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SYNTHESIS AND EUROPIUM SHIFTED NMR SPECTRA OF TRANS- AND CIS 4[β(1-NAPHTHYL)VINYL]PYRIDINE

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The reaction of choline with acetyl-CoA to acetylcholine is catalyzed by choline acetyltransferase (EC 2.3.1.6). In recent years much work has been done to find a potent inhibitor of this enzyme and most of this work emanates from Cavallito and his group. In 1967 they reported[1] a series of compounds potent in vitro among these 4[β(1-naphthyl)vinyl]pyridine (NVP). Recently Aquilonius et. al.[2] studied the in vivo activity of NVP and for this work the pure trans and cis isomers were needed.

A simple way to obtain both isomers was by the Wittig reaction[3,4]. When a mixture of 1-chloromethylnaphthalene (11.5 g) and triphenylphosphine (18.6 g) was heated at 150° for 10 min. (1-naphthylmethyl)triphenylphosphonium chloride was formed in 99 % yield. The crude (ethyl ether washed) phosphonium salt (13.2 g) and 4-formylpyridine (2.9 g) were dissolved in refluxing abs. ethanol (200 ml). Sodium (0.69 g) in abs. ethanol (50 ml) was added and the mixture refluxed for 1 h. The yield of crude trans and cis NVP was 98 %. GLC (5 % OV17 on Chromosorb W, 250°, 2 m x 2.2 mm (ID)) revealed 44 % trans, 52 % cis and about 2 % impurities.

The separation to pure cis and trans NVP could be performed either on an alumina or on a silica gel column with mixtures of cyclohexane and ethyl ether as eluants. The cis isomer was eluted first. Equally successful was chromatography on Sephadex G15. Elution with a solution containing 0.1 M NaCl and 0.1 M HCl clearly separated 1 g of the synthetic mixture on a Sephadex column (4 x 46 cm). Here also cis NVP was eluted first. The property of Sephadex to interact with aromatic structures was also employed in separating the trans- and cis-isomers of some quaternary NVP analogs not easily separated otherwise[5].

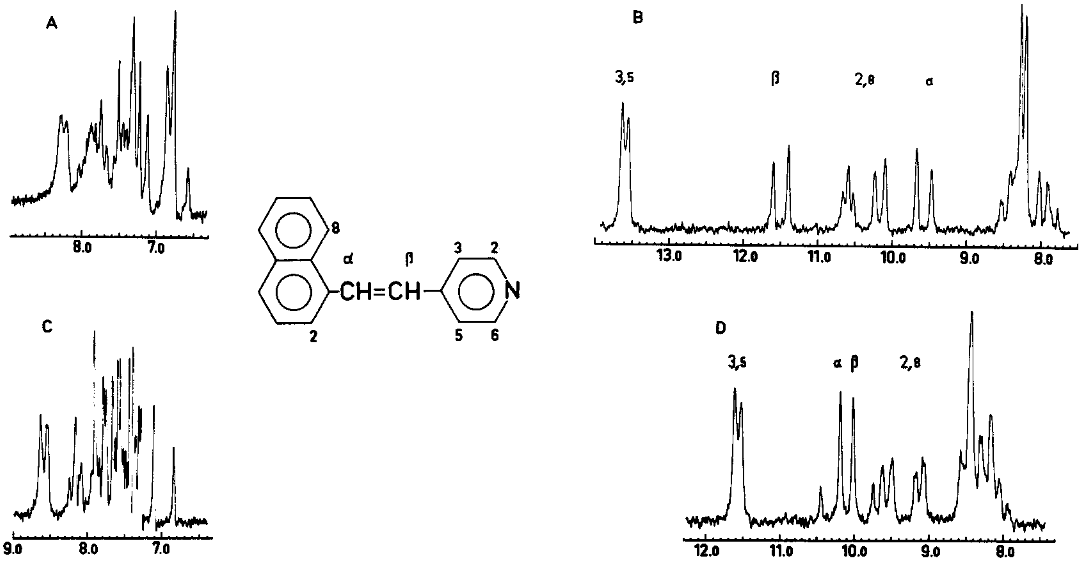

Figure 1. NMR spectrum of 4[β(1-naphthyl)vinyl]pyridine. A,C: *cis* and *trans* NVP; B: *cis* NVP with Eu(DPM)$_3$ (mole ratio Eu/NVP of 0.7); D: *trans* NVP with Eu(DPM)$_3$ (mole ratio Eu/NVP of 0.4). In B and D the second doublet from the pyridine protons (δ=27.73 and δ=20.82 respectively) are not shown.

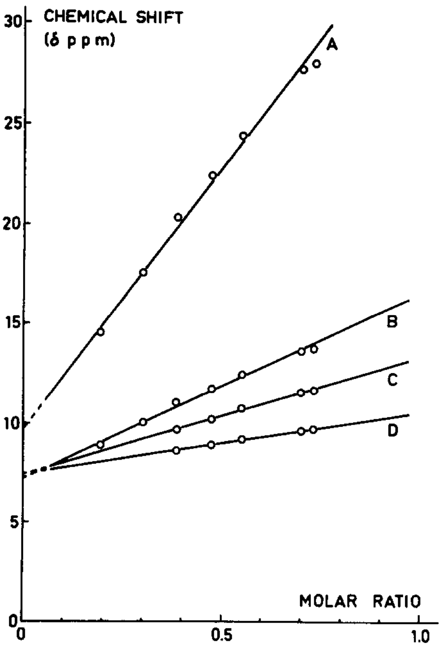

Figure 2. Variation of chemical shift with molar ratio Eu(DPM)$_3$/substrate for *cis* NVP in CCl$_4$ solution.
A: 2,6 pyridine protons, B: 3,5 pyridine protons, C, D: vinyl protons.

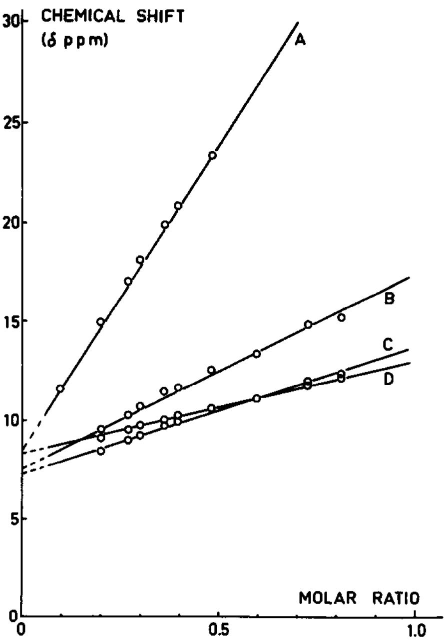

Figure 3. Variation of chemical shift with molar ratio Eu(DPM)$_3$/substrate for *trans* NVP in CCl$_4$ solution.
A: 2,6 pyridine protons, B: 3,5 pyridine protons, C, D: vinyl protons.

The NVP isomers were identified using m.p., IR- and UV-spectra[2]. NMR could not normally be used since the vinyl proton resonances are hidden in the naphthalene envelope (cf. spectra A and C of Fig. 1). However, recently it has been shown that tris-(dipivalomethanato)europium (III), Eu(DPM)$_3$, complexes with compounds containing free electron pairs on oxygen or nitrogen causing appreciable paramagnetic shifts in the NMR spectra[6]. The magnitude of the observed shifts depend upon the distance from the metal ion to the proton in the metal chelate-substrate complex[7].

Spectra B and D of Fig. 1 show the effect of addition of Eu(DPM)$_3$ to NVP[8]; the signals of the vinyl protons are clearly separated from two pyridine doublets, two one proton naphthalene signals and the bulk of naphthalene proton signals at ca 8 ppm.

The linearity between the observed chemical shift and metal ion concentration for different protons in trans and cis NVP is demonstrated in Figs. 2 and 3. The slopes of the lines give the Δ_{Eu} values i.e. chemical shift (ppm)/mol Eu(DPM)$_3$ per mole substrate (Table 1).

Table 1. Δ_{Eu} values recorded for different protons in NVP

	cis NVP	trans NVP
2,6 pyridine protons	26,3	30,5
3,5 pyridine protons	9,3	9,3
β vinyl	5,7	4,8
α vinyl	3,0	6,3

At a mole ratio of about 0.4, the AB spectrum of the cis-vinyl protons is clearly visible. When more Eu(DPM)$_3$ is added the AB quartet successively changes into an AX pattern. Between the two vinyl doublets (spectra B, Fig. 1), two one proton signals from the 2 and 8 position in the naphthalene ring are recognizable. Inspection of a Dreiding model reveals that the α vinyl proton is considerably more distant from the estimated position of Europium than the β proton and hence ought to show the smallest paramagnetic shift (Table 1). Both the 2 and 8 naphthalene protons are closer to Europium than the α vinyl proton and accordingly the signals shows up between those of the vinyl protons. Within the mole ratio limits studied the coupling constant for the cis-vinyl protons are 12 Hz in accordance with the typical values for cis protons[9].

The trans-vinyl protons are nearly equidistant from the Eu atom (according to a Dreiding model) with the α proton somewhat closer. Hence the difference in Δ_{Eu} between α and β trans is considerably smaller than for α and β cis, 1.5 compared to 2.7 (Table 1). A further fact which might reflect the nearly equal influence of Eu on the α-β trans protons is that the AB spectrum first observed at a mole ratio of 0.2 gradually transforms into an A_2 spectrum. At mole ratios higher than 0.6 the AB spectrum again appears. The two lines C and D in Fig. 3 represent the α and β vinyl protons respectively, but beyond the A_2 point the only support that the α proton has overtaken the β proton is the linearity usually found between chemical shift and mole ratio. The coupling constant in the whole range investigated is 16 Hz within the limits usually found[9] for trans protons.

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8. For NMR spectra 50 mg of either cis or trans NVP and the appropriate amount of $Eu(DPM)_3$ was dissolved in 1.5 ml CCl_4 in a NMR tube. Excess CCl_4 was distilled off from the tube equipped with a capillary for argon inlet. TMS was added and the volume adjusted to 0.5 ml. This technique provides the anhydrous conditions necessary for reproducible results. The spectra were measured on a Varian A 60A instrument.
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