RELATION OF SHIFT MAGNITUDE OF ALKYL SUBSTITUENTS TO AROMATIC SUBSTITUTION PATTERNS

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ABSTRACT OF THESIS

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This study was conducted to correlate shift magnitude with structural features of a molecule. The shift reagent Eu $(fod)_3$, tris (1, 1, 1, 2, 2, 3, 3-heptafluoro-7, 7-dimethyl-4, 6-octanedione) Europium (III), was used in the investigation. In the presence of the Eu $(fod)_3$ shift reagent, the induced shift (Hz) of a chosen substrate was linearly related to the mole ratio of shift reagent to substrate. A deviation from linearity was noted at high [shift reagent]/[substrate] values. Δ values, equal to the induced shift divided by the mole ratio of shift reagent to substrate, were calculated for various substrates using [Eu $(fod)_3$]/[substrate] values no larger than 0.40.

A preliminary investigation was conducted using substituted methylindoles. The compounds 5-bromo-2, 3-dimethylindole, 2, 3-dimethyl-5-nitroindole, and 5-amino-2, 3-dimethylindole were prepared by Fisher ring

closure. A comparison of Δ values for various substituted methylindoles indicated the upfield methyl peak in 2, 3-dimethylindoles was due to 3-substitution and the downfield methyl peak to 2-substitution.

Substituted anilines were chosen as substrates for the primary research. Three basic conclusions are apparent from this research. The induced shift will decrease with increasing distance between the paramagnetic center and the affected methyl substituent. A pattern became apparent in which the 2-substituted anilines had the largest Δ values, followed by the 3-substituted anilines, and the 4-substituted anilines had the smallest Δ values. The strongest Lewis bases produce the largest induced shifts of all methyl substituents. The basicity of the aromatic anilines were affected by substituents on the ring. An electron-releasing substituent such as $-OCH_3$ increased the basicity of aniline, and an electron-withdrawing substituent such as -Cl or -Br decreased the basicity. A shift rate decrease for N-substituted and 2-substituted anilines is due to steric hinderance of the metal complex attack. The peaks of the N-substituted anilines were broadened appreciably by addition of Eu $(fod)_3$, while those of the other substituted anilines remained well resolved.

The relation of shift magnitude to structural features of substituted anilines is analytically valuable if one has a basic idea about the ring substituted atoms or groups present, and how their structural position affects shift magnitude.

Accepted by Verne A. Simon, Chairman

Charles A. Payne

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(Date)

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INTRODUCTION

The purpose of the investigation reported herein was to correlate shift magnitude with structural features of a molecule.

It has been known since the early studies of nuclear magnetic resonance (n.m.r.) spectroscopy that proton resonance peaks will be spread across a broader range of magnetic field strength by addition of a paramagnetic species to the solution being studied. The general expectation is that the shift produced will decrease with increasing distance between the paramagnetic center and the affected proton (1). Most of work thus far has centered around the question of which metal will permit the observation of high-resolution n.m.r. spectra of its complexes without objectionable peak broadening.

Considerable interest has been shown in lanthanide shift reagents since Hinckley (2) has shown that the paramagnetic complex tris (2, 2, 6, 6-tetramethyl-3, 5-heptanedione) Europium (III) containing two molecules of pyridine, Eu $(dpm)_3(py)_2$, can be used to produce shifts of proton resonances in the ^1H n.m.r. spectrum of cholesterol. The metal chelate, Eu $(dpm)_3$, can be prepared by the method of Eisentraut and Sievers (3), and the adduct, Eu $(dpm)_3(py)_2$, obtained by recrystallization from pyridine. Narrow ^1H n.m.r. lines may be expected for solutions containing complexes of all the rare earths with the exception of gadolinium. The very short electron relaxation times of these metal ions in solution at normal temperatures can result in narrow ^{1}H n.m.r. absorptions (4). This is in contrast to the frequently extensive broadening caused by paramagnetic transition ions of the first and second series.

Sanders and Williams (5) reasoned that the pyridine-free adduct, Eu $(dpm)_3$, would be a superior shift reagent in coordinating more effectively with organic Lewis bases. The new Eu $(dpm)_3$ shift reagent increased proton shifts observed in cholesterol (2) by a factor of four at comparable concentrations. Most important, it was illustrated that Eu $(dpm)_3$ can produce dramatic shifts in ^{1}H n.m.r. spectra. Eu $(dpm)_3$ is also abbreviated Eu $(thd)_3$.

A quantitative study of the action of trivalent lanthanide chelate complexes of 2, 2, 6, 6-tetramethyl-3, 5-heptanedione, Ln $(dpm)_3$, Ln=Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, and Yb, has been reported (6). Upfield substrate ligand resonance shifts are obtained for the systems involving Pr, Nd, Sm, Tb, Dy, and Ho, while downfield shifts are observed for Eu, Er, Tm, and Yb. The later lanthanides, though better shifters, are also more efficient dipolar broadeners. The shifts caused by lanthanide shift reagents are exclusively or nearly exclusively dipolar in origin, but the mechanism of action of lanthanide shift reagents has not been definitely established.

Very recently, Rondeau and Sievers (7) have discovered new, vastly superior shift reagents, which are expected to have a great impact on the entire field of materials characterization and analysis. The new shift reagents, Eu $(fod)_3$ and Pr $(fod)_3$, tris (1, 1, 1, 2, 2, 3, 3-heptafluoro-7, 7-dimethyl-4, 6-octanedione) Europium (III) and Praseodymium (III), have a structural formula as follows:

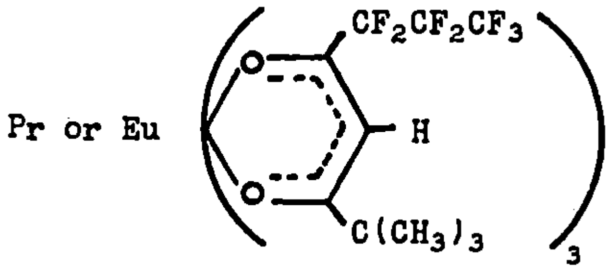

Figure 1

Europium and praseodumium chelates are superior to the dpm adducts with respect to both Lewis acidity and soluability. Substitution of fluorocarbon moieties in B-diketonate ligands increases the solubility of the metal complex, and the electron withdrawing fluorines increase the residual acidity of the cation, making it a better coordination site for weak donors. The fod chelates can be prepared by the method of Springer, Meek, and Sievers (8). The fod chelates of Eu (III) and Pr (III) are superior shift reagents and are highly desirable for ^1H n.m.r. research.

DISCUSSION

A search of Sadtler N.M.R. Spectra (1971) revealed that in substituted 2, 3-dimethylindoles there was considerable doubt as to which methyl peak appeared upfield. An investigation was undertaken using Eu $(fod)_3$ shift reagent.

It has been observed (9) that in the presence of a shift reagent the induced shift of a substrate is linearly related to the mole ratio of shift reagent to substrate. The shifts are concentration dependent which indicates a rapid metal complex-substrate exchange. This rapid labile equilibrium (6) may be represented as $S^* + Eu\,(fod)_3S \rightleftarrows Eu\,(fod)_3S^* + S$ where S represents a substrate molecule and the asterisk denotes the exchange of identical ligand molecules. A deviation from linearity (7) has been noted at high [shift reagent]/[substrate] values. This deviation from linearity indicates that the spectrum is now essentially that of a coordinated ligand rather than that of the average of the free ligand and complexed ligand.

The compounds 2-methylindole, 3-methylindole, and 2, 3-dimethylindole were obtained commercially while 5-bromo-2, 3-dimethylindole, 2, 3-dimethyl-5-nitroindole, and 5-amino-2, 3-dimethylindole were prepared by Fisher ring closure. All attempts to prepare 5-iodo-2, 3-dimethylindole were unsuccessful.

^{1}H n.m.r. spectra were obtained using deuteriochloroform solutions of the substituted indoles.

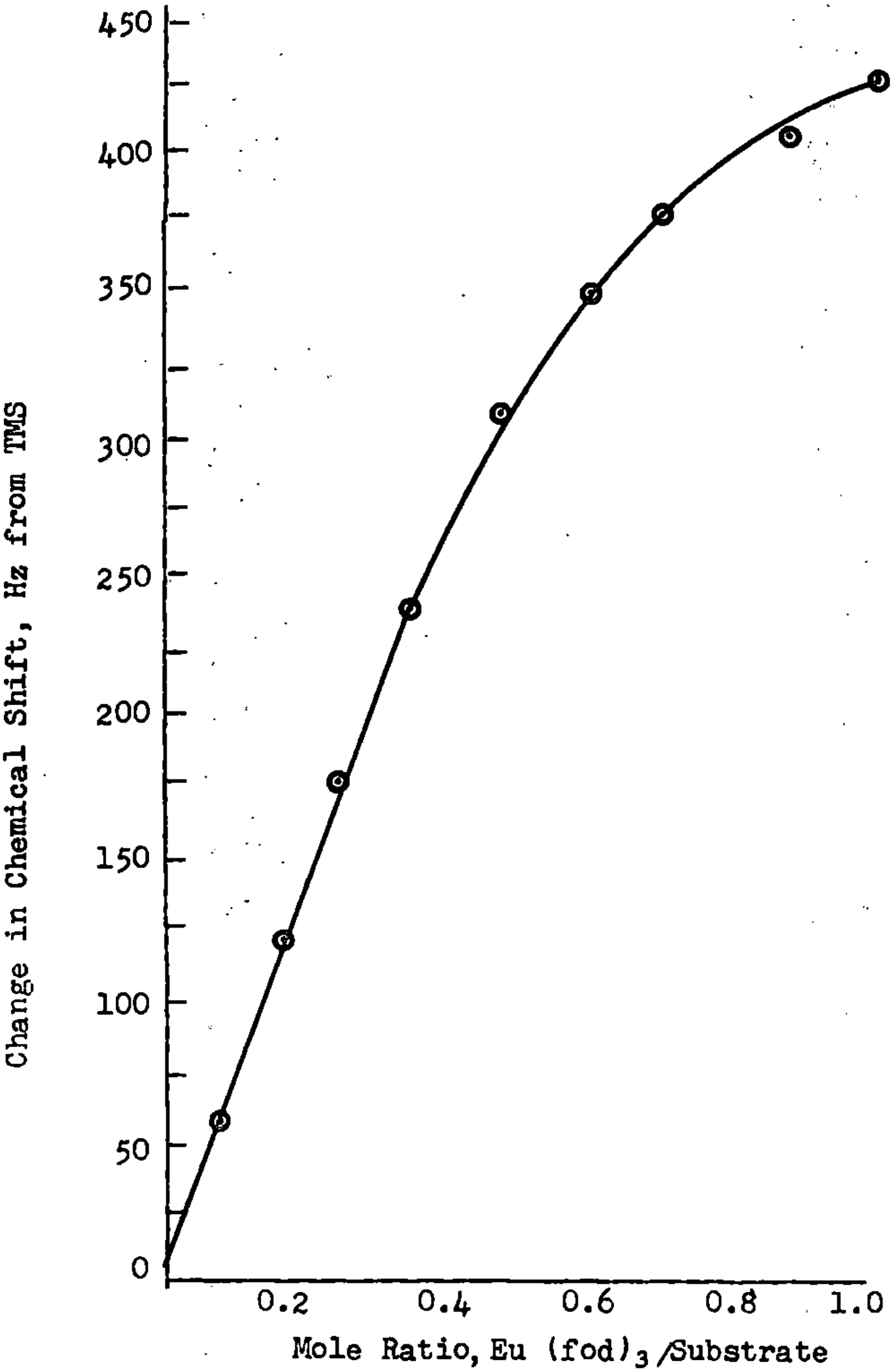

Figure 2

Induced Shifts of Methyl Resonances of 2-Methylaniline as a Function of Added Eu (fod)$_3$.

A linear plot of the induced shift versus the mole ratio of shift reagent to substrate for 2-methylaniline is shown in figure 2. This graph is typical of those obtained for various substrates throughout this research. Induced shifts are in hertz from TMS, the internal standard. The Δ value equals the induced shift divided by the mole ratio of shift reagent to substrate, [shift reagent]/[substrate]. A deviation from linearity was noted at mole ratios greater than 0.40, and Δ values throughout this research were calculated using [Eu $(fod)_3$]/[substrate] values no larger than 0.40. The various induced shifts for different mole ratios and the Δ values are given in Table 1.

The compounds 2-methylindole and 3-methylindole were chosen as standard compounds from which to obtain the Δ values for the 2-methyl and 3-methyl positions. The Δ values from Table 1 show that for 2-methylindole no shift occurred while for 3-methylindole a shift was detected. The Δ values for 2, 3-dimethylindole and 5-bromo-2, 3-dimethylindole fit the pattern of the previous experimental data. The upfield methyl peak of 2, 3-dimethylindole had a Δ value of 6.50, and the corresponding peak for 5-bromo-2, 3-dimethylindole was 1.30. No shift was obtained for the downfield methyl peak in either case. Induced shifts were observed for the downfield methyl peaks of 2, 3-dimethyl-5-nitroindole and 5-amino-2, 3-dimethylindole. The upfield methyl peak Δ value for both compounds was larger than the Δ value for the downfield methyl peak and were also

Table 1. Shift Data for Substituted Indoles

Substrate	$\frac{[Eu(fod)_3]}{[Substrate]}$	Induced Shift (Hz)		Δ (Hz)	
2-Methylindole	0.24	0		0	
	0.47	0			
	0.70	0			
	0.98	0			
3-Methylindole	0.23	0.75		3.30	
	0.43	1.65			
	0.68	2.10			
	0.89	3.45			
2, 3-Dimethylindole	0.30	1.95[a]	0[b]	6.50[c]	0[d]
	0.46	2.40	0		
	0.79	3.00	0		
	0.95	3.75	0		
5-Bromo-2, 3-Dimethylindole	0.24	0.30[a]	0[b]	1.30[c]	0[d]
	0.45	0.60	0		
	0.59	0.90	0		
	0.89	1.20	0		
5-Nitro-2, 3-Dimethylindole	0.17	0.90[a]	0.60[b]	5.30[c]	3.50[d]
	0.60	2.70	1.65		
	0.77	3.00	1.65		
	1.41	3.90	1.80		
5-Amino-2, 3-Dimethylindole	0.20	0.90[a]	0.22[b]	5.60[c]	1.80[d]
	0.41	1.80	0.45		
	0.84	3.00	1.35		
	1.09	3.45	1.80		

[a] Induced shift for upfield methyl peak. [b] Induced shift for downfield methyl peak. [c] Δ value for upfield methyl peak. [d] Δ value for downfield methyl peak.

larger than the Δ value obtained for 3-methylindole. The shift of the downfield methyl peak in 2, 3-dimethyl-5nitroindole and 5-amino-2, 3-dimethylindole may have been caused by

Table 2. Shift Data for Methyl Substituted Anilines

Substrate	$\frac{[\mathrm{Eu\ (fod)_3}]}{[\mathrm{Substrate}]}$	Induced Shift (Hz)	Δ (Hz)
N-Methylaniline	0.39	165.6	425
	0.59	216.3	
	0.74	264.9	
	0.96	303.6	
2-Methylaniline	0.18	105.15	584
	0.36	189.15	
	0.73	291.45	
	0.91	319.95	
3-Methylaniline	0.26	37.8	145
	0.40	53.7	
	0.67	74.1	
	1.00	84.45	
4-Methylaniline	0.29	12.3	42
	0.55	20.4	
	0.75	24.9	
	1.03	27.0	

The trend in the halogen substituted anilines generally followed that of the methyl substituted anilines. The 2-substituted position shifted most, followed by the 3-position, and the 4-position shifted least. This agreed with the general expectation that the shift produced will decrease with increasing distance between the paramagnetic center and the affected proton (1).

The availability of the unshared pair of electrons on the nitrogen atom appeared to have an effect on shift

Table 3. Shift Data for Halogen Substituted Methylanilines

Substrate	$\frac{[Eu(fod)_3]}{[Substrate]}$	Induced Shift (Hz)	Δ (Hz)
2-Chloro-6-Methylaniline	0.34	47.55	140
	0.42	56.25	
	0.62	71.88	
	0.89	90.45	
3-Chloro-2-Methylaniline	0.22	115.20	524
	0.35	165.45	
	0.56	220.05	
	0.85	267.90	
5-Chloro-2-Methylaniline	0.24	99.75	416
	0.46	162.45	
	0.81	222.75	
	0.90	236.55	
4-Bromo-2-Methylaniline	0.32	137.55	430
	0.53	202.05	
	0.85	269.55	
	0.92	311.85	
4-Chloro-2-Methylaniline	0.29	134.55	464
	0.60	221.55	
	0.75	248.85	
	1.01	280.35	
4-Bromo-3-Methylaniline	0.31	35.7	115
	0.44	48.0	
	0.70	64.8	
	0.90	70.8	
2-Chloro-4-Methylaniline	0.24	7.05	29
	0.37	10.35	
	0.63	15.15	
	0.90	19.05	

Table 3. (continued)

Substrate	[Eu (fod)$_3$] [Substrate]	Induced Shift (Hz)	Δ (Hz)
2-Bromo-4-Methylaniline	0.22	5.4	25
	0.34	7.8	
	0.61	11.25	
	0.86	13.65	
3-Chloro-4-Methylaniline	0.20	9.00	35
	0.44	19.20	
	0.66	24.45	
	0.89	28.05	

magnitude. The low basicity of aromatic amines is due to the fact that the amine is stabilized by resonance. The pair of electrons on the nitrogen is partly shared with the ring and less available for sharing with a Lewis acid. The basicity of an aromatic amine is affected by substituents on the ring. An electron-releasing substituent such as $-CH_3$ increases the basicity of aniline, and an electron-withdrawing substituent such as -Cl or -Br decreases the

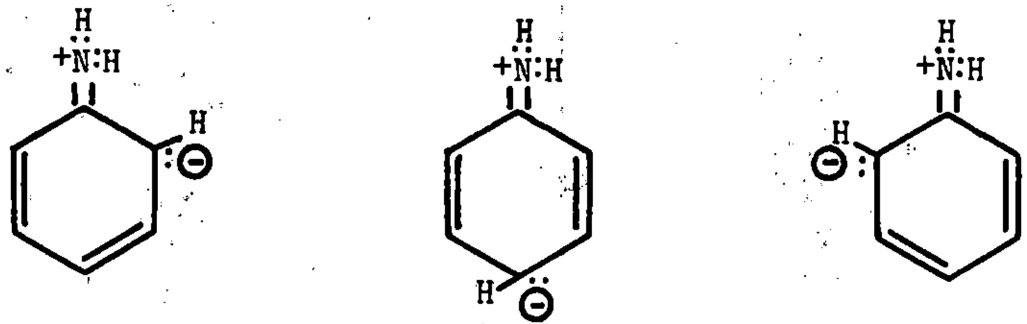

Figure 3

basicity. An electron-releasing group pushes electrons toward nitrogen and makes the pair more available for sharing with a Lewis acid, whereas an electron-withdrawing group helps pull electrons away from nitrogen and makes the pair less available for sharing. A list of pKa values for various substituted anilines are given in Table 4.

Table 4. pKa Values of Substituted Anilines in Aqueous Solution

Compound	pKa
N-Methylaniline	4.85
2-Methylaniline	4.44
3-Methylaniline	4.73
4-Methylaniline	5.08
2-Chloroaniline	2.65
3-Chloroaniline	3.46
4-Chloroaniline	4.15
2-Bromoaniline	2.53
4-Bromoaniline	3.86
N-Ethylaniline	5.12
2-Methoxyaniline	4.52
3-Methoxyaniline	4.23
4-Methoxyaniline	5.34
Aniline	4.63

Generally, the halogen substituted methylanilines had lower Δ values at equivalent substituted positions than did the methyl substituted anilines. The halogen substituted anilines have smaller pKa values than does aniline and are weaker Lewis bases. The larger induced shifts for stronger Lewis bases indicated that the rapid metal complex-substrate equilibrium was shifted in favor of the metal complex. The compound 4-chloroaniline has a larger pKa value than 4-bromoaniline, and 4-chloro-2-methylaniline had a larger Δ value than 4-bromo-2-methylaniline. Presumably in the case of chlorine, this is due to the greater importance of resonance forms in which the halogen has a double bond. Electrons are donated to the ring in these forms. Also, 2-chloroaniline has a larger pKa value than 2-bromoaniline, and 2-chloro-4-methylaniline has a larger Δ value than 2-bromo-4-methylaniline.

The shift magnitude of the halogen substituted methylanilines was also affected by the proximity of the halogen of the methyl group. The Δ value was larger the closer the halogen to the methyl substituent. The substrate 3-chloro-2-methylaniline had a larger Δ value than 5-chloro-2-methylaniline, even though, the chlorine is meta to the amino group in both compounds.

A discrepancy in the shift pattern appeared to occur with 2-chloro-6-methylaniline. The shift rate decrease was due to the ortho effect (10), which seemed primarily steric. Electron-releasing substituents weaken basicity when they are ortho to the amino group, and electron-withdrawing substituents do so to a much greater extent from the ortho position than from the meta or para position. The chlorine and methyl group flanking the amino group in 2-chloro-6-methylaniline sterically hindered the attack of the Eu $(fod)_3$ and lowered the basicity of the aniline. Bromine is larger than chlorine and should provide more steric hindrance. The substrate 2-bromo-4-methylaniline has a smaller Δ value than 2-chloro-4-methylaniline.

The spectra of other substituted anilines, including the anisidines and ethylanilines, were recorded. The various shifts for different [shift reagent]/[substrate] ratios and the Δ values are given in Table 5. The induced shifts for the ethylanilines were measured from tetramethylsilane to the highest peak in the methylene quartet. The peaks of N-ethylaniline were broadened appreciably.

The anisidines were chosen with the hope that an electron-releasing substituent such as $-OCH_3$ would increase the basicity of aniline thus producing a larger shift. The compound 4-methoxyaniline has a larger pKa value than 4-methylaniline, and 3-methoxyaniline has a smaller pKa value than 3-methylaniline. One would expect an increase in the Δ value of the 4-methoxyaniline compared to 4-methylaniline and a decrease in the Δ value of 3-methoxyaniline compared to 3-methylaniline. Experimental results showed

Table 5. Shift Data for Selected Substituted Anilines

Substrate	$\frac{[\mathrm{Eu\ (fod)_3}]}{[\mathrm{Substrate}]}$	Induced Shift (Hz)	Δ (Hz)
2-Methoxyaniline	0.38	204.45	538
	0.58	308.70	
	0.66	346.20	
	0.87	447.30	
3-Methoxyaniline	0.15	15.90	106
	0.39	35.40	
	0.59	46.80	
	0.88	58.35	
4-Methoxyaniline	0.24	22.05	92
	0.44	37.95	
	0.90	62.10	
	0.94	63.60	
N-Ethylaniline	0.22	88.50	402
	0.49	150.00	
	0.79	202.65	
	0.94	226.05	
2-Ethylaniline	0.32	168.60	527
	0.52	249.00	
	0.69	297.30	
	0.91	335.40	
4-Ethylaniline	0.16	10.65	66
	0.35	19.80	
	0.58	30.90	
	0.78	36.30	

an increase in the Δ value of 4-methyoxyaniline compared to 4-methylaniline and a decrease in the Δ value of 3-methoxyaniline compared to 3-methylaniline.

The substrate 4-ethylaniline had a larger Δ value than 4-methylaniline. By the inductive effect alone, the order of electron release for simple alkyl groups connected to an unsaturated system is ethyl greater than methyl. The ethyl group showes a larger shift due to increased aniline basicity. The Δ values of N-ethylaniline and 2-ethylaniline were in the approximate range of the Δ values for N-methylaniline and 2-methylaniline respectively but, in contrast, were smaller. The larger ethyl group provided more steric hindrance to the Eu $(fod)_3$ than the smaller methyl substituent.

The substrates 2, 4, 6-trimethylaniline and 2, 4, 5-trimethylaniline were selected as test compounds to determine if structural assignments of the methyl peaks could be made on the basis of the calculated Δ values. The various induced shifts and Δ values are reported in Table 6.

The two Δ values for 2, 4, 6-trimethylaniline appeared to correlate with previous experimental Δ values. The Δ value of methyl peak 1 (Table 6) corresponded to experimental Δ values of the 4-position, and the methyl peak 2 Δ value corresponded to those of the 2- or 6-position. The Δ value for the 2- and 6-methyl groups was lower than the Δ value for 2-methylaniline. The two methyl groups flanking the amino group sterically hindered the attack of the Eu $(fod)_3$ and lowered the basicity of the aniline.

The Δ values for 2, 4, 5-trimethylaniline also correlated with previous experimental Δ values. The Δ value of methyl peak 1 (Table 6) corresponded to experimental Δ values of the 4-position, methyl peak 2 to the 5-position,

Table 6. Shift Data for Trimethyl Substituted Anilines

Substrate	Peak	$\frac{[\mathrm{Eu\ (fod)_3}]}{[\mathrm{Substrate}]}$	Induced Shift (Hz)	Δ (Hz)
2, 4, 6-Trimethylaniline	1[a]	0.20	6.15	31
		0.48	13.05	
		0.71	16.95	
		1.02	20.25	
	2	0.20	64.95	325
		0.48	143.25	
		0.71	188.70	
		1.02	224.55	
2, 4, 5-Trimethylaniline	1[a]	0.24	8.40	35
		0.49	16.20	
		0.71	21.15	
		0.96	24.75	
	2	0.24	23.40	98
		0.49	42.75	
		0.71	52.95	
		0.96	59.25	
	3	0.24	120.15	501
		0.49	226.20	
		0.71	282.15	
		0.96	318.00	

[a] Most upfield peak after Eu $(fod)_3$ addition.

and methyl peak 3 to the 2-position. The steric hindrance observed in 2, 4, 6-trimethylaniline was not as great in 2, 4, 5-trimethylaniline, and the Δ values approached those of the toluidines.

EXPERIMENTAL

^1H n.m.r. spectra were recorded on a JEOL C-60HL high resolution instrument operating near 25°. Deuteriochloroform was the solvent and lines were measured relative to tetramethylsilane, TMS, as an internal standard. All substrates used, except certain indoles, were obtained commercially and not purified further. Eu $(fod)_3$ was purchased from Norell Chemical Co., Inc., and stored in a dessicator. All weights were taken on a Sartorius analytical balance.

Approximately 0.02 g. of substrate was dissolved in excess deuteriochloroform and the initial spectrum taken. The cap of the thin-walled n.m.r. tube was removed to allow escape of vaporized deuteriochloroform. The cap was replaced and a new weight obtained. A predetermined amount of Eu $(fod)_3$ was added, the weight obtained, and a spectrum taken of the complex. This process was repeated three additional times. The Eu $(fod)_3$ was returned to the dessicator after each addition. The induced contact shifts of methyl resonances from tetramethylsilane were obtained by inspection, and the mole ratios, [Eu $(fod)_3$]/[substrate], were calculated. A plot of mole ratio versus induced chemical shift in Hz was linear, and the slope (Δ value) of the line was calculated. Well-resolved spectra were obtained for all adducts studied with the exception of N-substituted anilines.

Preparation of 5-Bromo-2, 3-Dimethylindole

p-Bromoaniline (11)

A solution of bromine (16g.; 0.1 mole) in dioxane (160ml.) was added dropwise with good agitation at 5° to a solution of predistilled aniline (9.3g.; 0.1 mole) in dioxane (30ml.) and potassium hydroxide (5.6g.; 0.1mole) in water (20ml.). The addition was made over two hours. The organic layer was washed with potassium hydroxide (15 ml.; 40%) and distilled under reduced pressure to remove the solvent. The residue was collected and crystallized from aqueous ethanol to give 9.46 g. (55%) of white needles with a melting range of 65-66°.

p-Bromophenylhydrazine Hydrochloride (12)

In a 3-liter, 3-necked flask equipped with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel, were placed p-bromoaniline (17.2 g.; 0.1 mole), hydrochloric acid (750 ml.; sp. g. 1.19; 36%) and water (250 ml.). The mixture was heated to dissolve the p-bromoaniline. The reaction flask was placed in a dry ice-acetone bath and cooled rapidly to -25°. The temperature was maintained at -20 to -25°

while a solution of sodium nitrite (9 g.; 0.13 mole) in water (200 ml.) was added through a dropping funnel, the tip of which extended nearly to the bottom of the flask. The diazotization required about ten minutes after which a positive starch-iodide test was observed. The cold diazonium solution was allowed to warm to 0^0 and poured very slowly, with vigorous stirring into a cold (0^0) solution of stannous chloride (38 g.; 0.2 mole) in hydrochloric acid (500 ml.; sp. g. 1.19; 36%). The resulting mixture was stirred vigorously for one hour and stored at 0^0 overnight. The white solid was collected on a fritted glass filter, washed with saturated salt solution (200 ml.) and with 2:1 petroleum ether-ether (150 ml.). The solid was crystallized from aqueous ethanol, with charcoal treatment, to yield white needles. The yield of white needles was 4.05 g. (18%); the decomposition range was $123.5\text{-}125^0$.

2-Butanone-p-Bromophenylhydrazone (13)

p-Bromophenylhydrazine hydrochloride (6 g.; .027 mole), sodium acetate (4.1 g.; 0.05 mole), glacial acetic acid (20 ml.; sp. g. 1.06; 99%), and water (500 ml.) were placed in a 1-liter, 3-necked flask equipped with a mechanical stirrer and thermometer. The solution was heated to 85^0 and the temperature was allowed to drop below 80^0, the boiling point of 2-butanone. 2-Butanone (4 ml.) was added with vigorous stirring. The mixture was placed in a separatory funnel and sodium chloride was added to speed up separation of the layers. The organic layer was removed and used in the next step without further purification.

5-Bromo-2, 3-Dimethylindole

Method a. (14) p-Bromophenylhydrazine hydrochloride (8.94 g.; 0.04 mole), absolute ethanol (100 ml.), and 2-butanone (7 ml.) were placed in a 300 ml., 3-necked flask equipped with a mechanical stirrer, a reflux-condenser, a nitrogen inlet, and a dropping funnel. Hydrochloric acid (20 ml.; sp. g. 1.19; 36%) was added dropwise, and the mixture refluxed for three hours during which time a stream of dry nitrogen was passed through the apparatus. The reaction was poured slowly, with stirring, onto a mixture of crushed ice (100 g.) and water (200 ml.). The solid that precipitated was collected and recrystallized from aqueous ethanol, with charcoal treatment, to yield 3.42 g. (38%) of white crystals. Sublimation of the solid yielded white crystals whose melting range was 141-142°. The indole was quite readily oxidized by air and was therefore stored under nitrogen.

Method b. (15) In a 250 ml., 3-necked flask equipped with a reflux-condenser, a nitrogen inlet, and a thermometer were placed 2-butanone-p-bromophenylhydrazone (2.7 g.; 0.01 mole), 1:1 M aqueous ethanol (71 ml.), and sulfuric acid (22 ml.; sp. g. 1.84; 96%). A stream of dry nitrogen was forced through the system and maintained throughout the reaction. The mixture was heated under reflux for thirty minutes at 100-115°. The hot solution was then poured slowly with stirring into an ice-water mixture (200 ml.). After the mixture had cooled to room temperature, it was extracted twice with 100 ml. portions of chloroform and the combined chloroform extracts dried over sodium sulfate. The resulting solution was boiled to expel chloroform and concentrate the solution. An aqueous suspension of the product was filtered and recrystallization, with charcoal from 1:1 petroleum ether-ether yielded .1 g. (4%) of the white indole. Sublimation of the compound yielded a white solid with a melting range of 141-142°.

Attempted Synthesis of 5-Iodo-2, 3-Dimethylindole

p-Iodoaniline (16)

Predistilled aniline (11 g.; 0.12 mole), sodium carbonate (15 g.; 0.14 mole), and water (100 ml.) were placed in a 250 ml. beaker equipped with a magnetic stirrer. A small amount of ice was added to keep the temperature constant at 15° throughout the reaction. Powdered iodine (25.4 g.; 0.1 mole) was added, with stirring, in small portions over a thirty minute period. Stirring was continued an additional twenty minutes, at which time crude p-iodoaniline was separated by filtration. Petroleum ether (65-110°) was added to the residue and the resulting mixture was heated to obtain a solution which was then treated with charcoal and filtered. The yield of light tan solid was 6.93 g. (26%) of pure product which melted at 63-64°.

p-Iodophenylhydrazine Hydrochloride (12)

In a 3-liter, 3-necked flask equipped with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel, were placed p-iodoaniline (21.9 g.; 0.1 mole), hydrochloric acid (750 ml.; sp. g. 1.19; 36%), and water (250 ml.). The mixture was heated to dissolve the p-iodoaniline. The reaction flask was placed in a dry ice-acetone bath and cooled rapidly to -25°. The temperature was maintained at -20 to -25° while a solution of sodium nitrite (9 g.; 0.13 mole) in water (200 ml.) was added through a dropping dunnel, the tip of which extended nearly to the bottom of the flask. The diazotization required about ten minutes after which a positive starch-iodide test was observed. The cold diazonium solution was allowed to warm to 0° and poured very slowly, with vigorous stirring, into a cold (0°) solution of stannous chloride (38 g.; 0.2 mole) in hydrochloric acid (500 ml.; sp. g. 1.19; 36%). The resulting mixture was stirred vigorously for one hour and stored at 0° overnight. The tan solid was collected on a fritted glass filter, washed with saturated salt solution (200 ml.) and with 2:1 petroleum ether-ether (150 ml.). The filtered solid was added to a solution of sodium hydroxide

(20 g.; 0.5 mole) in water (500 ml.) and the hydrazine extracted three times with 100 ml. portions of ether. The combined ether extracts were washed with water (100 ml.), dried over sodium sulfate, decolorized with charcoal, and saturated with dry hydrogen chloride gas at ice-bath temperature. The crude product was dissolved in hot 1:1 methanol-chloroform and ether was added to the cloud point. The light tan solid that separated on cooling was collected and more ether was added to the mother liquor to obtain an additional crop of material. The precipitate that formed was collected and air dried. The yield of tan solid was 4.0 g. (15%); the decomposition range was 190-191°.

2-Butanone-p-Iodophenylhydrazone (13)

p-Iodophenylhydrazine hydrochloride (3 g.; 0.01 mole), sodium acetate (2 g.; 0.024 mole), glacial acetic acid (10 ml.; sp. g. 1.06; 99%), and water (250 ml.) were placed in a 500 ml., 3-necked flask equipped with a mechanical stirrer and thermometer. The solution was heated to 85° and the temperature was allowed to drop below 80°, the boiling point of 2-butanone. 2-Butanone (2 ml.) was added with vigorous stirring. The mixture was placed in a separatory funnel and sodium chloride was added to speed up separation of the layers. The organic layer was removed and used in the next step without further purification.

5-Iodo-2, 3-Dimethylindole

Method a. (14) p-Iodophenylhydrazine hydrochloride (3 g.; 0.01 mole), absolute ethanol (50 ml.), and 2-butanone (3 ml.) were placed in a 300 ml., 3-necked flask equipped with a mechanical stirrer, a reflux-condenser, a nitrogen inlet, and a dropping funnel. Hydrochloric acid (10 ml.; sp. g. 1.19; 36%) was added dropwise and the mixture refluxed for three hours during which time a stream of dry nitrogen was passed through the apparatus. The reaction was poured slowly, with stirring, onto a mixture of crushed ice (50 g.) and water (100 ml.). The black solid that precipitated was collected and attempted crystallization from aqueous ethanol was unsuccessful. The solution was concentrated by evaporation giving a black residue. Further attempts to recrystallize the solid from various organic solvents and purification by sublimation were unsuccessful and yielded a solid whose melting point was greater than 275°.

Method b. (15) In a 250 ml., 3-necked flask with a reflux-condenser, a nitrogen inlet, and a thermometer, were placed 2-butanone-p-iodophenylhydrazone (1.42 g.; 0.005 mole), 1:1 M aqueous ethanol (50 ml.), and sulfuric acid (10 ml.; sp. g. 1.84; 96%). A stream of dry nitrogen was forced through the system and maintained throughout the reaction. The mixture was heated under reflux for thirty minutes at $100\text{-}115^{\circ}$. The hot solution was then poured slowly, with stirring, into an ice-water mixture (100 ml.). The black solid that formed was collected and dried overnight to give a crude product with a decomposition range of 80-85^0. Attempts to recrystallize the solid from various organic solvents and purification by sublimation were unsuccessful.

Method c. (17) A 300 ml., 3-necked flask was equipped with a mechanical stirrer, a nitrogen inlet, and a reflux-condenser. To the flask were added ethylene glycol (100 ml.) and 2-butanone-p-iodophenylhydrazine (1.41 g.; 0.005 mole). The resulting solution was refluxed for three hours during which time a stream of dry nitrogen was passed through the apparatus. At the end of the reaction, the cooled solution was poured slowly, with stirring, into water yielding no precipitate. The water was extracted with two 100 ml. portions of ether, and the combined extracts dried over sodium sulfate. Evaporation of the extracts gave a black tar which could not be purified.

Method d. (18) A mixture of 2-butanone-p-iodophenylhydrazone (1.7 g.; 0.006 mole), powdered zinc chloride (9 g.; 0.o7 mole), and absolute ethanol (100 ml.) were placed in a 300 ml., 3-necked flask equipped with a mechanical stirrer, a reflux-condenser, and a nitrogen inlet. The mixture was stirred vigorously and heated to reflux temperature. After four hours refluxing, the solvent was removed by distillation and the water-insoluable residue collected by filtration. The residue was dissolved in ethanol, treated with charcoal, filtered, and allowed to crystallize. The tan needles appeared to be p-iodophenylhydrazine based on n.m.r. spectra identification.

Preparation of 2, 3-Dimethyl-5-Nitroindole

p-Nitrophenylhydrazine (12)

In a 3-liter, 3-necked flask equipped with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel, were placed p-nitroaniline (13.8 g.; 0.10 mole), hydrochloric acid (750 ml.; sp. g. 1.19; 36%), and water (250 ml.). The mixture was heated to dissolve the p-nitroaniline. The reaction flask was placed in a dry ice-acetone bath and cooled rapidly to -25^{0}. The temperature was maintained at -20 to -25^{0} while a solution of sodium nitrite (9 g.; 0.13 mole) in water (200 ml.) was added through a dropping funnel, the tip of which extended nearly to the bottom of the flask. The diazotization required about ten minutes after which a positive starch-iodide test was observed. The cold diazonium solution was allowed to warm to 0^{0} and poured very slowly, with stirring, into a cold (0^{0}) solution of stannous chloride (38 g.; 0.2 mole) in hydrochloric acid (500 ml.; sp. g. 1.19; 36%). The resulting mixture was stirred vigorously for one hour and stored at 0^{0} overnight. The solid was collected on a fritted glass filter, washed with saturated salt solution

(200 ml.) and with 2:1 petroleum ether-ether (150 ml.). The filtered solid was added with stirring to a solution of sodium hydroxide (20 g.; 0.5 mole) in water (500 ml.). The material was collected and crystallized from ethanol to give 8.1 g. (53%) of orange-red needles with a decomposition range of 156-158°.

2-Butanone-p-Nitrophenylhydrazone (19)

p-Nitrophenylhydrazine (5 g.; 0.033 mole) and 2-butanone (3 ml.) were heated together for one hour at 95°. The material was collected and crystallized from aqueous ethanol, with charcoal treatment, to yield 6.18 g. (91%) of yellow needles with a decomposition range of 123.5-125°.

2, 3-Dimethyl-5-Nitroindole (19)

2-Butanone-p-nitrophenylhydrazone (10 g.; 0.05 mole) and hydrochloric acid (100 ml.; sp. g. 1.19; 36%) were heated together at 95° for four hours. The product was collected by filtration and washed with hydrochloric acid (25 ml.). The product was dissolved in aqueous ethanol, treated with charcoal, filtered, and allowed to cool. The yield of yellow needles was 5.63 g. (60%); the decomposition range was 189-190°.

Preparation of 5-Amino-2, 3-Dimethylindole

5-Amino-2, 3-Dimethylindole (20)

2, 3-Dimethyl-5-nitoindole (1 g.; 0.005 mole) in absolute alcohol (100 ml.) was hydrogenated for one hour at room temperature and 2 atmospheres pressure over Raney Ni (1 g.). The catalyst was filtered and the ethanol evaporated under reduced pressure. An aqueous suspension of the product was filtered and recrystallization, with charcoal, from aqueous ethanol yielded .58 g. (72%) of white flakes with a decomposition range of 177.5-179°.

CONCLUSIONS

A significant correlation of the shift magnitude to structural features of substituted anilines has been determined. This correlation can be analytically valuable if one has a basic idea about the ring substituted atoms or groups present, and how their structural position can affect shift magnitude.

Three basic conclusions are apparent from this research. The induced shift will decrease with increasing distance between the paramagnetic center and the affected methyl substituent. The strongest Lewis bases produce the largest induced shifts of all methyl substituents. A shift rate decrease for N-substituted and 2-substituted anilines is due to steric hindrance of the metal complex attack.

Further work involving this investigation could be very rewarding. Values of pKa's should be determined where there are no literature values, especially for the 2, 6-disubstituted anilines. Research involving many different activating and deactivating substituted anilines should be carried out. Also, one could extend this work to other Lewis bases. Additional study along these lines may establish an important analytical method for structural identification of organic compounds.

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