^{1}H NMR Study of *cis–trans* Isomerization in Two Analogs of the Thiol Form of Thiamine

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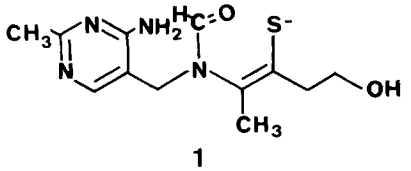
Proton magnetic resonance (^{1}H NMR) was used to study *cis-trans* isomerization in *N*-methyl-*N*-(1-methylthio-2-propenyl)formamide and *N*-benzyl-*N*-(1-methylthio-2-propenyl)formamide, two analogs of the thiol form of thiamine. Benzene dilution studies and shift reagent studies were used to make resonance assignments, which indicate that the predominant isomer for each analog has the C=C bond *trans* to the carbonyl oxygen. Shift reagent studies, using Pr(fod)$_3$ in CCl_4 or $CDCl_3$, suggest that the reagent may be bonding to both the nitrogen and oxygen atoms of the substrate. For some of the systems studied, varying ρ at constant temperature had the same spectral effect as varying temperature at constant ρ.

INTRODUCTION

In a study of properties of thiamine in alkaline solution, Maier and Metzler[1] showed that the thiazole ring of thiamine opens to form a complex amide (**1**) when reacted with base above pH 10. ^{1}H NMR spectra of this complex show the normal *cis–trans* isomers arising from hindered rotation around the N–CO amide bond. The *cis–trans* isomer ratio for this complex is approximately 15:85, as determined by electronic integration of its ^{1}H NMR spectra.

Hydrogen bonding studies on thiamine being conducted by the present investigators have led to the synthesis of a number of analogs of the thiol form of thiamine, two of which are *N*-methyl-*N*-(1-methylthio-2-propenyl)formamide (**2**) and *N*-benzyl-*N*-(1-methylthio-2-propenyl)formamide (**3**). These two compounds will hereafter be referred to as M(MPF) and B(MPF), respectively. They give ^{1}H NMR spectra similar to the spectrum of compound **1**, but their solubility in organic solvents makes them more suitable as compounds on which to carry out *cis–trans* isomer studies to determine the actual configuration of the predominant isomer. This paper reports the results of benzene dilution studies[2–4] and shift reagent studies of these two compounds.

Lewin[5] used shift reagents to assign proton resonances in a study of tertiary amides and thioamides. Hatton and Richards[2–4] proposed the theory on which the benzene dilution technique for making resonance assignments is based. This study combined both of these techniques to assign proton resonances to the *cis–trans* isomers of M(MPF) and B(MPF) and, thereby, deduce assignments for **1**.



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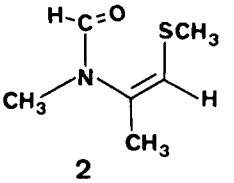

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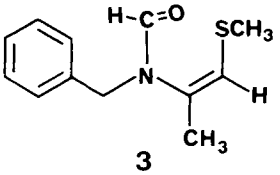

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EXPERIMENTAL

B(MPF) and M(MPF) were synthesized by quaternizing benzyl bromide and methyl iodide with 4-methylthiazole to form the corresponding thiazolium salts.[6,7] The thiazolium salts were reacted with sodium hydroxide and dimethyl sulfate to produce B(MPF) and M(MPF) according to the procedure of DiBella and Hennessy.[8] Purification was accomplished by liquid–liquid partition chromatography using an alumina column and 1:1 benzene–chloroform as the eluent.

An elemental analysis of liquid B(MPF) gave C 64.72, H 6.95, N 6.70%; calculated C 65.15, H 6.79, N 6.33%. M(MPF) (liquid) gave C 50.17, H 7.46, N 9.57%; calculated C 49.66, H 7.59, N 9.66%.

All ^{1}H NMR spectra were obtained on a 60 MHz Varian EM-360A spectrometer equipped with an EM-3640 variable-temperature accessory and an EM-3630 lock/decoupler. All chemical shifts were measured in ppm with respect to tetramethylsilane (TMS) as an internal reference.

Carbon tetrachloride (CCl_4) and chloroform ($CDCl_3$) were used as solvents in the shift reagent studies, which were divided into two parts: (1) constant-temperature studies at 35 °C and (2) variable-temperature studies. In the constant-temperature studies, the substrate (compound) concentration was held constant at 0.1 molar fraction

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while varying ρ, defined as n_R/n_S (moles of shift reagent divided by moles of substrate in solution). In the variable-temperature studies, ρ was held constant while the temperature was varied from 35 to −30 °C.

The shift reagents used were tris(dipivaloylmethanato)europium(III) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)praseodymium(III), abbreviated to Eu(dpm)$_3$ and Pr(fod)$_3$, respectively. These reagents were obtained from Stohler Isotope Chemicals, Waltham, Massachusetts, USA.

RESULTS AND DISCUSSION

In this discussion the *trans* isomer is defined as that structure whose C=C bond is *trans* to the carbonyl oxygen. Thus, structures **1**, **2**, and **3** are written as *cis* isomers.

Benzene dilution studies

Figure 1 shows two of the spectra obtained in the benzene dilution study of B(MPF). Peaks C, D, E and F are due to the propenyl proton, methylene protons, thiomethyl and propenyl methyl, respectively. The doublet arising for each peak is due to *cis–trans* isomerism. In the spectrum for neat B(MPF) the *cis* and *trans* peaks for resonance C overlap and the doublet for resonance E can be only slightly discerned.

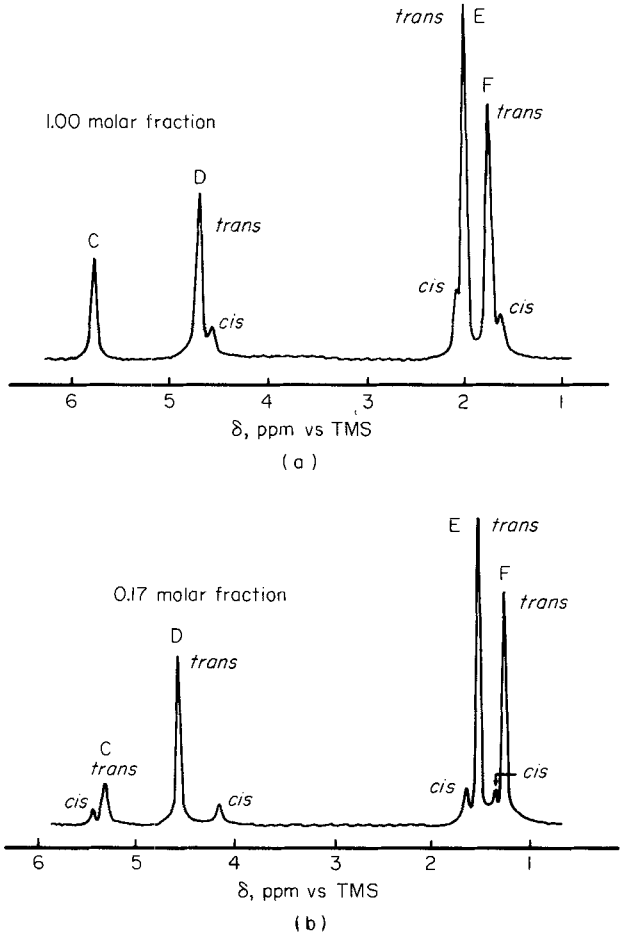

Figure 1. Partial 60 MHz spectra of B(MPF) at 35 °C at the indicated molar fractions in benzene.

In going from neat B(MPF) to 0.17 molar fraction of B(MPF), one observes a continuous upfield shift of each doublet as a whole; one peak of a given doublet, however, moves faster than the other peak. Hatton and Richards[2–4] proposed a specific interaction between the benzene π-electrons and the nitrogen atom (with partial positive formal charge) in which the negatively charged carbonyl oxygen is as far away from the center of the benzene ring as possible. In an *N,N*-disubstituted amide, this would result in a faster upfield shift of that peak (of a given doublet) arising from a given *N*-substituted group in a position *trans* to the carbonyl oxygen as more benzene is added. In keeping with this theory, the faster moving peak of the doublet for a given set of protons is assigned to that isomer which has the given set of protons *trans* to the carbonyl oxygen. The predominant isomer of B(MPF), therefore, is the *trans* isomer, as defined above. Integration shows the *trans–cis* isomer ratio to be approximately 7:1. Reasoning that the bulkier substituent on nitrogen prefers to lie *trans* to the carbonyl oxygen, one concludes from this result, as expected, that the substituted propenyl group is bulkier than the benzyl group.

Table 1 shows chemical shift data from four spectra recorded in the benzene dilution study of B(MPF). This table shows that the *trans* peaks of the thiomethyl and propenyl methyl resonances have the greater $\Delta\delta$, while the *cis* peak of the methylene resonance has the greater $\Delta\delta$. These observations are consistent with the fact that the thiomethyl and propenyl methyl are *trans* to the carbonyl oxygen in the *trans* isomer (as defined above), while the methylene group is *trans* to the carbonyl oxygen in the *cis* isomer.

Figure 2 shows how the doublet of the *N*-methyl of M(MPF) behaves on dilution with benzene. Since the smaller peak has the faster upfield shift, it is assigned to the *cis* isomer, which has the *N*-methyl group *trans* to the carbonyl oxygen. The *trans–cis* isomer ratio of M(MPF), as indicated by integration of the *N*-methyl peak, is approximately 7.5:1.

Benzene dilution studies show the *trans* isomer to be the predominant configuration of both B(MPF) and M(MPF).

Table 1. Chemical shifts of B(MPF) in benzene at 35 °C

B(MPF) concentration (molar fraction)	δ (ppm with respect to TMS)[a]					
	D	D′	E	E′	F	F′
1.00	4.67	4.53	2.00	2.05	1.70	1.60
0.33	4.25	4.05	1.48	1.60	1.23	1.20
0.23	4.10	3.80	1.23	1.37	0.95	1.05
0.17	4.05	3.70	1.10	1.25	0.85	0.97
$\Delta\delta$ (ppm)[b]	0.62	0.83	0.90	0.80	0.85	0.63

[a] D = methylene protons; E = thiomethyl; F = propenyl methyl. D′, E′ and F′ represent the corresponding *cis* isomers.
[b] $\Delta\delta = \delta_{1.00} - \delta_{0.17}$.

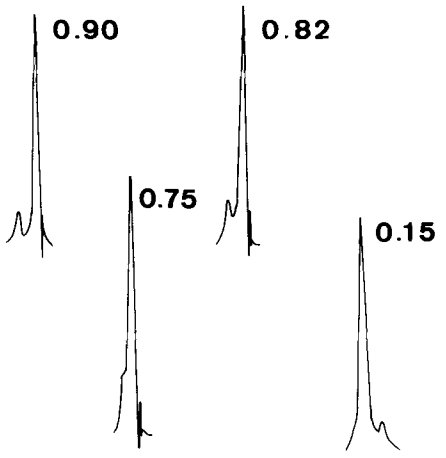

Figure 2. 60 MHz resonance of the *N*-methyl of M(MPF) in benzene at the indicated molar fractions of M(MPF) at 35 °C.

Shift reagent studies at constant temperature

Figure 3 shows the effect of variable amounts of $Pr(fod)_3$ on the ^{1}H NMR spectrum of B(MPF) in $CDCl_3$ at constant temperature and substrate concentration. A, B, C, D, E and F denote resonances of the carbonyl, ring, propenyl, methylene, thiomethyl, and propenyl methyl protons, respectively. The methylene and propenyl methyl clearly show two distinct isomers, where D′ and F′ denote the *cis* isomer. Resonance G is attributed to the *tert*-butyl group of $Pf(fod)_3$. (The *tert*-butyl group of fod shift reagents is known to resonate at 1–2 ppm when the reagent is complexed to a substrate.[9])

At $\rho = 0.0163$, F′ and G coincide, and the carbonyl proton resonance (A) clearly emerges on the upfield side of the ring resonance (B); the ring protons also begin to display an element of nonequivalence. The fact that F′ moves upfield faster than F implies, in agreement with benzene dilution studies, that the *cis* isomer is the non-predominant isomer.

Effects of variable amounts of $Pr(fod)_3$ on the constant-temperature ^{1}H NMR spectra of B(MPF) in CCl_4 and M(MPF) in CCl_4 or $CDCl_3$ parallel the effect depicted in Fig. 3. Spectra of these systems, therefore, are not shown.

Table 2 gives chemical shifts of the protons of B(MPF) in $CDCl_3$ as a function of ρ at constant temperature. Table 3 shows how $Pr(fod)_3$ alters the chemical shifts of M(MPF) in $CDCl_3$. In these tables the lanthanide-induced shift, $\Delta\delta_{LIS}$, for a given set of protons is equal to $\delta_0 - \delta_R$, where δ_0 is the chemical shift at zero concentration of shift reagent and δ_R is the chemical shift at the specified concentration of shift reagent. Tables of chemical shifts of B(MPF) and M(MPF) in CCl_4 as a function of ρ are not shown, since the chemical shift trends and relative magnitudes in CCl_4 were found to be essentially the same as the trends and magnitudes in $CDCl_3$.

The $\Delta\delta_{LIS}$ values in Table 2 clearly show that the magnitudes of the chemical shift changes of the carbonyl and methylene protons are significantly greater than those of the other protons. Data in this table indicate that the general order of decreasing $\Delta\delta_{LIS}$ is carbonyl > methylene > propenyl methyl > propenyl proton = ring > thiomethyl. The results of previous shift reagent studies of various thioformamides and tertiary amides have indicated reagent sulfur coordination as well as reagent oxygen coordination. In B(MPF) and M(MPF), one would expect to see evidence of reagent-sulfur coordination in the form of significant shifting of the thiomethyl protons. In both B(MPF) and M(MPF), however, the thiomethyl protons have the smallest $\Delta\delta_{LIS}$ values. Clearly, there seems to be no coordination at the sulfur atom.

The large upfield shift of the carbonyl proton in both compounds implies coordination at the carbonyl oxygen, as expected. $Pr(fod)_3$ also causes significant upfield shifting of the methylene and *N*-methyl resonances in B(MPF) and M(MPF), respectively. These observations imply that coordination may also be occurring at the nitrogen in these two compounds. Two other possibilities are (1) that the $Pr(fod)_3$ interacts with the methylene (or *N*-methyl) by a contact shift

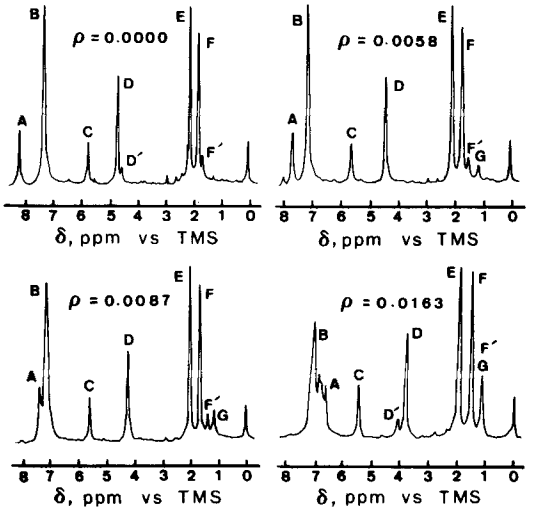

Figure 3. 60 MHz spectra of B(MPF) (0.1 molar fraction) in $CDCl_3$ at the given ρ values, variable amounts of $Pr(fod)_3$ at 35 °C.

Table 2. Chemical shifts of protons of B(MPF) in $CDCl_3$ [0.1 molar fraction of B(MPF) at 35 °C] as a function of the molar ratio of $Pr(fod)_3$ to B(MPF)

$\frac{n_R}{n_S}$	Carbonyl proton	Ring protons	Propenyl proton	Methylene	Thiomethyl	Propenyl methyl
0.0000	8.13[a]	7.25	5.70	4.65 (4.50)[c]	2.08 (2.13)	1.78 (1.63)
	(0.00)[b]	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
0.0012	8.02	7.22	5.67	4.58 (4.48)	2.05 (2.13)	1.75 (1.60)
	(0.11)	(0.03)	(0.03)	(0.07)	(0.03)	(0.03)
0.0023	7.83	7.15	5.62	4.47 (4.43)	2.02 (2.10)	1.70 (1.53)
	(0.30)	(0.10)	(0.08)	(0.18)	(0.06)	(0.08)
0.0058	7.67	7.12	5.60	4.38 (4.38)	2.02 (2.10)	1.68 (1.50)
	(0.46)	(0.13)	(0.10)	(0.27)	(0.06)	(0.10)
0.0070	7.52	7.12	5.58	4.30 (4.30)	2.00 (2.10)	1.65 (1.43)
	(0.61)	(0.13)	(0.12)	(0.35)	(0.08)	(0.13)
0.0087	7.32	7.10	5.57	4.18 (4.30)	2.00 (2.01)	1.63 (1.36)
	(0.81)	(0.15)	(0.13)	(0.47)	(0.08)	(0.15)
0.0116	7.08	7.08	5.52	4.05 (4.20)	1.98 (2.01)	1.58 (1.26)
	(1.05)	(0.17)	(0.18)	(0.60)	(0.10)	(0.20)

[a] Observed chemical shifts in ppm with respect to TMS.
[b] Lanthanide-induced shifts, $\Delta\delta_{LIS}$.
[c] Observed shifts for the *cis* isomer.

Table 3. Chemical shifts of protons of M(MPF) in $CDCl_3$ (0.1 molar fraction of M(MPF) at 35 °C) as a function of the molar ratio of $Pr(fod)_3$ to M(MPF)

$\frac{n_R}{n_S}$	Carbonyl proton	Propenyl proton	*N*-methyl	Thiomethyl	Propenyl methyl
0.0000	7.97[a]	5.78	2.93 (3.01)	2.22 (2.53)	1.90 (2.03)
	(0.00)[b]	(0.00)	(0.00)	(0.00)	(0.00)
0.0033	7.73	5.75	2.82 (2.93)	2.20	1.87
	(0.24)	(0.03)	(0.11)	(0.02)	(0.03)
0.0077	7.53	5.75	2.72 (2.90)	2.20	1.82 (1.70)
	(0.44)	(0.03)	(0.21)	(0.02)	(0.08)
0.0132	7.22 (7.12)[c]	5.67	2.53 (2.80)	2.15	1.77 (1.58)
	(0.75)	(0.11)	(0.40)	(0.07)	(0.13)
0.0221	6.73 (6.60)	5.67 (5.53)	2.28 (2.67)	2.15	1.70 (1.40)
	(1.24)	(0.11)	(0.65)	(0.07)	(0.20)
0.0254	6.42 (6.27)	5.53 (5.37)	2.15 (2.57)	2.07	1.65 (1.30)
	(1.55)	(0.25)	(0.78)	(0.15)	(0.25)
0.0309	6.05 (5.87)	5.50 (5.27)	1.97 (2.45)	2.03	1.58 (1.20)
	(1.92)	(0.28)	(0.96)	(0.19)	(0.32)
0.0342	5.80 (5.62)	5.45 (5.20)	1.82 (2.37)	2.03	1.53 (1.07)
	(2.17)	(0.33)	(1.11)	(0.19)	(0.37)

[a] Observed chemical shifts in ppm with respect to TMS.
[b] Lanthanide-induced shifts, $\Delta\delta_{LIS}$.
[c] Observed shifts for the *cis* isomer.

through the O=C and C—N bonds of the substrate or (2) that the geometry of the substrate–reagent complex is such that the Pr atom is close enough to the CH_2 group to cause large pseudocontact shifting.

Figure 4 shows plots of observed δ values (which are the same as δ_R or δ_0 previously defined) versus ρ for the carbonyl and methylene protons of B(MPF) in CCl_4 and $CDCl_3$ at 35 °C. Over the range of ρ values considered, these plots follow the linear relationship $\delta_R = S_0\rho + \delta_0$, where S_0 is the shift gradient, surprisingly well. In the CCl_4 plot (Fig. 4(a)), the extrapolated δ_0 differs from the observed δ_0. The extrapolated and observed δ_0 values in $CDCl_3$ are the same within experimental error (Fig. 4(b)). In both CCl_4 and $CDCl_3$, the carbonyl shift gradient is approximately twice as large as the methylene shift gradient.

Figure 5 shows plots of observed δ values versus ρ for the carbonyl and *N*-methyl protons of M(MPF) in CCl_4 and $CDCl_3$ at 35 °C. These plots parallel those in Fig. 4. Again, the plots are linear; the carbonyl shift gradient is approximately twice as large as the *N*-methyl shift gradient; the extrapolated and observed

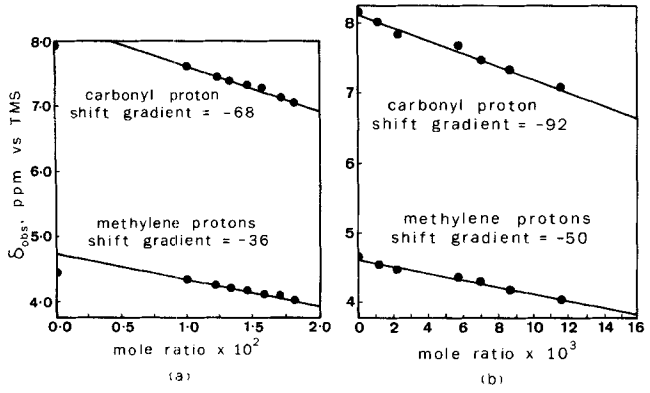

Figure 4. Chemical shifts of carbonyl and methylene protons of B(MPF), 0.1 molar fraction, at 35 °C: (a) in CCl_4; (b) in $CDCl_3$.

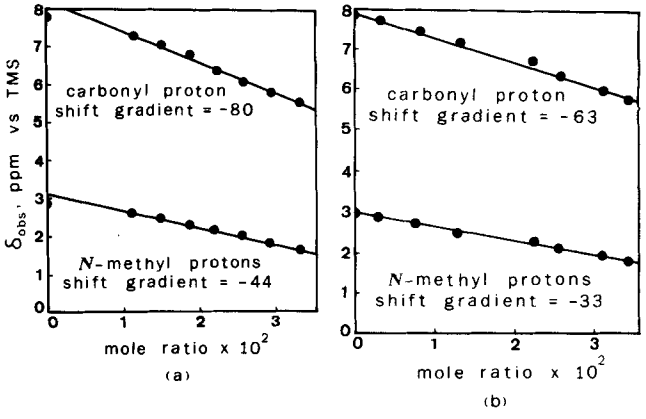

Figure 5. Chemical shifts of carbonyl and methyl protons of M(MPF), 0.1 molar fraction, at 35 °C: (a) in CCl_4; (b) in $CDCl_3$.

δ_0 values in $CDCl_3$ agree in value, while those in CCl_4 do not agree. One noticeable difference is that the shift gradients for the CCl_4 plots (Fig. 5(a)) are greater than the corresponding gradients for the $CDCl_3$ plots (Fig. 5(b)). In Fig. 4 the opposite is true.

Variable-temperature shift reagent studies

Ahmad *et al.*[10] reported that varying temperature at constant ρ produces essentially the same effect as varying ρ at constant temperature. As a check on this report, we ran variable-temperature ^1H NMR spectra of B(MPF)–$Pr(fod)_3$–CCl_4, B(MPF)–$Pr(fod)_3$–$CDCl_3$, B(MPF)–$Eu(dpm)_3$–$CDCl_3$ and the corresponding M(MPF) systems.

For each system studied, spectra were obtained at constant ρ at temperatures of 35 to −30 °C. Variable-temperature spectra of the $Pr(fod)_3$ systems substantiated the report of Ahmad *et al.*; with $Pr(fod)_3$ as the

shift reagent, varying temperature at constant ρ produced the same spectral effect as varying ρ at constant temperature. Varying temperature at constant ρ did not produce significant chemical shifts in the $Eu(dpm)_3$ systems.

CONCLUSION

Shift reagent and benzene dilution studies conducted on B(MPF) and M(MPF) lead to the same assignments of *cis–trans* isomer resonances in the ^{1}H NMR spectra of these two compounds. Results of both studies indicate the *trans* isomer, as previously defined, to be the predominant configuration of each compound. Integration of the ^{1}H NMR spectra shows the *trans–cis* isomer ratios to be 7:1 and 7.5:1 for B(MPF) and M(MPF), respectively, in benzene. These results are very close to the 85:15 (approximately 6:1) conformational ratio of the water-soluble complex amide **1** produced from thiamine, and imply that the predominant isomer of compound **1** is the same as that of B(MPF) and M(MPF).

Shift reagent studies of both M(MPF) and B(MPF) lead to the conclusion that the shift reagent bonds to the oxygen of the substrate, as expected. Large $\Delta\delta_{LIS}$ values for the methylene in B(MPF) and the *N*-methyl in M(MPF) suggest that the shift reagent may also be bonding to the nitrogen of the substrate.

In both B(MPF) and M(MPF), $Pr(fod)_3$ was found to produce significant upfield shifts at variable ρ and constant temperature or variable temperature and constant ρ. $Eu(dpm)_3$ produced significant downfield shifts at constant temperature and variable ρ but did not produce significant shifts at variable temperature and constant ρ.

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