STUDIES ON THE NATURE OF VITAMIN B$_6$ INTERMEDIATES

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The extent of intramolecular hydrogen-bonding of Pyridoxal analogs can be determined by the phenoxyl H chemical shift.

In the course of our investigations on Vitamin B$_6$ (Pyridoxal) model systems our attention has been drawn to substituent effects in strongly intramolecular hydrogen-bonded species.[1] More specifically, we have studied the Schiff bases of ortho - hydroxy pyridine aldehydes (I and II) in which the phenolic hydrogen is strongly bridged to the azomethine nitrogen (III, IV).
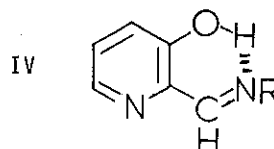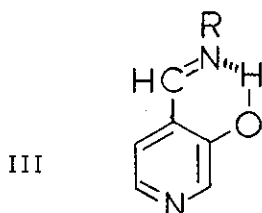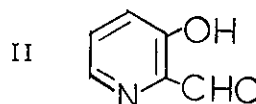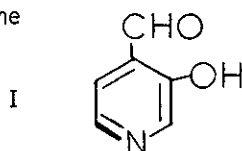
Because of the similarities in substituent placement in Vitamin B$_6$ and our model compounds, we have examined the substituent effects in the following series of

compounds:
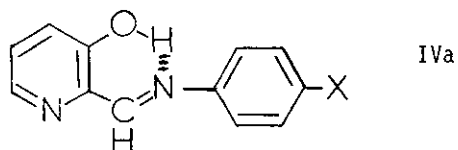
The Schiff bases were prepared by condensation of 3-hydroxypyridine-2-aldehyde with the appropriate substituted aniline in absolute ethanol (or methanol). No catalyst was required for this reaction and the resulting bright orange to yellow compounds were recrystallized from ethanol.[2]

The commonly employed technique[3-5] of proton nmr spectroscopy was used to examine the intramolecular hydrogen bonds in this study. The chemical shift of the phenoxyl hydrogen atom were correlated with the Hammett σ constants.[6] Figure 1 is the Hammett plot for the para-substituted series (IVa). Each point represents an average of at least two determinations. The average deviation for all measurements was 0.03 δ units.[7] The straight line in the Hammett plot was determined by a least squares linear regression analysis[8] that has the form:

$$\delta = -0.858\,\sigma + 13.10$$

Table I shows the deviation of the individual substituents from the straight line determined by the above method. All spectra were run on a Varian Associates A-60 spectrometer at 35°C using deuterochloroform as solvent and tetramethylsilane as an internal reference standard. Although we have previously noted[1] that the chemical shift of the intramolecularly phenoxyl bonded hydrogen is not concentration dependent, all compounds studied were analyzed at a sample concentration of about 0.2 M, hence any intermolecular hydrogen-bonding effects should be constant and negligible.

As is shown by the Hammett plot, correlation between the phenoxyl hydrogen chemical shift and the para substituent's electron-attracting ability is excellent

with a correlation coefficient of 0.993. These results are similar to those of
Klicnar, et al.[9,10] who used infrared and proton nmr techniques to study a series
of anils that included the system V.

V
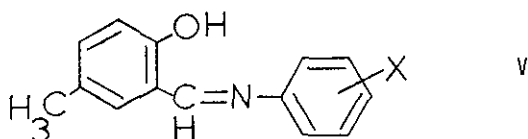
These investigators obtained a correlation for this system that can be repre-
sented by the equation: $\delta = -1.29 \ \sigma^- + 9.22$. A comparison of the results for
the two systems reveals a remarkable similarity and demonstrates the dependence
of the intramolecular hydrogen-bond strength upon the electronic factors within
the amine moiety.

In recent work, El-Bayoumi[11,12] has proposed that in Schiff bases such as
benzylideneanilines the two aromatic rings are non-coplanar. This is suggested
by the fact that the uv spectrum of benzylideneaniline does not resemble that
of the coplanar compound stilbene, but rather that of a combination of spectra
of benzaldehyde and aniline. Moreover, this suggests that the non-bonded lone
pair electrons of the azomethine nitrogen are in strong conjugation with the π
electron system of the aniline ring. Therefore, the electron withdrawing ability
of the substituted aniline influences the basicity of the azomethine nitrogen
which, in turn, affects the strength of the intramolecular hydrogen bond. Hence,
strong electron attracting groups on the aniline will reduce the electron
density at the Schiff base nitrogen leading to a relatively weak hydrogen bridge.
That this is indeed the case, can be seen where X = NO_2 and the phenoxyl hydrogen
is most strongly influenced by oxygen's electron density resulting in a chemical
shift upfield relative to where X = H.[7,10,13]

Our data are entirely consistent with the above interpretation. Moreover, our

Table I

0.2 M in CDCl$_3$
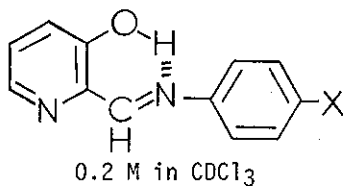
X	OH Chemical Shift (δ) Determination		Ave.	Dev.	Deviation from straight line	σ [a]
	1	2				
NO$_2$	12.46	12.38	12.42	0.08	0.00	+0.788
CO$_2$CH$_3$	12.78	12.78	12.78	0.00	0.01	+0.385
Br	12.84	12.83	12.84	0.01	0.06	+0.232
Cl	12.84	12.86	12.85	0.02	0.06	+0.227
H	13.16	13.14	13.15	0.02	0.05	0
CH$_3$	13.27	13.34	13.31	0.06	0.06	-0.170
OCH$_3$	13.34	13.38	13.36	0.04	0.03	-0.268
N(CH$_3$)$_2$	13.75	13.76	13.76	0.01	0.05	-0.830

average deviation = 0.03 δ

[a] Hine, Physical Organic Chemistry, McGraw-Hill, Inc., New York, 1956, p. 87.
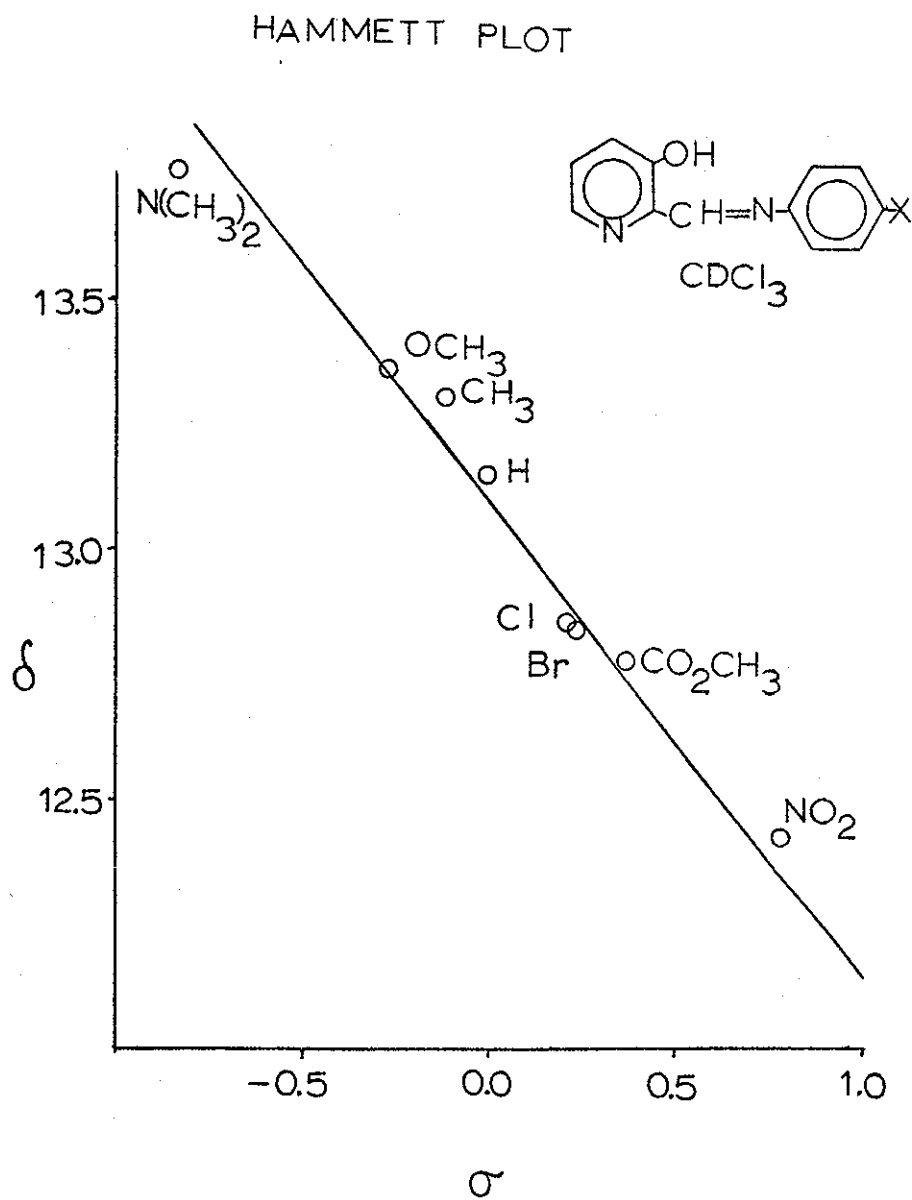
HAMMETT PLOT

Figure 1

results are an interesting and forceful demonstration of the striking sensitivity of the chemical shift of the phenoxyl proton in the _para_ substituted aniline Schiff bases of these vitamin B_6 analogs.

REFERENCES

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2 Satisfactory elemental analyses and spectral data were obtained for all compounds reported herein.

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7 See Table I.

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