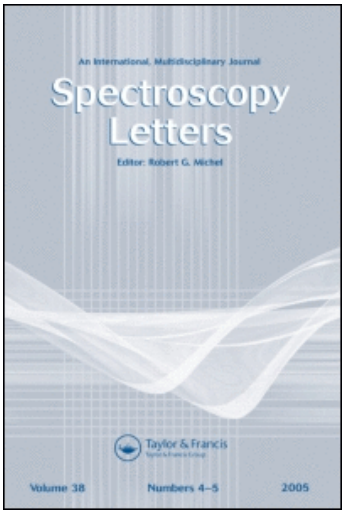

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NMR Studies of Drugs: Antipyrine and Analogs. I. Use of Achiral and Chiral Lanthanide Shift Reagents to Examine Hindered Rotation.

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NMR STUDIES OF DRUGS: ANTIPYRINE AND ANALOGS. I. USE OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO EXAMINE HINDERED ROTATION.

Key Words: 1,2-Dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one; 2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one; LSR; $Eu(FOD)_3$; $Eu(HFC)_3$; Analysis; Dynamic NMR; ^1H NMR; Lanthanide-induced shifts.

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ABSTRACT

The 200 MHz ^1H NMR spectra of the analgesic, antipyrine, 1, have been studied in $CDCl_3$ solution at ambient temperatures with the achiral lanthanide shift reagent (LSR) tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), $Eu(FOD)_3$, 2, and with the chiral LSR, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), $Eu(HFC)_3$, 3. Lanthanide-induced shift (LIS) magnitudes and broadening of selected signals are

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consistent with predominant LSR binding at the carbonyl oxygen with either 2 or 3. Of the different possible conformational regimes for the N-phenyl group of 1, our results appear to rule out a slow exchange limit (SEL) system with the N-phenyl coplanar with the heterocyclic ring. Perpendicular rings in an SEL regime can not be ruled out. A rapidly-rotating N-phenyl (fast exchange limit, FEL system) would also be consistent with observed results. Accurate chemical shifts for the aryl protons (overlapped in the 200 MHz spectrum of unshifted 1) are determined from spectra with added LSR by extrapolation to zero molar ratios of [LSR]:[1]. Relative slopes in the plots of chemical shift versus [LSR]:[1] molar ratios are calculated for each proton signal of 1.

INTRODUCTION

Antipyrine, 1, known as 1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one or as 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, has analgesic properties. The partial structure of 1 is found in numerous pharmaceuticals and analogs, such as famprofazone, aminopropylon, aminopyrine, ampyrone (4-aminoantipyrine), nifenazone (N-antipyrinylnicotinamide), and dipyrone [(antipyrinylmethylamino)methanesulfonic acid sodium salt]. See Figure 1 for structures. We have recently published the results of lanthanide shift reagent (LSR) studies on famprofazone (1), which is one of the drugs based on antipyrine. Unusual signal broadening effects in the ^{1}H NMR spectra of famprofazone with added LSR, especially for the resonances of the N-C_6H_5 and isopropyl group near the carbonyl, led us to consider possible contributions to the line broadening due to different conformations associated with hindered rotations of these groups. However, famprofazone itself was a rather complex system to examine for these potential rotational factors, because of the presence of the "methamphetamine"-moiety as a substituent, which introduced another potential binding site (i.e., the

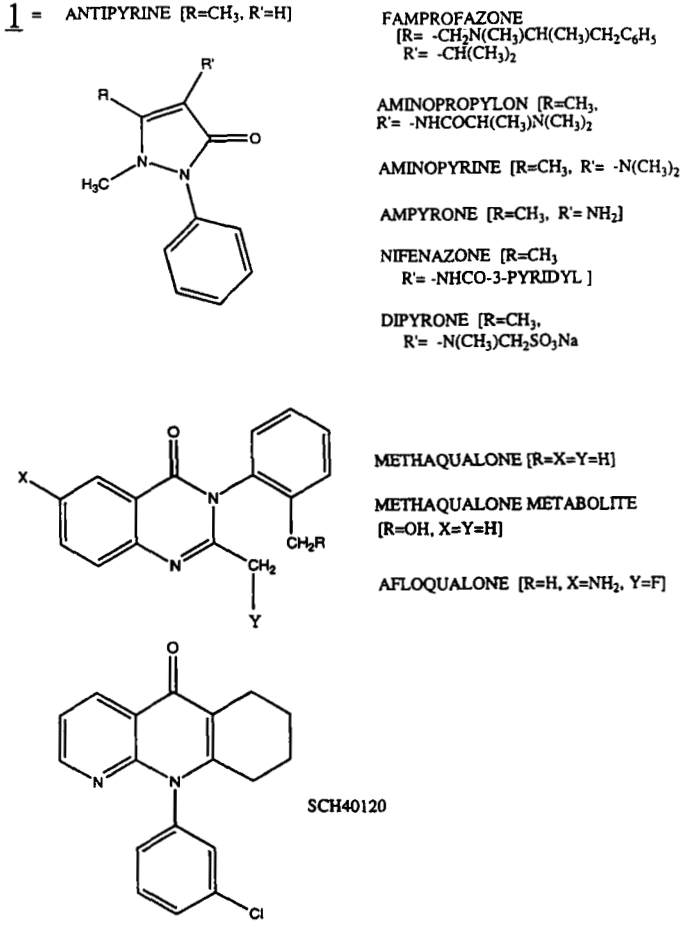

Fig. 1. Structures of compounds cited.

tertiary amine in the sidechain) and a chiral center, as well as numerous additional resonances in the ^{1}H NMR spectra. Preliminary NMR studies of another antipyrine analog, aminopropylon, also showed striking signal broadening with added LSRs (unpublished results). Aminopropylon also presents the complexities of additional possible LSR binding sites, potential bidentate chelation of lanthanide, and a chiral center in the sidechain. (Our studies of famprofazone and aminopropylon had, in part, been driven by an interest in determining enantiomeric excess by use of chiral LSR.)

In order to focus an examination on the N-phenyl conformations and rotations in the extremely important antipyrine system, we report here the results of ^{1}H NMR studies of 1 using the achiral LSR, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, known as Eu(FOD)$_3$, and the chiral LSR, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), 3, known as Eu(HFC)$_3$ or Eu(HFBC)$_3$. We were hoping to gain some insight to distinguish between four possible limiting conditions for 1 with respect to the N-phenyl group: (a) coplanar with the heterocyclic ring at the slow exchange limit (SEL); (b) coplanar with the heterocyclic ring at the fast exchange limit (FEL); (c) perpendicular to the heterocyclic ring at the SEL; and (d) perpendicular to the heterocyclic ring at the FEL.

In the course of these studies on 1 and analogs, we believe that we have seen evidence for a simple and useful NMR method for evaluating the preferred N-phenyl conformation in this class of compounds. These results are presented in the accompanying paper.

Hindered aryl ring rotations can lead to enantiomerism due to axial chirality, as in methaqualone (a sedative/hypnotic) (2) and one of its metabolites (3), afloqualone (a skeletal muscle relaxant) (4), or Schering SCH40120 (a potential antipsoriatic agent) (5). Even with an unsubstituted phenyl ring, hindered rotations can lead to NMR spectral anomalies, with broadened signals or extra

resonances resulting from intermediate exchange rates or SEL regimes, as observed for the benzodiazepine, ketazolam (6,7) and in the bridgehead phenyls for numerous Diels-Alder adducts of phencyclone (8).

EXPERIMENTAL

Antipyrine, $CDCl_3$ (99.8 at % D) and shift reagents were obtained from Aldrich Chemical Corp. (Milwaukee WI 53201). The $CDCl_3$ was dried and stored over 3Å molecular sieves. Drug and LSRs were stored in a desiccator over P_2O_5 and were used as supplied. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS), used as internal reference at 0.00 ppm. In runs with LSR, increments of LSR were accurately weighed into a 5 mm NMR tube containing an aliquot of a standard solution of 1. The LSR was dissolved by shaking and the spectra were then acquired. NMR studies were performed with a Bruker AC200-F Fourier transform (FT) NMR spectrometer with Aspect 3000 data system operating at a ^1H observe frequency of 200.13 MHz. Spectra were obtained in the FT mode at ambient temperatures using a switchable $^1H/^{13}C$ probe. Typical FT-NMR parameters were as follows: 4 KHz spectral width (about -4 to +16 ppm) over 64K complex data points collected in the quadrature detection mode for a digital resolution of ca. 0.12 Hz/point, pulse width 3 μs, ca. 8s acquisition time, 1s relaxation delay; 64 FIDs were accumulated. No line broadening or resolution enhancement was applied.

RESULTS AND DISCUSSION

Data for 1 with 2 were obtained using 0.05162 M 1 for 2:1 molar ratios up through 0.664. For 2:1 molar ratios of 0.853-1.716, a stock solution of 0.05086 M 1 was used. At the lowest molar ratios of 2:1, the ortho, meta and para proton signals of 1 were not resolved, but with 2:1 ratios of 0.13 or greater these signals were sufficiently separated to permit distinct assignments. For runs with the added chiral LSR, 3, a solution of 0.04706 M 1 was employed, with 3:1 molar ratios up to 0.872. The results of these runs with added 2 or 3 are shown in Figures 2 and 3, respectively,

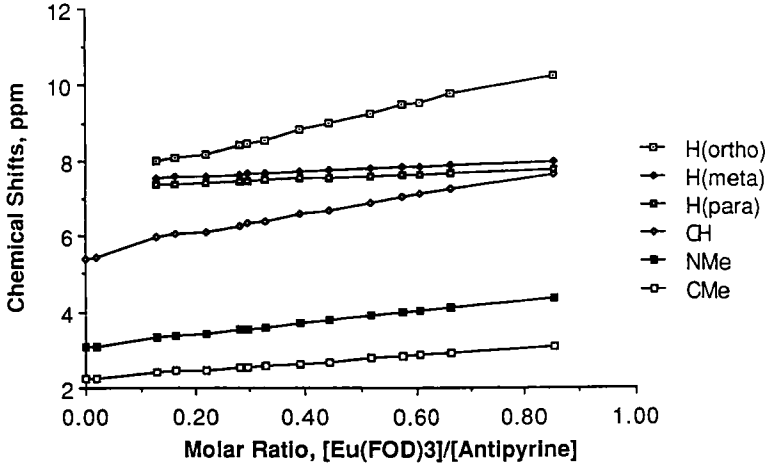

Fig. 2. Variations of chemical shift with molar ratio of $[Eu(FOD)_3]$: [1].

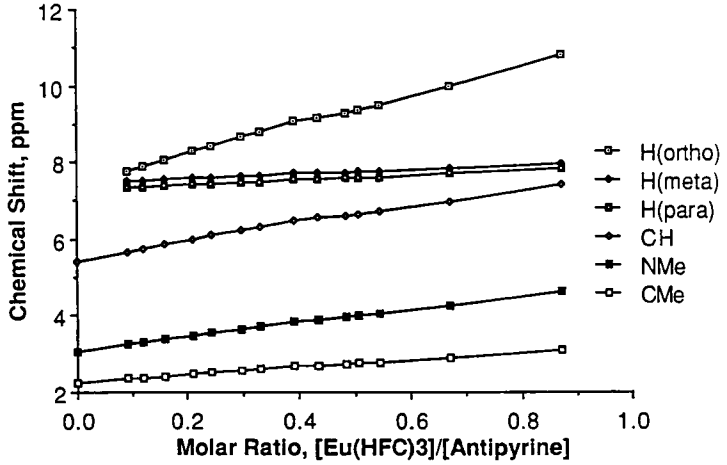

Fig. 3. Variations of chemical shift with molar ratio of $[Eu(HFC)_3]$: [1].

illustrating the variations in chemical shifts for the nuclei of 1 versus the [LSR]/[antipyrine] molar ratios. In Table 1, the line equations from least squares line fitting of the data in Figures 2 and 3 are collected, together with the "normalized slope" values. Since some deviations from linearity were apparent at higher molar ratios, only those data points for which good linearity was evident were used for the line equations. For example, slopes for the three aryl protons with added 2 were calculated over a 2:1 molar ratio range of ca. 0.22-0.66 (at lower molar ratios, the ortho, meta and para proton resonances were not well resolved and these points are not shown in Fig. 2.) For the signals of the CH, NCH_3 and CCH_3, data points for 2:1 molar ratios up to 0.66 were used. With 3, data points for the three aryl protons were used for 3:1 molar ratios from 0.09-0.39, and for the remaining three proton signals, 3:1 ratios up to 0.39 were used. The quality of the data is suggested by correlation coefficients, R, equal to 1.00 for all line equations except H(para) with 2, for which R=0.99.

For unshifted 1 in $CDCl_3$, the aryl proton signals appeared as a complex band in a narrow multiplet from ca. 7.23-7.51 ppm. The methine CH appeared at 5.405 ppm as a quartet due to long range (^4J = 0.90 Hz) splitting by the allylic methyl. The N-methyl resonance was a singlet at 3.064 ppm, and the allylic methyl, CCH_3, appeared as a doublet (^4J = 0.90 Hz) at 2.240 ppm. After the first one or two LSR increments, line broadening obscured the allylic coupling. With 2:1 ratios of 0.13 or more, distinct separated signals for the ortho, meta, and para signals were seen, with recognizable gross triplet structure for the latter two signals; the ortho signal was extremely broad even with low levels of added LSR. The observed average splittings for H(meta) were ca. 7.65 Hz, and for H(para) ca. 7.40 Hz. With 2, the H(ortho) signal was initially very broad, with gross doublet structure appearing only for 2:1 molar ratios ca. 0.33-1.27. The apparent observed splitting increased monotonically from ca. 4.29 Hz (2:1 ratio 0.39) to

ca. 6.9 Hz (2:1 ratio 0.85). Higher LSR levels again caused broadening. We believe that this apparent change in the observed coupling to H(ortho) is largely artifactual due to increased resolution rather than to true changes in J values. In contrast, with added 3, H(ortho) appeared consistently as a very broad signal, with some doublet structure (observed J ca. 6.6 Hz) seen only at the highest 3:1 ratio of 0.872. The triplets seen for H(meta) and H(para) with added 3 were comparable to results with 2; the multiplet structure was not resolvable for 3:1 ratios of 0.67 or more. The phenomenon that NMR absorption signals may, in some cases, exhibit maximum line broadening at an intermediate [LSR]:[substrate] molar ratio (i.e., 0.33) and then become sharper as the LSR level is further increased, has been previously discussed (9,10).

We note that there is good agreement between the observed shifts for the CH, NCH_3 and CH_3 resonances of 1 without LSR, and the intercepts in the calculated equations; similarly, good agreement (i.e., ± 0.01 ppm) is seen between calculated intercept values for all six nuclei from data of both 2 and 3. Using the average of these values for 2 and 3, chemical shift values of ca. 7.375 (ortho), 7.452 (meta), and 7.281 ppm (para) may be assigned for "unshifted" 1. Note that this is a relatively narrow range; this will be discussed further in the accompanying paper.

The normalized slopes in Table 1 are presented relative to the signal for the CCH_3. This signal was selected as a reference since it is far from the putative LSR binding site (at the carbonyl). Observed lanthanide-induced shifts (LIS) should, therefore, essentially result from dipolar pseudocontact shifts rather than Fermi contact shifts or complexation shifts (11). The comparable values of the normalized shifts determined for data from either 2 or 3 implies similarity in the structures of the bound complexes of 1 with either LSR. The largest normalized slope values are seen for the methine alpha to the carbonyl and for the ortho protons; this is strong evidence for primary lanthanide

Table 1. Equations from least squares line fittings of chemical shifts vs. [LSR]/[1] molar ratios.

	$Eu(FOD)_3$, 2		$Eu(HFC)_3$, 3	
Nucleus		Normalized Slopes		Normalized Slopes
H(ortho)	y = 7.364 + 3.630x	3.562	7.386 + 4.262x	3.816
H(meta)	7.458 + 0.630x	0.618	7.446 + 0.631x	0.565
H(para)	7.285 + 0.587x	0.576	7.276 + 0.663x	0.594
CH	5.426 + 2.836x	2.783	5.427 + 2.702x	2.419
NCH_3	3.054 + 1.607x	1.577	3.074 + 1.982x	1.774
CCH_3	2.237 + 1.019x	1.	2.249 + 1.117x	1.

Notes: Line equations are based on least squares line-fittings for linear, lower molar ratio regions of plots of chemical shifts vs. molar ratios. All correlation coefficients, R, were equal to 1.00 except for H(para) with 2 (for which R = 0.99). "Normalized Slope" values are given relative to a value of 1.0 for the slope of the line assigned to the CCH_3 resonance for each LSR. See Results and Discussion.

complexation at the carbonyl. However, it is not obvious why the normalized slope for the para protons are slightly greater than for the meta protons with added 3; this may simply be experimental error. The significantly larger values for normalized slope of the NCH_3 compared to the CCH_3 with either 2 or 3 is surprising, and we can not rule out the possibility of some contributions from a bound complex in which lanthanide is proximal to the NCH_3 nitrogen.

For this study, the most striking results would seem to be the apparent presence of a single signal for the ortho protons, and a single signal for the meta protons. We interpreted this in the following way. The relative values of the normalized slopes seen here for 1 with added 2 or 3 imply predominant LSR binding at the carbonyl, as was also observed for famprofazone (1). If lanthanide is bound at the oxygen, and if the N-phenyl is effectively coplanar with the heterocyclic ring and is rotating slowly (i.e., on the NMR timescale: an SEL regime), then the two ortho positions of the phenyl ring (H-2',6') would dramatically differ from one

another with respect to their proximity and geometry relative to the carbonyl and bound LSR. Large differences in the LIS values and two distinct signals should be the result (12,13). Two discrete signals might also be expected for the meta protons (H-3',5') as well. If the N-phenyl were rotating rapidly on the timescale of the NMR experiment (FEL regime) then the two ortho positions should be sharply averaged and a single 2H intensity "doublet" signal for H-2',6' might be observed (and, similarly, the two meta H-3',5' hydrogens should give one 2H intensity "triplet" signal, where the gross multiplicity is determined by the number of vicinal proton neighbors). This situation should obtain whether achiral (2) or chiral (3) LSR is used, since there are no enantiotopic nuclei in 1 with the phenyl and heterocyclic rings coplanar. In contrast, for a conformer of 1 in which the phenyl is perpendicular to the heterocyclic ring (to reduce steric repulsions), the two ortho positions become enantiotopic by internal comparison (and similarly for the two meta positions). If the system is SEL with the phenyl "perpendicular," then a chiral LSR but not an achiral LSR might elicit unequal LIS magnitudes for the enantiotopic nuclei. Thus, enantiomeric shift differences ($\Delta\Delta\delta$) and different observed chemical shifts might be seen for the enantiotopic ortho protons, leading to two 1H intensity "doublets."

Whether the preferred N-phenyl conformation of 1 is coplanar with or perpendicular to the heterocyclic ring should be potentially distinguishable, so long as the phenyl rotation rate is slow enough to provide an SEL regime. If the phenyl rotated rapidly (fast exchange limit, FEL), then averaging of the ortho positions (2',6') and meta positions (3',5') would result in observing only single sets of resonances, whether an achiral or chiral LSR is used. With $Eu(FOD)_3$, 2, added to 1, a 2:1 molar ratio of 0.13 is sufficient to clearly separate the ortho, meta and para signals of th N-phenyl. Broadening of the ortho resonance has eliminated any valley in the expected "doublet" signal,

but the meta and para signals are distinct triplets with little broadening. This situation obtains up through a 2:1 molar ratio of ca. 0.33, but with higher 2:1 ratios (i.e., 0.39 or more) the ortho resonance exhibits progressively sharper doublet structure: the valley becomes more apparent. The ortho signal doublet structure and the clean triplet structures for the meta and para signals are distinct to a 2:1 molar ratio of at least 1.27. We believe that this must rule out an SEL system with coplanar N-phenyl. Either a perpendicular N-phenyl or FEL regime are consistent with these results with 2.

Additions of the chiral $Eu(HFC)_3$, 3, appear to produce more broadening of the ortho signal, with no hint of any valley that would suggest doublet structure, beginning at the low 3:1 molar ratio of ca. 0.09 (which separated the ortho, meta and para signals clearly). However at a 3:1 ratio of 0.67, some "flattening" of the top of the ortho signal may be discerned, and with a 3:1 ratio ca. 0.87 the ortho signal has sharpened to give a distinct valley, confirming the doublet structure. At no 3:1 ratio examined here was there any evidence for any "doubling" of ortho or meta signals that might result from enantiomeric shift differences. While this could result from a rapidly rotating phenyl (FEL regime) we can not rule out the possibility of an SEL system with the phenyl perpendicular to the heterocyclic ring of 1. While the presence of $\Delta\Delta\delta$ would strongly support a perpendicular phenyl with SEL, the absence of $\Delta\Delta\delta$ does not allow us to rigorously rule out this alternative. Use of a chiral LSR does not always induce experimentally observable enantiomeric shift differences for enantiotopic nuclei in a given system (13, 14). In particular, obtaining observable $\Delta\Delta\delta$ for nuclei which are enantiotopic by internal comparison, as the ortho protons in 1 would be if the N-phenyl and heterocyclic rings are perpendicular, may be especially uncertain. Nevertheless, numerous successful examples have been reported; the chiral LSR 3 used by us in this present work has been found more effective than $Eu(FACAM)_3$ (14).

In contrast to the antipyrine system of 1 and its analogs, the methaqualone-type systems are much more hindered with respect to N-aryl rotation for two reasons. Firstly, these compounds possess an aryl substituent (CH_3 or CH_2OH) at the 2′ position, and secondly, aryl attachment to a six-membered ring must lead to more crowding with the proximal carbonyl and C-CH_3 (or C-CH_2F) groups than in the smaller five-membered rings of antipyrine and analogs. In the more hindered systems, the N-aryl groups must clearly be perpendicular to the heterocyclic rings and in an SEL regime to allow observed enantiomeric shift differences (or chromatographic resolutions of enantiomers). The less-hindered SCH40120 has the N-aryl group on a six-membered ring, but the N-aryl substituent is now at the 3′ position. Nevertheless, the chlorophenyl ring is still perpendicular to the central heterocyclic ring of SCH40120 and in the SEL regime on the NMR time scale. The lower activation energies for the chlorophenyl rotations in SCH40120 lead to more facile enantiomerizations (5) compared to the methaqualone analogs.

Since antipyrine and analogs have a less hindered system, with an unsubstituted N-phenyl on a five-membered ring, the barrier to N-phenyl rotation should be still lower, suggesting fast N-phenyl rotations, fully consistent with our observed spectra of 1 with added 2 or 3. On the timescale of the NMR LSR experiments, the system of 1 may well be an FEL system. While we believe that a conformation with the N-phenyl perpendicular to the heterocyclic ring of 1 is lower energy than with coplanar rings, the situations may be indistinguishable for the LSR technique used here. In fact, we believe that alternative NMR methods with an "intrinsically shorter experimental timescale" can effectively be used to distinguish a preferred N-phenyl conformation even with fast rotation rates. This will be presented in the accompanying paper.

CONCLUSIONS

We have examined the 200 MHz ^1H NMR spectra of antipyrine, 1, in $CDCl_3$ solution at ambient temperatures with

added achiral LSR, $Eu(FOD)_3$, 2, and chiral LSR, $Eu(HFC)_3$, 3. Relative slopes in the plots of chemical shift versus [LSR]:[1] molar ratios were determined for each nucleus of 1, and precise chemical shifts for the N-phenyl ortho, meta and para protons of 1 were calculated by extrapolation from the shifted spectra of 1 with added LSR back to unshifted 1. Relative slopes imply predominant LSR binding at the carbonyl of 1. With added 2, an SEL system with coplanar phenyl and heterocyclic rings would be expected to show separate signals for the two ortho protons (and possibly the meta protons) but only one signal for each of these protons was seen, ruling out the SEL coplanar possibility. If two separate ortho signals had been observed with added chiral LSR, 3, but not with achiral 2, this would be consistent with perpendicular phenyl and heterocyclic rings in an SEL regime. The two ortho protons would then be enantiotopic by internal comparison for free 1 or for 1 bound to achiral LSR, 2. But with 1 bound to a chiral LSR, 3, these enantiotopic protons become diastereotopic, with potentially different chemical shifts. In fact, no enantiomeric shift differences were seen with added 3 for the ortho or meta protons. All of these results are explainable by an FEL system, with either coplanar or perpendicular rings as preferred conformations; an SEL system with perpendicular rings is possible and can not be ruled out.

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