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METAL ION SITE COMPLEXATION OF POLYFUNCTIONAL LIGANDS.[1] NICOTINAMIDES WITH NMR SHIFT REAGENTS.

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Application of shift reagents has become an excellent, inexpensive technique in the elucidation of complex organic structures.[2] We herein report the use of the shift reagent $Eu(FOD)_3$ to ascertain information on potential site(s) of metal ion complexation within polyfunctional macrocycles, and structural conformation of several disubstituted N,N-dimethylnicotinamides.

The pivotal starting material for construction of our pyridine-linked nucleotide models was 2,6-dichloronicotinamide (1), whose synthesis (95+%) from 2[3] was previously described.[1] Treatment of 1 with sodium ethoxide afforded both 2,6-diethoxy-N,N-dimethylnicotinamide (3) [60%; bp 140°C (1 mm)] and 2-ethoxy-6-chloro-N,N-dimethylnicotinamide (4) [27%; mp 65-65.5°C], whose structure was ascertained by chemical conversion to 2-ethoxy-N,N-dimethylnicotinamide.[1] In order to spectrally establish the structure of 4 as well as determine the site(s) of complexation on simple representative compounds with shift reagents, variable amounts of $Eu(FOD)_3$[4] were added to $CDCl_3$ solutions of 4 and 3; the results of the first order analysis are shown in Figure 1 and 2, respectively. Both 3 and 4 interact with the shift reagent through the amide carbonyl oxygen, as demonstrated by the greater induced shift of the Z over E amide methyl groups (eg Figure 3). Thus, the amide function is a stronger coordinating group to lanthanide ions than the other pyridine substituents. To be noted in 3, the α and β hydrogens are shifted farther than the corresponding α' and β' hydrogens; thus, comparison of the slope for the ethoxy group in 4 to that of 3 substantiate the structural assignment of 4.

Incorporation of the nicotinamide moiety into a crown-ether ring was accomplished by treatment of 1, under established procedures , with an appropriate disodium salt of tetra-, penta-, and hexaethyleneglycol to afford 5a [20%; bp 205°C (0.3 mm)]; 5b [32%; bp 220°C (0.4 mm)]; and 5c [17%; bp 240°C (0.3 mm)], respectively.[6] Free energies of activation ($\Delta G^{\ddagger}$) of 5 were determined in $CDCl_3$ from coalescence temperatures of the diastereotopic N-methyl signals, and shown

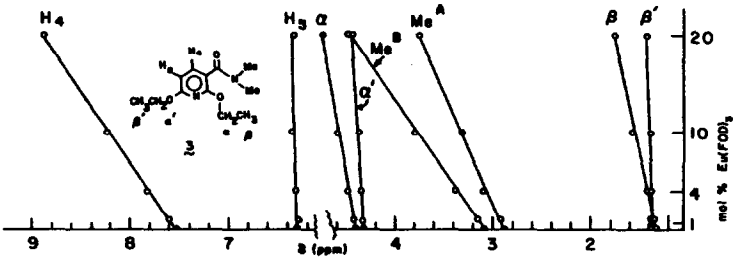


Figure 1. Amide 3 with Eu(FOD)$_3$

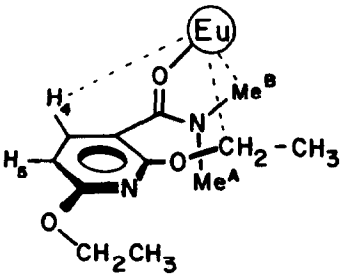


Figure 3.

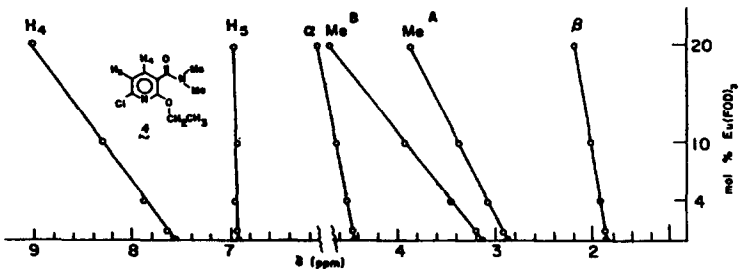
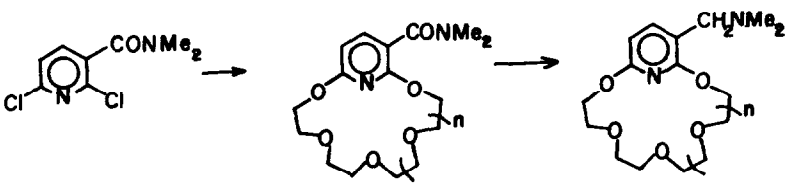


Figure 2. Amide 3 with Eu(FOD)

to be 17.13 ± 0.1 Kcal/ mol — a value in accord with 3 ($\Delta G^{\ddagger}$=17.10 Kcal/mol)[1] and indicative of enhanced C-N amide double-bond character. Attempted 1,4-reduction[7] of 5 with sodium bis(2-methoxyethoxy)aluminum hydride ("Vitride", 70% in benzene) gave exclusively the corresponding amine 6 via predominant (>95%) reduction of the amide function; whereas, with other reducing agents ($Na_2S_2O_4$, NaH, $NaBH_4$, Selectride) no reaction was observed. Thus, from VTNMR studies and hydride reduction of 5, a preferred coordination with the amide oxygen is indicated.



1

5a (n=1)
b (n=2)
c (n=3)

6

In order to ascertain the preferred site of coordination in these polyfunctional macrocycles (5), Eu(FOD)$_3$ was added in increasing increments to 5b. Figure 4, shows the effects of 0-20 mol % of added shift reagent, in which the amide carbonyl group coordinates almost exclusively to Europium ion (see Figure 5). The strong similarity between the slopes of the N-methyls, H-4, α, and β hy-

drogens is shown by comparisons of Figures 1 and 4. The total lack of bridged oxygen-coordination in 5b is demonstrated by the inability to differentiate the γ,δ,ε,ε',δ',γ' hydrogens, and further, by the ill-defined nature of the β-hydrogens except at increased shift reagent concentrations. The corresponding unsubstitu-

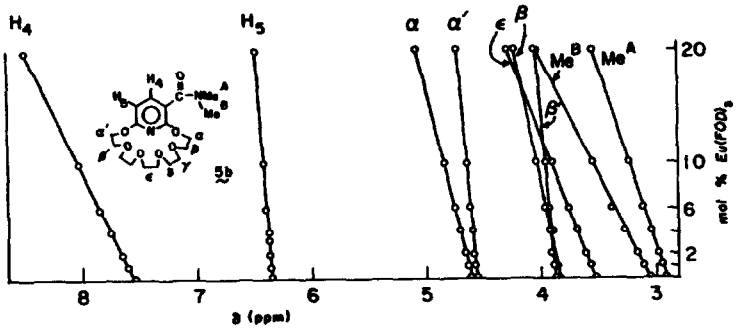


Figure 4. Amide 5b with $Eu(FOD)_3$

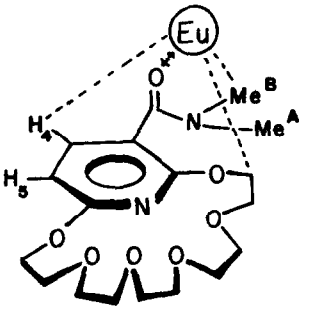


Figure 5.

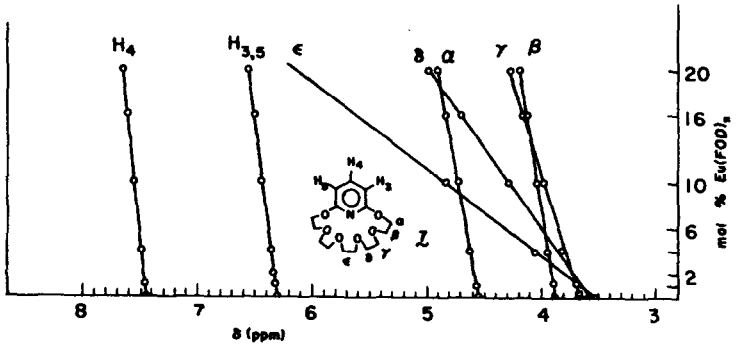


Figure 6. Macrocycle 7 with $Eu(FOD)_3$

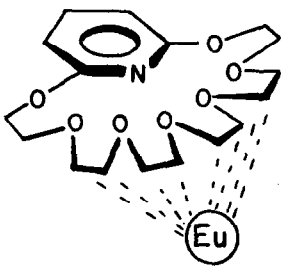


Figure 7.

ted macrocycle 7, however, gives a totally different site of coordination with $Eu(FOD)_3$ as demonstrated from the data in Figure 6 and illustrated in Figure 7. The singlet for the ε-hydrogens is immediately shifted from the maze of bridge hydrogens, whereas the remaining bridging methylene groups are shifted to a lesser amount as their distance increases from the central bridge (ε) position. The slope for the α-hydrogens in 7 is reminiscent of the α'-hydrogens in 4, in which the latter exhibit little or no induced shift.

Preferred site of coordination to this shift reagent need not be indicative of the direct metal ion complexation within the macrocyclic cavity but does afford direct information about (1) the availability of competitive sites for metal ion complexation, and (2) the potential location of metal complexation prior to a chemical reaction.

Various competitive reactions of macrocycles possessing subheterocyclic rings, with and without substituents, are currently in progress.[8]

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