Calculation of Steric Interactions between a Lanthanide Shift Reagent and Substituted Pyridines

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Steric interactions between a lanthanide-shift reagent (LSR) and ligands have been examined in detail by calculating the intramolecular non-bonded energy of interaction in Eu(dpm)$_3$py$_2$, (where py = pyridine or one of its methyl-substituted derivatives) as py is translated and/or rotated with respect to the remainder of the Eu(dpm)$_3$py complex. The various calculations performed indicate that pyridine and 3,5-dimethylpyridine bind well to the LSR with a minimum amount of steric interference in the crystal conformation; however, for 2-methylpyridine and especially for 2,6-dimethylpyridine, steric interference of the methyl groups with the LSR are significant. Furthermore, the non-bonded energy of interaction becomes very high when the unsubstituted pyridine ring is moved away from its crystal conformation. This shows that only a small pocket is available for the pyridine molecule or its derivatives in the octahedral LSR complex. The lanthanide-shift reagent studied here is widely used in conformational analysis by n.m.r.; our results show that steric interactions between this LSR and substrate molecules can be severe and hence may be expected to cause conformational alterations of some types of flexible ligands.

The lanthanide-shift reagents are high molecular weight (*ca.* 1 000) complexes of a rare earth metal with three bidentate organic ligands, *e.g.* Eu(dpm)$_3$† or Pr(fod)$_3$.‡ Typically, one or two additional nucleophiles also bind to the metal, increasing its co-ordination number [1] to 7 or 8. Such a complex may have severe steric constraints owing to the large size of the dpm or fod ligands, and these constraints may be expected not only to influence the association constants for the seventh and eighth ligands, but may conceivably also cause conformational changes of the ligands themselves in the case of flexible molecules. Since the lanthanide-shift method is now widely used as a method for obtaining conformational information about molecules in solution by n.m.r., it is of considerable interest to determine whether these purely steric factors may induce conformational alterations in the compounds being studied.

As an initial step in answering this question we have carried out conformational energy calculations on the interaction of pyridine and its ring-methyl derivatives with the widely used n.m.r. shift reagent Eu(dpm)$_3$. This system was chosen since the co-ordinates of Eu(dpm)$_3$py$_2$ are available from the crystal literature.[2] Our objective was to determine the steric constraints on pyridine and its derivatives when associated with Eu(dpm)$_3$. Since the pyridine derivatives are not conformationally mobile (except for methyl-group rotations), the present paper does not deal with the problem of LSR-induced conformational changes; that subject will be taken up separately. The results of the present calculations show, however, that the pyridine ligands fit into narrow clefts in the Eu(dpm)$_3$ complex, which allows very little freedom of lateral or rotational movement of the pyridine molecules. As the degree of methyl-substitution on the pyridine ring increases in the position adjacent to the nitrogen atom, the steric interactions increase dramatically.

Methods

Geometry.—Co-ordinates for the atoms of the LSR complex were taken directly from the crystal structure determination [2] of Eu(dpm)$_3$py$_2$. This structure is described as a square antiprism. It has approximate (non-crystallographic) two-fold symmetry, with the two-fold axis bisecting one of the dpm ligands (Figure 1). The two pyridine rings are related by the two-fold axis; the Eu atom does not lie in either of the pyridine ring planes [the Eu–N–C(4) angle is 172°].[2] Computations on the interaction between one pyridine ligand and the remainder of the complex, *i.e.* Eu(dpm)$_3$py, were carried out using idealized (*i.e.* planar, symmetrical) pyridine or methyl-substituted pyridine co-ordinates, which were obtained from the crystal literature.[2-4] The Eu(dpm)$_3$py structure was held fixed in the crystal conformation. The pyridine geometry is given in Figure 2; for methyl-substituted pyridines, the same ring geometry was employed, but methyl groups were added at the desired locations, using a C–CH$_3$ bond length of 1.51 Å. The pyridine ring was initially placed in the Eu(dpm)$_3$py co-ordinate system with both N and C(4) lying on the Eu–N vector found in the Eu(dpm)$_3$py$_2$ crystal structure, and with C(2) lying in the same plane as the corresponding atom of pyridine in the crystal structure. This orientation defines the zero reference point for molecular rotation of the pyridine

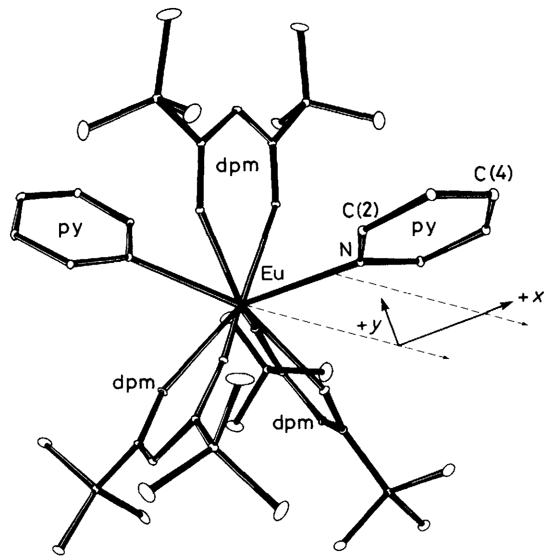

Figure 1. The crystal structure of the Eu(dpm)$_3$py$_2$ complex (ref. 2)

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† Dpm = 2,2,6,6-tetramethylheptane-3,5-dione ligand.

‡ Fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione ligand.

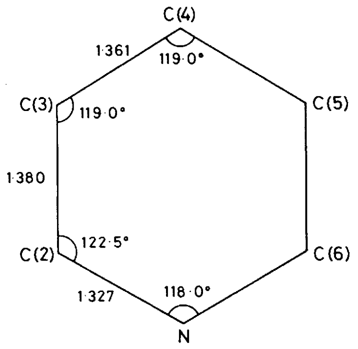


Figure 2. Geometry of the pyridine ring

ring. [Note, however, that in the crystal structure, the best-fit pyridine plane is slightly twisted away from the Eu–N vector, so that C(4) does not lie on the vector, and hence its position deviates slightly from our zero-reference point for the idealized pyridine ring.]

Calculations were carried out on only one of the two pyridine ligands, since their environments are similar, owing to the approximate two-fold symmetry of the complex and since the two pyridine rings are far enough apart as to be sterically non-interacting (Figure 1).

A right-handed Cartesian co-ordinate system was used to define the relative orientation of the pyridine ring to the Eu(dpm)$_3$py complex. The Eu–N vector was taken as the x-axis with positive x being in the Eu to N direction. Eu, N, and C(2) define the x,y plane, with C(2) being in the positive y direction; z is perpendicular to this plane. The origin was placed on Eu. (None of these axes correspond to the two-fold molecular axis.) Positive rotation about a given axis is clockwise, when viewing along the axis in question in the positive direction.

Energy.—The non-bonded energy of interaction between pyridine or its methyl derivatives and the remainder of the Eu(dpm)$_3$py complex was computed as a function of relative orientation and distance of separation. The non-bonded energy was computed as the sum of all pairwise interatomic interactions between the two molecules, using the Lennard-Jones 6—12 equation and the energy parameters given by Momany *et al.*[5] and Dunfield *et al.*[6] The 'united atom' method[6] was used for CH, CH$_2$, and CH$_3$ groups, which eliminates the necessity of specifying the co-ordinates of the H atoms or the dihedral angles of rotation of the methyl groups. Explicitly omitted from the non-bonded energy calculation are all terms involving Eu, since no reliable energy parameters are available for interactions involving rare earths. There is obviously an attractive force between Eu and N, however, which means that the real Eu–N separation distance may be expected to be shorter than that calculated here. For a similar reason, electrostatic energies were not calculated since no suitable method was available for assigning partial charges to the Eu complex. The non-bonded energy gives a quantitative measure of essentially steric interactions, however, which is the quantity of interest in the present work.

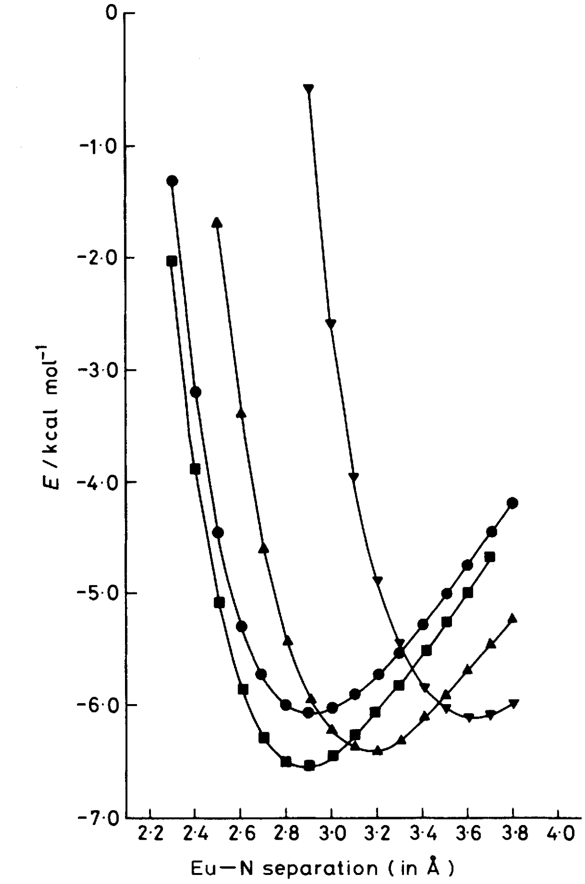


Figure 3. The non-bonded energy of interaction, E, *versus* the Eu–N separation for py · · · Eu(dpm)$_3$py, where py = pyridine (●), 3,5-dimethylpyridine (■), 2-methylpyridine (▲), and 2,6-dimethylpyridine (▼). At each value of R, energy minimization was carried out as a function of rotation of the pyridine ring about the x- and z-axes

Table 1. Values of the Eu–N distance (R) at the energy minimum (E) and best values for angles of rotation about the x- and z-axes for pyridine and some methyl-derivatives interacting with Eu(dpm)$_3$py [a]

Molecule	R/Å	E/kcal mol^{-1}	x-rotation (°)	z-rotation (°)
Pyridine	2.90	−6.08	11.3	0.8
3,5-Dimethylpyridine	2.90	−6.56	13.3	0.6
2-Methylpyridine	3.20	−6.41	186.3	3.1
2,6-Dimethylpyridine	3.65	−6.12	9.2	−16.2

[a] The energy was calculated at values of R from 1.50 to 3.80 Å at intervals of 0.05 Å.

Results

We report here the results of non-bonded energy calculations for the interaction between Eu(dpm)$_3$py and pyridine, 2-methylpyridine (2-picoline), 2,6-dimethylpyridine (2,6-lutidine), and 3,5-dimethylpyridine (3,5-lutidine). The energy is reported as a function of the Eu–N separation for each of these complexes, and also as a function of rotations about the x-, y-, and z-axes described in the Methods section. In each case, all geometrical parameters not explicitly being varied were held at the positions found in the Eu(dpm)$_3$py$_2$ crystal structure.[2]

Distance Dependence.—The computed non-bonded interaction energy between pyridine, 2-methylpyridine, 2,6-dimethylpyridine, or 3,5-dimethylpyridine and the rest of the Eu(dpm)$_3$py complex is plotted as a function of the Eu–N distance in Figure 3. The Eu–N distance (R) was varied from

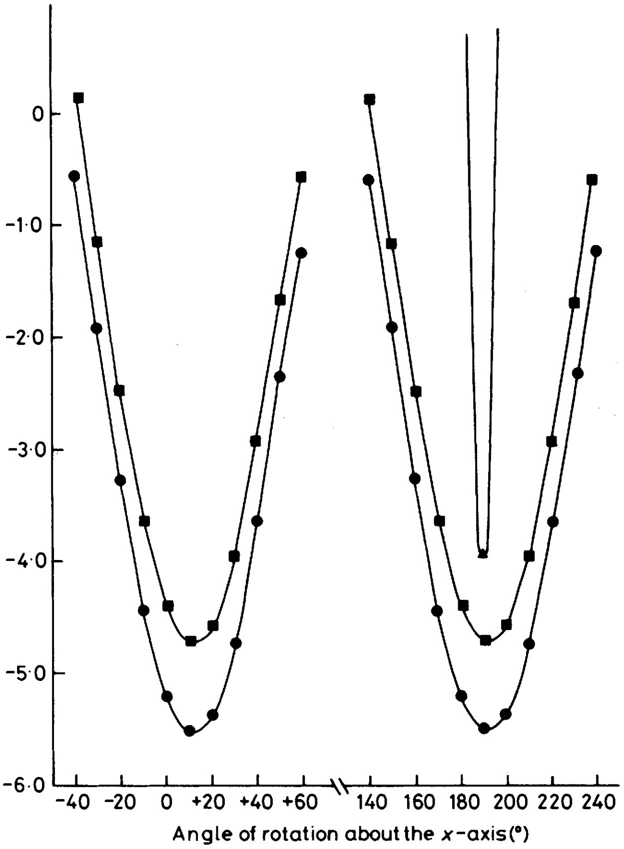


Figure 4. The non-bonded energy of interaction, *E*, *versus* the angle of rotation of the py ring about the *x*-axis for py = pyridine (●), 3,5-dimethylpyridine (■), and 2-methylpyridine (▲)

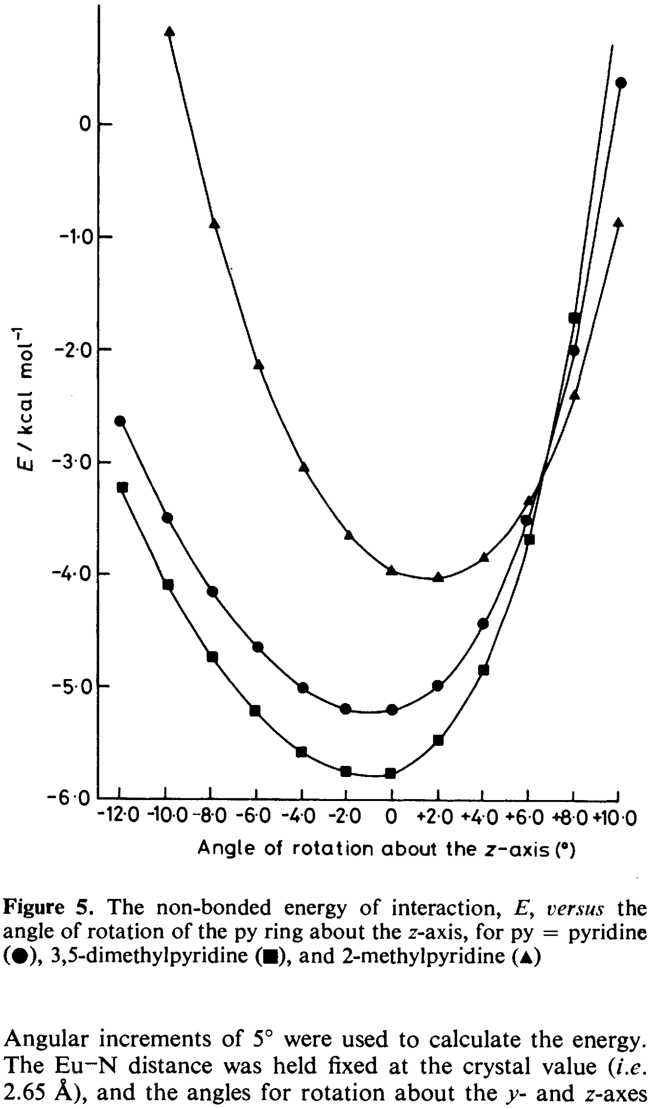


Figure 5. The non-bonded energy of interaction, *E*, *versus* the angle of rotation of the py ring about the *z*-axis, for py = pyridine (●), 3,5-dimethylpyridine (■), and 2-methylpyridine (▲)

1.50 Å to 3.80 Å in increments of 0.05 Å. At each value of *R*, energy minimization was carried out as a function of rotation of the pyridine ring about the *x*- and *z*-axes. These minimum energy values are given in Table 1. With pyridine as the ligand, the intermolecular energy at 2.65 Å (crystal structure position) is −5.55 kcal mol^{-1}, as compared with −6.08 kcal mol^{-1} at the non-bonded energy minimum, (2.90 Å). We attribute this difference to the fact that no energy terms were included for the interactions between Eu and the atoms of the pyridine ring. 3,5-Dimethylpyridine gave an energy *versus* distance profile that is very similar to that of pyridine, showing that methyl groups in these positions are far enough away from the dpm ligands in the complex as to be sterically non-interacting.

With 2-methylpyridine, however, substituting the methyl-group in the same direction as the +*y*-axis (Figure 1) causes large steric interactions with the dpm ligands, which can be reduced by substituting the methyl-group in the −*y*-direction. (The angle of 186.3° reported in Table 1 for the *x*-rotation of 2-methylpyridine corresponds to the ' flipping ' of the ring required to obtain the lowest non-bonded energy.) However, the value of *R* obtained at the non-bonded energy minimum is unusually large for both 2-methylpyridine (3.20 Å) and 2,6-dimethylpyridine (3.65 Å). Furthermore, a rotation of 16.2° about the *z*-axis would be required to minimize the energy in 2,6-dimethylpyridine. This rotation would further distort the octahedral geometry of the complex.

Angular Dependence.—Figure 4 shows the non-bonded interaction energy *versus* the angle of rotation about the *x*-axis. This corresponds to rotation about the Eu–N bond. Angular increments of 5° were used to calculate the energy. The Eu–N distance was held fixed at the crystal value (*i.e.* 2.65 Å), and the angles for rotation about the *y*- and *z*-axes were held at 0° (crystal structure position); for this reason the lowest energies found here will not be as low as the energies found for Figure 3. The steric interactions relax somewhat when the pyridine ring is rotated approximately +10° about the *x*-axis from its initial position. For example, in pyridine, the calculated non-bonded energy is lowered by 0.31 kcal mol^{-1} upon a 10° *x*-axis rotation. (Owing to the symmetry of pyridine, a 190° rotation is equivalent to a 10° rotation.) Essentially identical results are obtained for 3,5-dimethylpyridine. This is not true for 2-methylpyridine, where rotation brings the energy down from 129 kcal mol^{-1} at 0° to 47.9 kcal mol^{-1} at 10°; a positive non-bonded energy of this magnitude implies that there must be strong steric interaction between the 2-methyl group and Eu(dpm)$_3$py. A 190° rotation about the *x*-axis lowers the energy to −3.95 kcal mol^{-1}, however, showing that the steric interactions are relieved in this position. The non-bonded energy remains high, as expected, at both 10 and 190° for 2,6-dimethylpyridine (49.5 kcal mol^{-1}).

Figure 5 gives the energy as a function of rotation about the *z*-axis. Since the *z*-axis is perpendicular to the plane of the pyridine ring, this rotation corresponds to movement of the ring in its own plane (*i.e.* the *x*,*y* plane) pivoting on Eu, with Eu–N–C(4) remaining colinear (see Figure 1). The minima are very narrow and centred at −1° for pyridine and 3,5-dimethylpyridine, but are asymmetric, showing that the ring has a greater latitude of freedom on one side than the other. Results

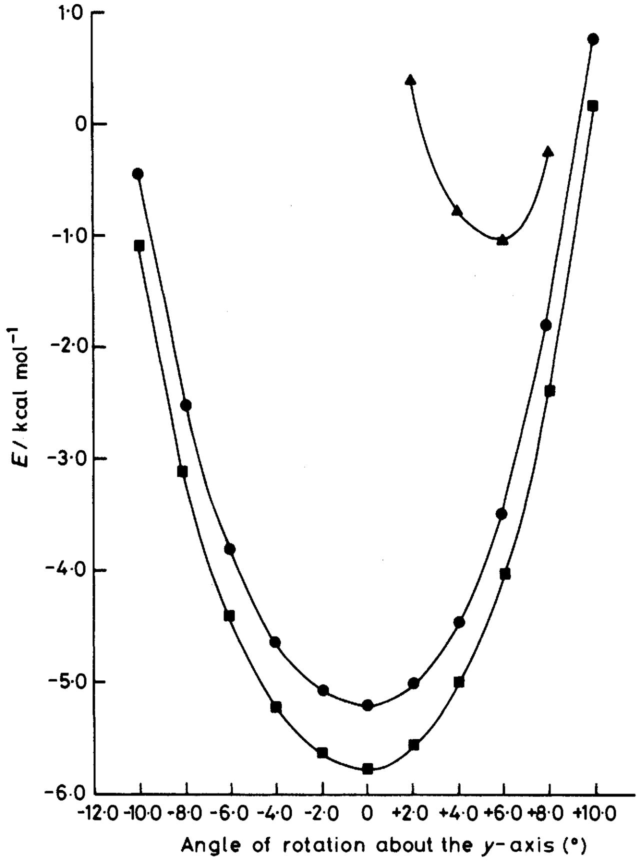


Figure 6. The non-bonded energy of interaction, E, *versus* the angle of rotation of the py ring about the y-axis, for py = pyridine (●), 3,5-dimethylpyridine (■), and 2-methylpyridine (▲)

are very similar for pyridine, 3,5-dimethylpyridine, and 2-methylpyridine (when the 2-methyl-group is set at a sterically favourable position, namely by making the angle of rotation about the x-axis 190°) as shown in Figure 5. The minimum energy calculated for 2,6-dimethylpyridine is $+38.8$ kcal mol^{-1}, at a rotation of $-10°$ about the z-axis.

In Figure 6, the angle of rotation about the y-axis is varied. This motion corresponds to bending the pyridine ring up or down toward the positive or negative z-axis, respectively, bringing it into close contact with the dpm ligands. The energy minima are at 0° (the crystal structure position) for pyridine and 3,5-dimethylpyridine, and at $+6°$ for 2-methylpyridine and are very narrow. Even though the angle of rotation about the x-axis was set at 180° for 2-methylpyridine, the minimum energy calculated is -1.04 kcal mol^{-1} at $+6°$ (Figure 6). The energy is even higher for 2,6-dimethylpyridine; the minimum energy calculated is 137 kcal mol^{-1} at 0° rotation about the y-axis.

It may be noted that rotations of the pyridine ring about the y- or z-axes perturb the square antiprism geometry of the complex (it is, however, already distorted [2]) but a rotation about the x-axis does not, since the x-axis is defined as the Eu–N–C(4) axis (Figure 2). This is undoubtedly related to the fact that the energies for rotation of the pyridine ring (through 360°) about the x-axis never get larger than a few kcal mol^{-1} and the energy minima are much wider (Figure 4) than those for rotation about the y- or z-axes (Figures 5 and 6).

Energy Minimization.—Once the regions of minimum energy were mapped out, a minimization of the non-bonded energy (E) with respect to R, and the x- and z-angles of rotation were carried out for pyridine. The values of E, R, and the angles of rotation about the x- and z-axes are -6.08 kcal mol^{-1}, 2.89 Å, 12.3°, and 0.3°, respectively, virtually the same as the results obtained by mapping and minimizing the energy (Table 1).

Atoms Related by Short (<3 Å) *Distances of Interaction.*—When the distances between atoms in the pyridine or methyl-substituted pyridine moiety and the atoms in the dpm ligands become too small, the non-bonded energy of interaction rises. In order to determine which atoms are sterically interacting, all non-bonded atoms less than 3 Å from one another were examined at a Eu–N distance of 2.90 Å. This value, the value at which the non-bonded energy in pyridine is a minimum (Table 1), was chosen for all molecules studied so that they could be compared at the same Eu–N distance. For pyridine and 3,5-dimethylpyridine, no atoms from the pyridine ring and the dpm ligands approached closer than 3.0 Å.

The same was true of 2-methylpyridine (if subject to an x-rotation of 190°). However, for 2-methylpyridine or for 2,6-dimethylpyridine at an x-rotation of the ring of 0 or 10°, short distances were found between the ring methyl-substituents on the pyridine and several of the t-butyl methyl groups on the Eu(dpm)$_3$py complex. Short distances were also found between the ring methyl substituents and certain ring oxygen atoms in the dpm ligands. These calculations reveal the positions of strong steric interactions, and show why 2-methyl- and 2,6-dimethyl-pyridine do not bind as well to the LSR as does pyridine (this will be discussed in the next section).

As the Eu–N bond is lengthened beyond 2.90 Å the intermolecular interactions between the Eu(dpm)$_3$py complex and the pyridine ring methyl substituents at distances of <3.0 Å disappear. This is why the energy minimum is found at progressively longer values of the Eu–N distance as the substitution of the pyridine ring at the α-N position increases (Table 1).

Discussion

This work has focused on the steric interactions between a typical lanthanide-shift reagent and a rigid ligand (pyridine or one of its methyl-substituted derivatives). The non-bonded interaction energy is found to be low only at positions of the pyridine ring that are very close to those reported for the crystal structure of Eu(dpm)$_3$py$_2$. The picture that these calculations give is one of the pyridine ring fitting into a relatively small pocket as it binds to the Eu(dpm)$_3$py. The three dpm bidentate ligands of Eu(dpm)$_3$py undergo significant steric interactions with an additional pyridine molecule in the square antiprism complex studied here. As the methyl substitution α to the nitrogen atom of the pyridine increases, the steric interactions also increase. This is reflected in Table 1, which shows that the energy minimum is at larger values of R (Eu–N distance) as α-methyl substitution increases. This does not, of course, mean that R will actually increase; these calculations include only non-bonded steric interactions and do not take into account attractive forces between the Eu and the N atoms, inductive forces, or possible rearrangements of the complex when ligands other than pyridine are used. Since the largest lanthanide–nitrogen distance reported in a recent review [7] of LSR adducts is 2.65 Å (X-ray crystal structure) for Eu(dpm)$_3$py$_2$ and Ho(dpm)$_3$(4-methylpyridine)$_2$, it is likely that the Eu–N distances reported here are too large, even in solution where rapid exchange (on the n.m.r. time scale) occurs among the ligands.[8]

The calculations reported here are for the 2 : 1 octacoordinate complexes, and therefore do not rule out the pos-

Table 2. Equilibrium constants for pyridines binding to Eu(dpm)$_3$ [a]

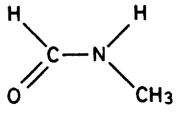
Compound	K	pK_a
Pyridine	333	5.21
2-Methylpyridine	83.1	5.94
2-6-Dimethylpyridine	8.7	6.60

[a] Determined for the 1 : 1 complex by n.m.r. at 27 °C in CDCl$_3$; ref. 10.

sibility that bulky ligands such as 2,6-dimethylpyridine may form heptaco-ordinate, 1 : 1 complexes with Eu(dpm)$_3$. Such a complex has been reported for Lu(dpm)$_3$(3-methylpyridine).[9] Heptaco-ordination would be expected to reduce somewhat the steric interactions between the ligand and the LSR complex. However, the general conclusions regarding the importance of steric interactions in the octahedral complexes should hold as well for the heptaco-ordinated complexes.

Examination of distances of interaction of less than 3 Å between the atoms of pyridine (or its derivatives) and those of Eu(dpm)$_3$py reveal that the shortest interactions are those between the α-methyl atoms on the pyridine ring and the t-butyl atoms or the oxygen atoms in the dpm ligand. All of the data presented here, therefore, indicate that groups near the binding site of the pyridine (*i.e.* groups substituted α to the N atom) will undergo severe steric interactions with the Eu(dpm)$_3$py complex. Experimental evidence [10] to support this conclusion is given in Table 2. The equilibrium constant for binding of pyridines to Eu(dpm)$_3$ is seen to decrease four-fold when one α-methyl is added to pyridine and another ten-fold when a second α-methyl is added. That this effect cannot be ascribed to an inductive effect rather than a steric effect is shown by the pK_a values of the pyridines. As the pK_a value rises, and the basicity, therefore, increases, the ligand would be expected to bind to the Lewis acid Eu(dpm)$_3$ with a higher equilibrium constant. The decrease in K observed is due to steric interactions caused by the α-methyl substituents.

The results presented here are directly relevant to the use of LSR complexes in n.m.r. conformational studies. The LSR cause large perturbations in the n.m.r. chemical shift of all of the magnetic nuclei in the substrate molecule. Although the total observed shift will often contain contributions from contact and pseudo-contact interaction as well as from complex formation, the pseudo-contact term may be separated out from the rest,[11] and it is this pseudo-contact (or dipole–dipole) interaction which gives rise to the ‘ geometric factor’, which in turn is related to molecular geometry. Despite some misgivings [12] concerning the assumptions implicit in the use of the one-term McConnell–Robertson [13] equation to relate the lanthanide-induced shift (LIS) to molecular geometry, lanthanide-shift reagents are now regarded as effective probes of molecule geometry in solution and are increasingly used in conformational analysis.[14] It must be assumed, when using LSR probes, that the conformation of the ligand does not change upon binding to the LSR. If it does change, (or if the populations of the preferred conformations change) then it is the structure of the LSR–ligand complex which is found, and not that of the ligand itself. We have shown here that steric interactions between the LSR and groups near to the binding site of the substrate can be severe. Indeed, if the interaction is sufficiently large, it is conceivable that it could change the conformation of a non-rigid substrate. We have recently shown [15] that the *cis* : *trans* ratio in *N*-methylformamide (NMF) changes from 8 : 92 in the absence of LSR to 44 : 56 when the molar ratio of LSR to amide is 0.5 (CCl$_4$ solution). This change has been attributed to the *trans*-NMF isomer having larger steric interactions with the LSR than does the *cis*-NMF isomer.[15] We intend to study the non-bonded interaction energy of amides with LSR in order to understand how the LSR can cause such a significant population change in NMF.



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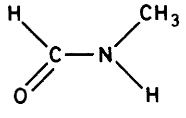

cis

In evaluating the importance of steric interactions on the substrate conformation as determined by n.m.r., it must be kept in mind that in solution, at ambient temperature, both pyridine and dpm ligands are undergoing fast exchange on the n.m.r. time scale.[8] The conformation or conformations in solution are therefore not necessarily identical to the crystal structure conformation that was used as a starting point for the calculations presented here. Furthermore, since low potential energy barriers exist among the idealized hepta- or octaco-ordination polyhedra,[16] it is possible that one or more of the other allowed geometrical isomers exist in solution, especially with different substrates. Nevertheless, these calculations reveal that the Eu(dpm)$_3$ shift reagents are bulky molecules whose atoms may undergo many close contacts with the atoms of the substrate molecule causing large non-bonded interaction energies. Exactly what effect this may have on the conformation of a flexible substrate molecule remains to be determined.

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