridine nitrogen in the case of tertiary *N*,*N*-dimethylamines and the steric relationships could be determined independently of an *a priori* knowledge of the structure. However, the LSR has comparable affinity for the two binding sites in the case of secondary *N*-methylamines. A bidentate complex is proposed for the *Z*-isomer to explain the anomalous induced shift of the 2- and 6-pyridyl protons. More sterically hindered secondary amines with the *Z*-configuration, *i.e.* *N*-ethyl and *N*-propyl, showed a markedly diminished affinity to the aliphatic nitrogen and the binding appears as a combination of that observed for the *N*,*N*-dimethyl- and *N*-methylamines. The configuration can be established for tertiary allylamines with a 3-pyridyl as well as a 4-pyridyl ring in the 3-position by the use of LSR.

Zimelidine (*1*, (*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine) is a new and interesting antidepressant agent.[1] The assignment of the geometrical relationships in zimelidine has been attempted by UV and NMR spectroscopy, but no conclusive evidence was forthcoming.[2] An X-ray single-crystal analysis established the *Z*-configuration of zimelidine.[2] In connection with the synthesis of related compounds, it was of interest to have an alternative way of determining the configuration. UV spectra have been used to correlate secondary amine analogs to zimelidine.[3] However, for compounds with other phenyl substituents in various positions, it is desirable to use a complementary and more general method.

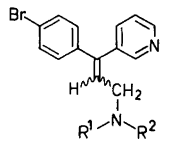

Fig. 1. 3-(4-Bromophenyl)-3-(3-pyridyl)allylamines.

Z-Isomer	R^1	R^2	*E*-Isomer
1	CH_3	CH_3	*2*
3	H	CH_3	*4*
5	H	C_2H_5	
6	H	C_3H_7	

Coordination of lanthanide shift reagents (LSR) to pyridine in preference to a tertiary aliphatic nitrogen has been observed for nicotine.[4,5] Pyridine is probably the stronger donor also in *N*,*N*-dimethyl-3-phenyl-3-(3-pyridyl)allylamines, exemplified by the diastereomers *1* and *2* (see Fig. 1). Thus, the influence of LSR on the ^1H NMR spectra was investigated. The spectra were run on a 60 MHz instrument in deuteriochloroform with $Eu(fod)_3$ as the chosen LSR. The lanthanide induced shifts (LIS) of the most important protons of the two isomers *1* and *2* are shown in Fig. 2 and Table 1. The gradient (*G*) refers to the slope of shift diagrams according to the nomenclature in Ref. 6. Of the two competing binding sites, the pyridine nitrogen has the highest affinity in both cases (*cf.* the induced shift gradient ratio *G*(2-pyridine)/G(NMe_2) in Table 1). Besides, the magnitudes of the gradients *G*(2-pyridine) and

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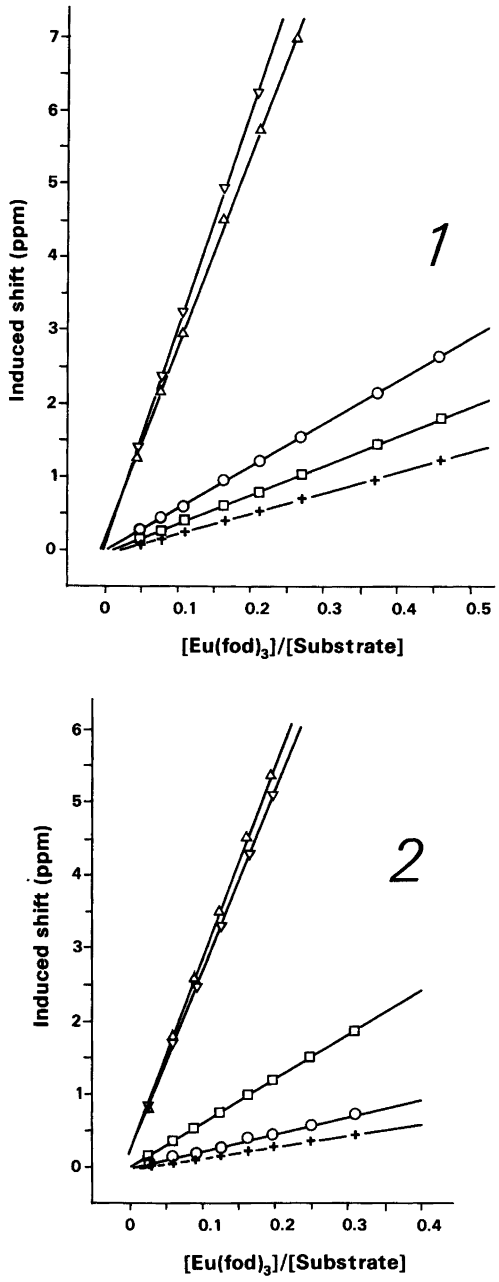

Fig. 2. Induced chemical shifts of protons of compound *1* (0.38 M, above) and compound *2* (0.45 M, below) in $CDCl_3$ as a function of the molar ratio of the initial concentrations of $Eu(fod)_3$ and substrate. The symbols refer to the 2-pyridyl (△), 6-pyridyl(▽), allyl (○), vinyl (□) and NMe_2 (+) protons.

G(6-pyridine) are very similar for the two isomers, which indicates the same type of complex with the pyridine moiety. After having established the coordination site of europium, the correct configuration can be determined by comparison of the gradients *G*(allyl) and *G*(vinyl).

Dreiding models of the complexes with a distance of 3 Å between the pyridine nitrogen and europium, in accordance with Ref. 7, were inspected. The angle between the vector joining the metal atom to the vinyl or allyl hydrogen nuclei and the principal magnetic axis was estimated to be less than 55° in all conformers, *i.e.* only downfield shifts are observed.[6] In one case (*1*), the *G*(allyl)/*G*(vinyl) ratio is markedly larger than 1 and the opposite is found for the other isomer (*2*). This establishes the configuration even if these molecules are rather flexible and the europium atom can adopt several conformations in relation to the allyl and vinyl hydrogens. However, on an average europium will be closer to the allyl hydrogens in the *Z*-form and to the vinyl hydrogen in the *E*-form, which is, of course, in agreement with the X-ray investigation.[2] Furthermore, the gradient $G(NMe_2)$ of zimelidine (*1*) is larger than that of *2*. This is most likely due to the proximity effect of europium and not to the presence of a bidentate ligand binding in the case of *1* since, as already mentioned, the gradients *G*(pyridine) are almost identical for the two isomers (*vide infra*).

A direct LIS analysis of pharmacologically interesting secondary methylamines such as *3* and *4* was attempted. However, the two binding sites are of similar affinity in these cases as indicated by $G(2\text{-pyridyl})/G(NCH_3) \approx 1$ (Table 1). Accordingly, the ratio *G*(allyl)/*G*(vinyl) will be of little value for determining the configuration since *G*(allyl) and *G*(vinyl) are mostly affected by the coordination to the aliphatic nitrogen, which explains why the same ratio is obtained for the two isomers. Comparison of the gradients of the 2-pyridyl and the 2,6-phenyl protons in *3* and *4* was also considered. However, the *G*(2-pyridyl)/*G*(2,6-phenyl) ratios were identical (3.4) for the two isomers.

The change from a dimethylamine to a monomethylamine has a considerable effect on the binding. In order to see how steric hindrance will affect the interaction with the secondary amine, compounds *5* and *6* were studied. It was found that even the change from methyl (*3*)

Table 1. $Eu(fod)_3$ induced shifts of 3-(4-bromophenyl)-3-(3-pyridyl)allylamines in deuteriochloroform at 37 °C.[a]

Compound	Induced shift gradient[b] G (ppm)							Gradient ratio		
	2-py	6-py	allyl	vinyl	NCH_2	NCH_2CH_2	NH	allyl / vinyl	2-py / NCH_2	2-py / 6-py
1	25.8 0.999 6	29.3 0.999 5	5.71 1.000 8	3.85 1.000 8	2.68 0.998 8	–	–	1.48	9.62	0.88
2	26.5 1.000 6	24.9 1.000 6	2.35 0.999 8	5.98 0.998 8	1.58 0.998 8	–	–	0.39	16.7	1.06
3	12.9 0.999 6	11.6 0.999 6	14.8 0.999 5	10.1 0.998 4	11.6 0.999 6	–	43.4 0.996 4	1.47	1.11	1.11
4	15.2 0.999 6	13.0 0.999 6	16.6 0.999 5	11.1 0.999 4	13.4 0.999 6	–	[c]	1.50	1.13	1.17
5	14.8[de] 0.995 7	15.0[df] 0.994 7	7.12 1.000 7	4.95 0.999 7	4.79 1.000 7	3.33 1.000 7	32.5 1.000 6	1.44	3.08	0.98
6	12.5[dg] 0.993 6	12.3[dh] 0.991 6	6.40 0.999 6	4.57 1.000 4	4.24 0.998 6	3.26 0.998 6	29.8 0.999 4	1.40	2.95	1.02

[a] The molar ratio [$Eu(fod)_3$]/[substrate] was increased by incremental addition of solid $Eu(fod)_3$ to a *ca.* 0.5 M solution of the substrate. The final [$Eu(fod)_3$]/[substrate] ratios were between 0.31 and 0.47. [b] Calculated by linear least-squares fit of manually measured induced shifts *vs.* [$Eu(fod)_3$]/[substrate]. The values in each set indicate from above the gradient (slope) G, the coefficient of correlation (r) and the number of observations. [c] Not observed. [d] Actually concentration dependent induced shift (LIS) fitting the power curve $LIS = G([Eu(fod)_3]/[substrate])^b$ having $0.80 < b < 0.83$ with $r > 0.998$. [e] $G = 13.7$ ppm. [f] $G = 14.0$ ppm. [g] $G = 12.1$ ppm. [h] $G = 11.9$ ppm.

to ethyl (*5*) gave a pronounced diminished binding to the aliphatic nitrogen (*cf.* the ratio G(2-pyridyl)/$G(NCH_2)$ in Table 1). The data for the propylamine *6* were the same. It can also be seen that the G(NH) values for the larger amines *5* and *6* are smaller than for *3*. The G(allyl)/G(vinyl) ratios are in agreement with the *Z*-configuration (*cf. 1*), but it cannot be ruled out that the binding to the aliphatic nitrogen, although smaller, still has the dominant influence on the ratio. A study of the *E*-isomer of the ethylamine would be interesting in this respect.

The 2- and 6-pyridyl protons have different relative shifts in the *Z*- and *E*-isomers. The 6-pyridyl proton resonance (double doublet) is downfield in the *Z*-isomers, but the 2-pyridyl resonance (narrow multiplet) is slightly downfield in the *E*-isomers. For all compounds except *3*, the relative position of the 2- and 6-pyridyl protons is maintained even after the addition of shift reagent. However, for compound *3*, a cross-over in shift is observed, which explains why G(2-pyridyl)/G(6-pyridyl) is <1 for the tertiary amine *1* and >1 for the methylamine *3*. This might be explained by a bidentate complex with *3*, which would lock the rotation of the pyridine ring and place the 2-pyridyl proton closer than the 6-pyridyl to the mean magnetic axis. Accordingly, the angle factor and the LIS will be larger for the 2-pyridyl proton. Compounds *5* and *6* behave as a combination of *1* and *3* in this respect, with G(2-pyridyl)/G(6-pyridyl) ≈ 1. Besides, no true linear relationship was found for the 2- and 6-pyridyl protons (*cf.* Table 1), which indicates a change in stoichiometry or coordination site.

The configurations of various tertiary amines with

different phenyl substituents containing 3-pyridyl as well as 4-pyridyl moieties have been determined by this method. The assignment of secondary amines requires a deactivation of the competing binding site, *e.g.* by conversion to a tertiary amine.

The use of LSR has considerable potential in the analysis of mixtures of the isomers. In this case it is sometimes more convenient to compare the *G*(allyl)/*G*(2-pyridyl) ratios, since the vinyl triplet from the minor component is more difficult to detect than the allyl doublet due to the presence of signals from aromatic protons. The *G*(allyl)/*G* (2-pyridyl) is 0.22 for the *Z*-isomer *1* and 0.09 for the *E*-isomer *2*, which confirms the configuration.

EXPERIMENTAL

The amines were extracted from an alkaline aqueous solution with ether and dried over magnesium sulfate. Dry dichloromethane was added and the solvents were evaporated under reduced pressure. Deuteriochloroform (Uvasol, Merck) was used as solvent and tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)-europium [$Eu(fod)_3$, Ciba-Geigy] was used as shift reagent as purchased, with no extra purification. The amines were dissolved and solid $Eu(fod)_3$ was added in increments to the solution. The ^{1}H NMR spectra were run on a Varian T60 spectrometer at 37 °C and the chemical shifts were related to internal TMS.

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