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I am submitting herewith a dissertation written by Clarence Dixon Blue entitled "The Use of Copper Acetylacetonate Induced C-13 NMR Line Broadening in the Determination of the Stereochemistry of Rigid Cyclohexylamines." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Fred M. Schell, Major Professor

We have read this dissertation
and recommend its acceptance:

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Graduate Studies and Research

THE USE OF COPPER ACETYLACETONATE INDUCED C-13 NMR LINE BROADENING IN THE DETERMINATION OF THE STEREOCHEMISTRY OF RIGID CYCLOHEXYLAMINES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Clarence Dixon Blue

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ABSTRACT

Small amounts of copper acetylacetonate [$Cu(acac)_2$] produce ^{13}C nmr line broadening in amines. This work describes an attempt to quantify this effect to aid in distinguishing between axial and equatorial cyclohexylamines. Data were obtained for a variety of amines by running a series of ^{13}C nmr spectra containing a $Cu(acac)_2$:amine mole ratio of about 10^{-5} to 10^{-2}.

Two problems were encountered. First, the linewidths [at a given $Cu(acac)_2$ concentration] tended to increase with time. Apparently $Cu(acac)_2$ is an effective catalyst for the reaction of amines with the halogenated solvents ($CHCl_3$, CH_2Cl_2) used to dissolve the $Cu(acac)_2$. The reasons for this linewidth increase were not completely determined. In the case of cyclohexylamine, the addition of a small amount of cyclohexylisocyanide to a $Cu(acac)_2$-cyclohexylamine solution resulted in an immediate increase in the nmr linewidth. The second difficulty was that the plots of linewidth vs. mole ratio of $Cu(acac)_2$ were curved, the slope becoming less at higher concentrations. This complicated the assignment of values to the amount of line broadening. Various explanations were advanced but none were completely satisfactory. Some other copper β-diketonates were used and they produced plots with both more and less curvature. Similar results were found for the small paramagnetic shifts.

In spite of these difficulties, the data were applied to the original stereochemical problem. As expected, the γ carbons were found to broaden considerably more for equatorial cyclohexylamines than for axial cyclohexylamines. The requirements for maximum line broadening appear to be similar to those for long range nmr coupling. Thus, the equatorial amines have the best "W" configuration between the metal and the γ carbon. While the actual values varied considerably, particularly between amines on secondary and tertiary centers, a good correlation was obtained by expressing the amount of γ carbon line broadening in terms of the β carbon line broadening. When this was done, the amines studied fell into two groups, axial and equatorial, with the amount of γ line broadening differing by about a factor of 10.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

FIGURE PAGE

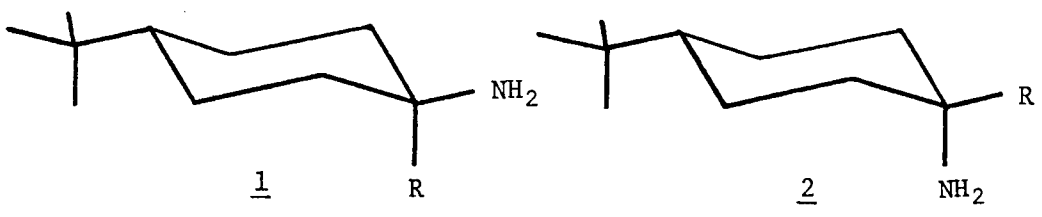
FIGURE PAGE

CHAPTER I

INTRODUCTION

One of the most important uses of nuclear magnetic resonance (nmr) is the determination of structures of organic compounds. The addition of small amounts of Cu(acetylacetonate)$_2$ [Cu(acac)$_2$] to an amine causes certain ^{13}C nmr lines to broaden due to the effect of the unpaired electron of the copper. Described here is some work which uses this effect to assign the nmr resonances and determine the stereochemistry of a few simple, cyclic amines.

In the course of some other work in this laboratory there arose the need to unequivocally assign the stereochemistry of amines such as 1 and 2. If both stereoisomers were available, ^{13}C chemical shifts would have probably been sufficient. However, only one was obtained and another method, independent of chemical shifts, was sought to distinguish between axial and equatorial amines. The nmr line broadening effect of Cu(acac)$_2$ with amines is known to depend on stereochemistry. The work described here is an attempt to quantify this effect using amines of known stereochemistry so that the stereochemistry of amines such as 1 and 2 can be determined even if only one isomer is available.



1 2

A brief explanation of the effects of paramagnetic materials on nmr spectra follows, with the emphasis on showing why nmr lines broaden.[1,2]

There are many examples of nmr spectra of paramagnetic species. The review in Chapter III considers only those results which have definite points of similarity to this work. Thus included are examples of Cu(II) (and some other first row transition metals), generally in the form of a stable complex, being used to determine the structures of simple amines or alcohols and/or assigning resonances in nmr spectra.[3]

CHAPTER II

THEORETICAL BACKGROUND

There are two basic methods of obtaining nmr spectra: "continuous wave" or "steady state" and "pulsed" or "Fourier transform" (FT). In pulsed nmr (which became common only after 1970), a very short pulse of rf power is used to excite the nuclei and the response of the sample is then monitored as a function of time. A mathematical operation, the Fourier transform, converts this "time domain" information into the more familiar "frequency domain." The following discussion will be from the point of view of a pulsed experiment since the work described in Chapter IV was done in that manner and since the explanation of relaxation is simplified.[2,4]

Consider a typical pulsed nmr experiment with a nucleus of spin 1/2. When placed in a magnetic field, H_o, a nucleus will precess about H_o at the characteristic Larmor frequency, ω, in a manner analogous to a gyroscope in a gravitational field (Figure 1a, p 4). A net magnetic moment results which can be aligned with or against H_o.

Assuming thermal equilibrium, a collection of nuclei will contain a small excess aligned with H_o. This results in a net magnetization, M, of the sample along the z axis (Figure 1b, p 4). Application of an rf pulse in the xy plane, of the proper frequency and power, "tilts" M towards the xy plane where it precesses about the z axis at a frequency ω (Figure 1c, p 4). M can be divided into two components, M_{xy} and

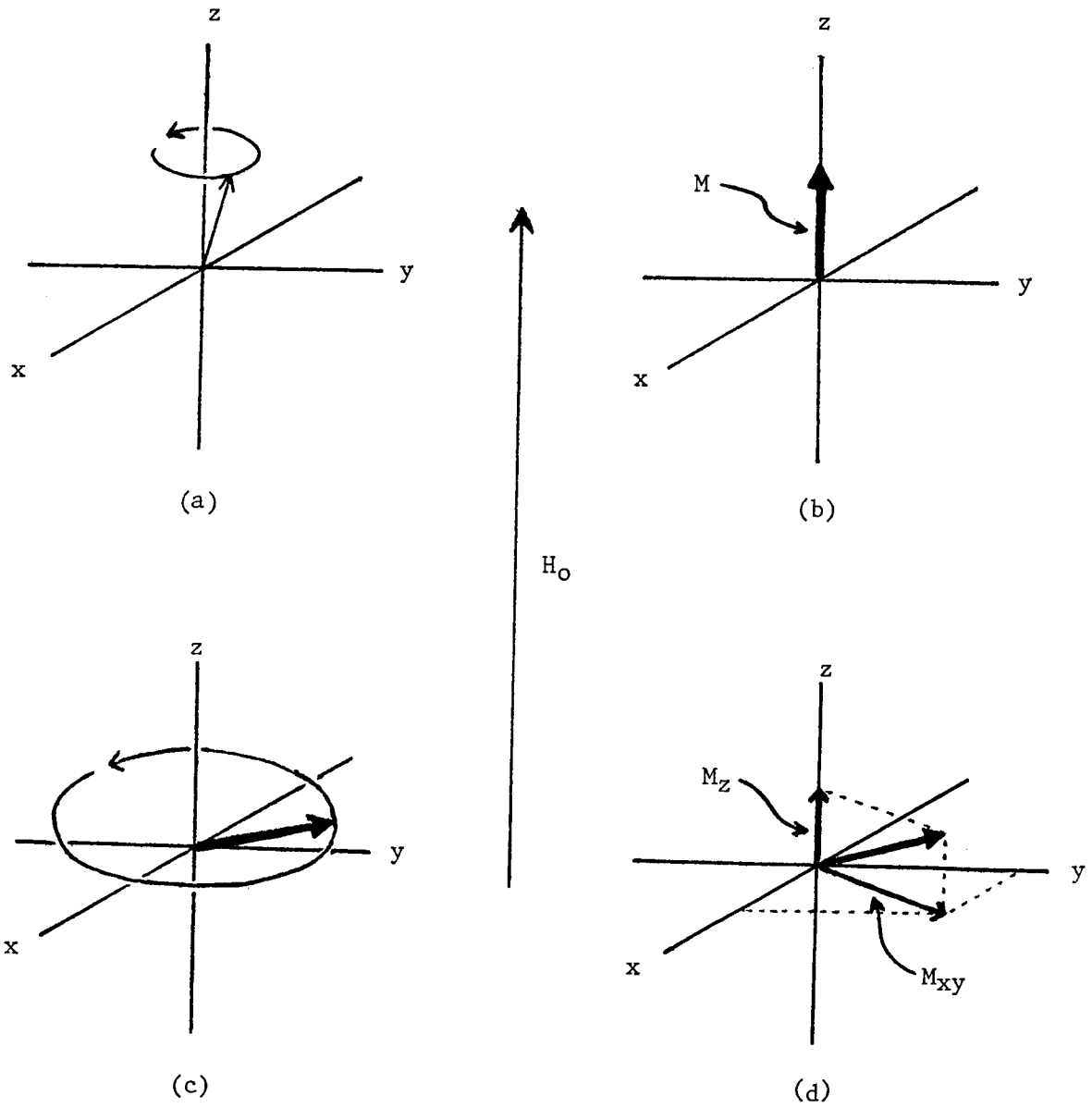


Figure 1. Vector diagrams.

M_z (Figure 1d, p 4). The rotation of the M_{xy} vector is detected as the nmr signal.

If there were no relaxation, that is a tendency for the magnetization to return to the original equilibrium condition, the signal would be an infinite sine wave corresponding to the net magnetization in the xy plane. The Fourier transform of this signal would be a line with height but no width (a delta function). However, relaxation does occur and can be described by the Bloch equations, given here in a simplified form (Equation 1).[1] T_1 describes the rate at which the net magneti-

$$\frac{d M_z}{dt} = - \frac{M_z - M_o}{T_1} \quad ; \quad \frac{d M_{xy}}{dt} = - \frac{M_{xy}}{T_2} \qquad (1)$$

zation, M, returns to its equilibrium value M_o, or the rate at which M_o would disappear if H_o were removed. T_2 describes the rate at which the rotating xy components of the individual nuclei lose phase coherence resulting in the disappearance of M_{xy} (Figure 2a, p 6, dashed line). Following a pulse, M_x will decay such that $M_x = (e^{-t/T_2})\cos(\omega_o - \omega)t$ (Figure 2a, p 6, solid line) which after Fourier transformation gives a Lorentzian peak with a width at half maximum of $2\pi/T_2$ rad/sec (or $1/T_2$ cycles/sec) (Figure 2b, p 6).[2] As T_2 becomes shorter the signal decays more quickly and the width of the nmr line increases.

The uncertainty principle can be used to show why nmr lines have width. For diamagnetic solutions, T_1 and T_2 (the uncertainty in time)

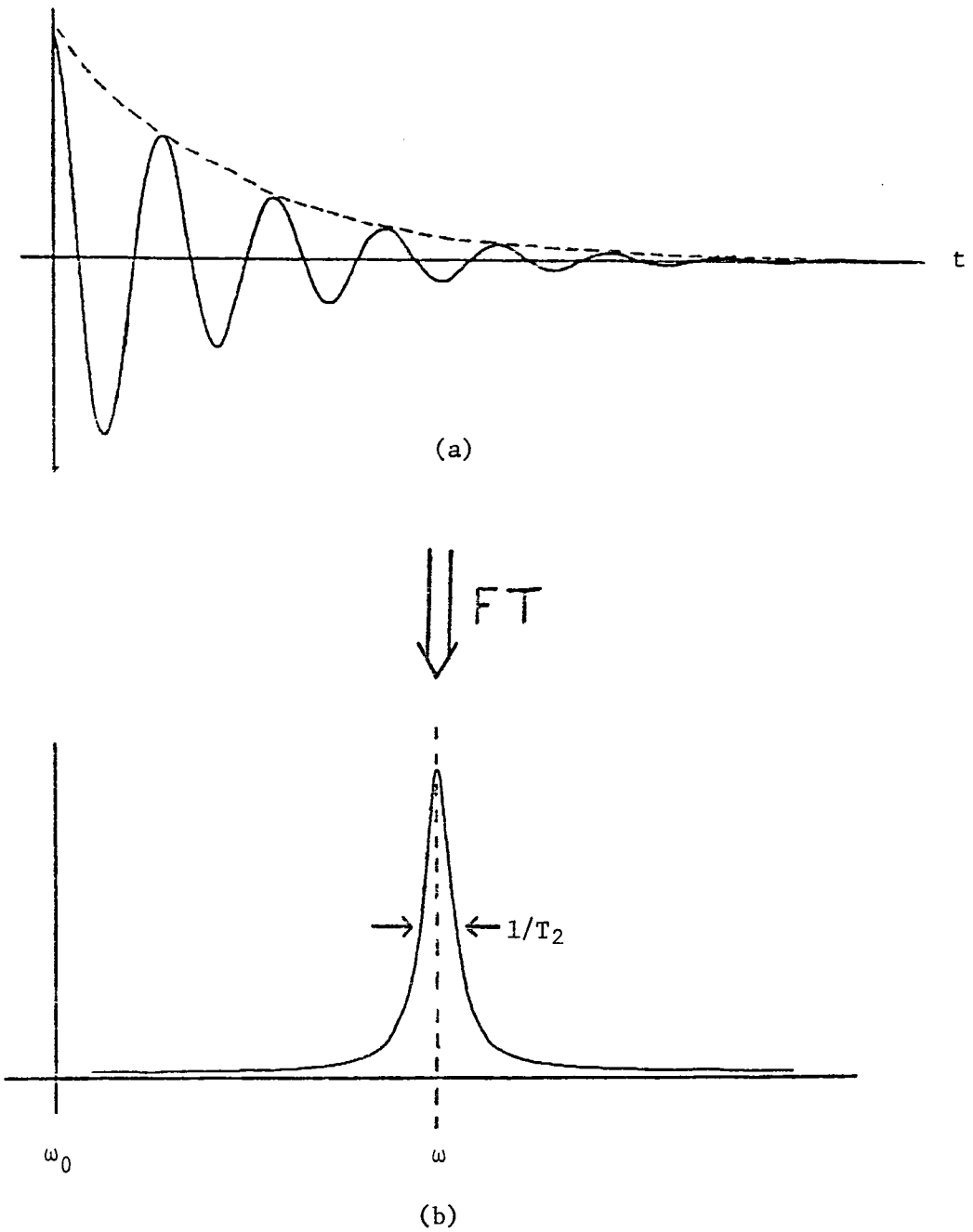


Figure 2. Fourier transformation of an exponentially decaying cosine wave.

are in the range of 0.01-100 sec, so $\Delta\nu$ (the line width) will correspondingly be about 100-0.01 sec^{-1} (Equation 2).

$$\Delta E \Delta t \simeq h \qquad \text{or} \qquad \Delta\nu\Delta t \simeq 1 \tag{2}$$

So far, nothing has been said about processes that affect the lifetimes of nuclei in their spin states and thus T_1 and T_2. The following is a brief qualitative description of these processes.[1,2] The nmr experiment is possible because an external oscillating magnetic field (the rf pulse) can induce transitions between the nuclear spin states. In the liquid state, molecules constantly experience rapid, random motions relative to each other. Since molecules can contain magnetic nuclei and electric dipoles, these thermal motions cause rapid, random changes in the local magnetic field experienced by each nucleus. Motions which produce an oscillating magnetic field with a frequency ω can induce transitions between spin states. This couples the nuclei to their surroundings (the lattice) and the transfer of energy allows the net magnetization to reach thermal equilibrium. The first order rate constant for this process, spin lattice relaxation, is T_1.

If this were the only process available, T_1 would equal T_2. However, there is another method by which spin flips can occur which affects the phase coherence of the individual xy vectors. If two nuclei with opposite spins are near each other, a spin exchange can occur. No net change in energy results, but there is a contribution

to the loss of phase memory, an entropy process. This is called spin-spin relaxation, and since it affects only T_2, $T_2 \leq T_1$. Inhomogeneities in H_o due to magnet defects will also produce line broadening which is difficult to distinguish from real T_2 processes.

The system under consideration consists of an aliphatic amine ligand in the presence of a paramagnetic metal complex, $Cu(acac)_2$. The electron has a magnetic moment about 1000 times larger than that of the proton, which has the largest for a nucleus. Thus, it is not surprising that unpaired electrons are very effective in inducing transitions in nuclei, which affect T_1 and T_2. One mechanism of interaction, dipole-dipole or pseudo-contact, involves the through space interaction of nuclear and electron spins. The second interaction, contact or scalar, involves coupling of the electron to a nucleus through bonds, i.e., the probability of finding the unpaired electron at that nucleus. Contributions to T_1 and T_2 from pseudo-contact and contact interactions are given by the Solomon-Bloembergen equations.[1] The expression for T_2 is given (Equation 3) with the pseudo-contact part first. The spin

$$\frac{1}{T_2} = \frac{1}{15} S(S+1) \left(\frac{g_e^2 g_n^2 \beta_e^2 \beta_n^2}{h^2 r^6} \right) \left(7\tau_c + \frac{13\tau_c}{1 + \omega_s^2 \tau_c^2} \right) + \frac{1}{3} S(S+1) \frac{a^2}{h^2} \left(\tau_e + \frac{\tau_e}{1 + \omega_s^2 \tau_e^2} \right) \qquad (3)$$

of the electron(s) is S [copper(II) has one unpaired electron]; g_e and g_n are g values for the electron and nucleus; β_e and β_n are the electron and nuclear magneton; r is the distance from the electron to the nucleus; ω_S is the electron resonance frequency; $a/\hbar$ is the electron-nuclear hyperfine coupling (the esr splitting frequency); τ_c is the correlation time for dipolar interaction ($\tau_c \simeq 10^{-11}$ sec, which is the time for molecular reorientation of the complex); τ_e is the correlation time for contact interaction ($\tau_e \simeq 10^{-9}$ sec, which is the electron spin relaxation time). Correlation times, which are similar to rate constants, are influenced by various time dependent processes, but are dominated by the fastest of the molecular processes which affect them. At 14 kgauss, ω_s is about 2×10^{10} sec^{-1} so,

$$\omega_s^2\tau_e^2 >> 1 \qquad \text{and} \qquad \omega_s^2\tau_c^2 << 1 \qquad (4)$$

With these simplifications, and using a "large" hyperfine coupling constant of 10^6 sec^{-1} (which can be expected for ^{13}C),[5,6] the contact part of Equation 3 (p 8) is found to be about 10^4 larger than the pseudo-contact part. Thus, this theory predicts that line broadening of complex ligands in this system will be due primarily to contact interactions and any differences between nuclear centers (i) will be due to variations in a_i.

Another effect of paramagnetic materials is to shift nmr lines. Consider a nucleus coupled to an electron. If the electron relaxation

time τ_e is very long ($>10^{-5}$ sec) so that

$$1/\tau_e \ll a/\hbar \ , \qquad (5)$$

then the nmr spectrum would contain a doublet (Figure 3, p 11). However, τ_e is almost always less than 10^{-8} and $a/\hbar \leq 10^6$ sec^{-1} so τ_e^{-1} is much greater than $a/\hbar$ and a single line is observed.[1,7] Compared to nuclei in a magnetic field, the populations of the upper and lower spin states for the electron are much more unequal and the single line is shifted from the center of the theoretical doublet. This is the contact shift (Equation 6). Substitution of "reasonable" values into Equation 6

$$\frac{\Delta H}{H_o} = - \frac{g_e \beta_e S(S+1) a}{3 g_n \beta_n kT} \qquad (6)$$

and the contact part of Equation 3 (p 8) shows that for complexes with a large $a/\hbar$ ($\sim 10^6$ sec^{-1}) and a long τ_e ($\sim 10^{-9}$ sec) there will be extensive line broadening with only small contact shifts. Equations 3 (p 8) and 5 show the relationship between τ_e and the ability to obtain nmr or esr spectra of a paramagnetic material. If τ_e is long ($\sim 10^{-9}$ sec), then sharp esr lines can be observed, but the nmr spectrum is so broad that it is unobservable. On the other hand, an extremely short τ_e [$\tau_e \simeq (a/\hbar)^2 \leq 10^{-11}$ sec] will result in narrow nmr lines and no observable esr spectrum. The complete range of these effects is shown in the acetylacetonate (acac) complexes of transition metals. $Cu(acac)_2$

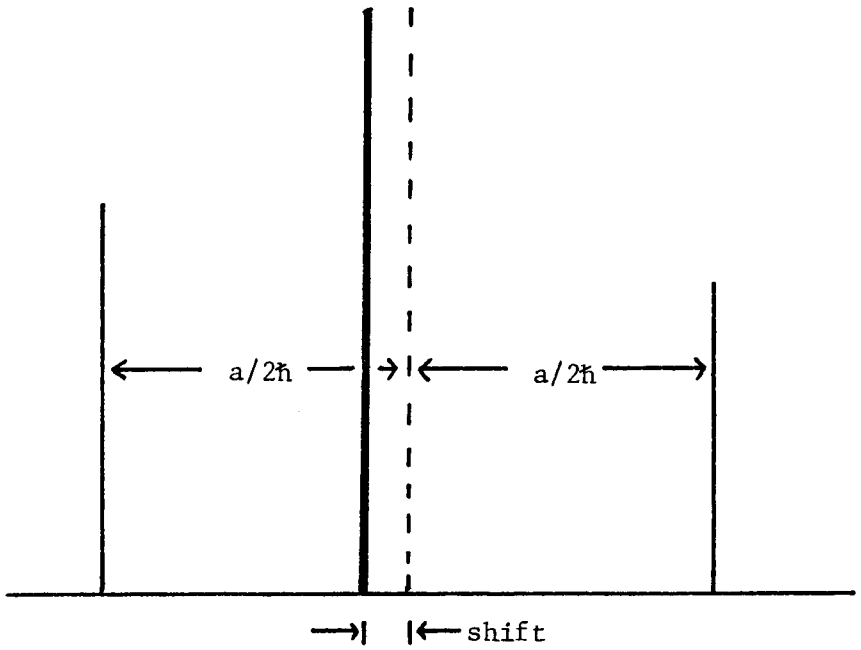


Figure 3. Paramagnetic contact shift.

gives a sharp esr spectrum but no nmr.[8] A $Cu(acac)_2$ complex with pyridine shows a Cu-N hyperfine coupling of about 5×10^7 sec^{-1}.[9] These observations indicate that the assumptions and approximations made in the above discussion are reasonable.

As with line broadening, there is also a pseudo-contact or dipole interaction which can produce nmr line shifts (Equation 7).[1] The important point about this equation is that the shift can be highly dependent on direction as well as distance. Lanthanide shift reagents are an example of compounds which cause pseudo-contact shifts.

$$\frac{\Delta H}{H_o} = \frac{(3\cos^2\theta - 1)\beta_n g_n \beta_e}{3r^3} F(g_e) \qquad (7)$$

Another source of nmr line shifts is the change in bulk magnetic susceptibility upon addition of paramagnetic materials.[1] This can be thought of as a "pseudo-contact shift" which occurs equally for all parts of the sample volume due to the average effect of the paramagnetic material. Thus, all nmr resonances are shifted equally and the effect is generally not noticed when using an internal standard.

In the system studied here, and in much of the previous work which is reviewed in Chapter III, there is a large excess of ligand in equilibrium with a paramagnetic metal. The width of an nmr line of the ligand is given by

$$W = \frac{1}{\pi T_2} = W_c f + W_a(1 - f) \qquad (8)$$

where W is the observed line width (in Hz), W_c the line width for the complex, W_a the line width for the free ligand, and f is the fraction of complexed ligands.[1] Thus, for small values of f, the increase in line width should be proportional to the amount of added metal. Equation 8 assumes there is rapid exchange of the ligands which is true for relatively weak complexes such as $M(acac)_n$ and amines.[10-13] A similar argument can be used to show that nmr line shifts are also proportional to added metal.

CHAPTER III

HISTORICAL BACKGROUND

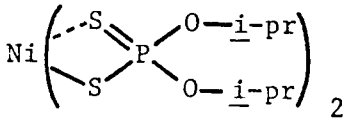
Fricke studied the proton nmr shifts produced by addition of $Ni(acac)_2$ and $Co(acac)_2$ to some simple amines.[14-16] Downfield shifts were observed with $Ni(acac)_2$ and larger upfield shifts with $Co(acac)_2$. Shifts were proportional to the concentration of metal over a metal to amine mole ratio of 0.01 to 0.2. From previous work, it was assumed that $Ni(acac)_2$ gave contact shifts and $Co(acac)_2$ gave an equal contact shift plus an opposite pseudo-contact shift. For the acyclic amines and $Co(acac)_2$, characteristic pseudo-contact shifts were found which decreased with distance from the metal ($\sim$ -4500, -2250, -1100, and -700 Hz/mole $Co(acac)_2$ for β, γ, δ, and ε protons at 14 kgauss). Six separate resonances were observed for n-hexylamine with 0.2 mole $Co(acac)_2$.[14] Cyclic amines gave different shifts for axial and equatorial protons. In the case of cis-t-butyl cyclohexylamine, $Ni(acac)_2$ shifted the β-equatorial proton much more than the β-axial. This would not be expected if the contact shift operated in a manner similar to nmr spin coupling and a direct, through space interaction was proposed. Another inconsistency was shown with the α protons, which shifted less than the β protons with $Co(acac)_2$.[15]

Work by Roberts demonstrated further complexities of these shifts.[17] NMR spectra (^1H and ^{13}C) were obtained for some simple

alcohols and amines in the presence of $Ni(acac)_2$ and $Co(acac)_2$. Again, the α ^1H and ^{13}C pseudo-contact shifts were much less than would be expected from the β and γ shifts using a simple distance theory and the relative amount of α shift decreased with increasing substitution on the α carbon. Also, the $Ni(acac)_2$ shifts showed a distinct tendency to alternate in direction and/or magnitude with distance from the metal. The suggestion was made that two contact processes were operating, one of which is large at short distances but decreases much more rapidly than the other at larger distances. Thus α carbons would be the most sensitive to steric interference. Roberts also questioned the original assumptions concerning the relative importance of contact and psuedo-contact shifts for $Ni(acac)_2$ and $Co(acac)_2$. In both of these studies, line broadening was mentioned as a problem in observing some nmr lines but no quantitative data were given.

In a relatively qualitative paper, Baird reported the effects of $Co(acac)_2$, $Ni(acac)_2$, and $Cu(ethylacetoacetate)_2$ on nmr spectra of several alcohols and a few amines.[18] Only the α and hydroxyl protons of alcohols showed any significant shifts. However, line broadening effects were observed which decreased with distance from the metal along a saturated molecule. This effect was most pronounced for amines with $Cu(ethylacetoacetate)_2$. With diethylamine, 3×10^{-5} M Cu(II) completely destroyed the methylene resolution. At 3.4×10^{-3} M, the methylene resonance disappeared but the methyl was still a recognizable triplet. Unlike $Co(acac)_2$ or $Ni(acac)_2$, $Cu(ethyl\ acetoacetate)_2$ caused

no shifts with either alcohols or amines. Baird also reports the use of $Co(acac)_2$ to differentiate between cis- and trans-1,2-cyclohexanediol.[19] The α methylenes in the cis compound shift more than the trans. This is explained by noting the complex is a fused 6,5 ring system which is known to be more stable in the cis form. Wasson used 3 and 4 to obtain shifts in the proton nmr spectra of several amines.[20] Shifts were proportional to added metal. Values of $a/\hbar$ were reported; for example with 3, $a/\hbar$ is 2.2×10^5 sec^{-1} for the CH proton of isopropylamine.



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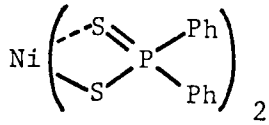

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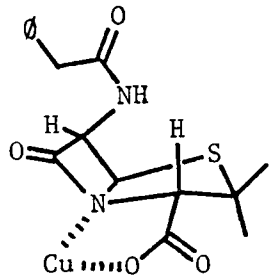
An important use of paramagnetic metals is aiding the interpretation of nmr spectra of biological compounds which have potential metal binding sites. One of the first examples was by Li, who studied the line broadening due to Cu(II) and Mn(II) in some mono-, di-, and tripeptides and their esters.[21] In the presence of 10^{-4} M $CuCl_2$ the α amino protons broadened enough to be unobservable while the others were almost unaffected. A more recent study by Fazakerley reported the use of $Cu(ClO_4)_2$ and $Mn(ClO_4)_2$ to interpret the nmr spectrum of benzylpenicillin (5, p 17).[10] Many of these studies have assumed that only pseudo-contact interactions are important; that is, the nmr assignments can be made or the metal location determined using a $1/r^6$ (or $1/r^3$) relation between internuclear distance and the line width (or shift)



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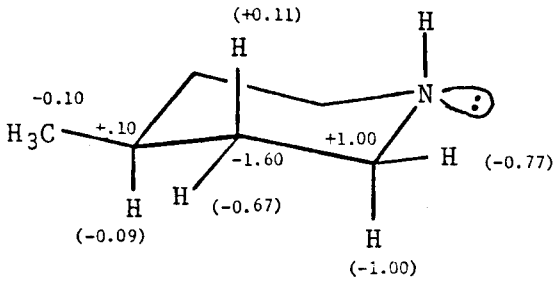
(Equations 3 and 7, pp 8 and 12).[22] More recent results indicate this is not true for Cu(II). Wasylishen showed that for Cu(II)-imidazole and Mn(II)-imidazole systems, contact interactions were the major source of line broadening.[11] Separate papers by Martin[12] and Freeman[13] gave detailed accounts of the limitations of using Cu(II), primarily with regard to "biological" systems. Typically, copper is added to these compounds in the form of a simple salt ($CuSO_4$, $CuCl_2$) which results in rather stable complexes compared to those formed from aliphatic amines and $Cu(acac)_2$. Thus, assumptions about rapid exchange and 1:1 complexes are often not valid. They also gave evidence that Cu(II) line broadening is due primarily to contact interactions (almost entirely for simple amines).

Morishima has reported several ^1H and ^{13}C nmr studies involving amines in the presence of $Co(acac)_2$ and $Ni(acac)_2$. Compounds 6-9 (p 18) show the relative ^{13}C and (^1H) shifts caused by $Ni(acac)_2$ (plus is upfield).[23] The amount of line broadening is approximately proportional to the magnitude of the shift. These results were explained by assuming the unpaired electrons of nitrogen (or in the complex the N-metal "bond") exist in the conformation shown and contact effects are transmitted in a manner analogous to proton nmr spin-spin coupling. In



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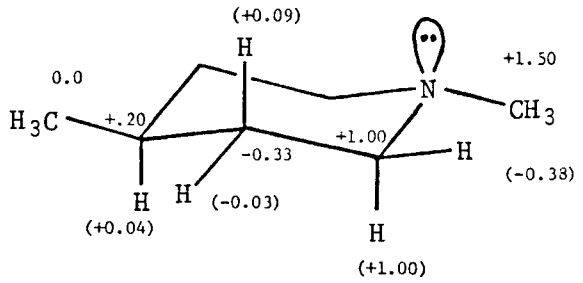

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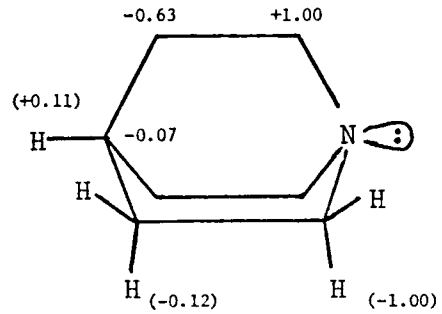

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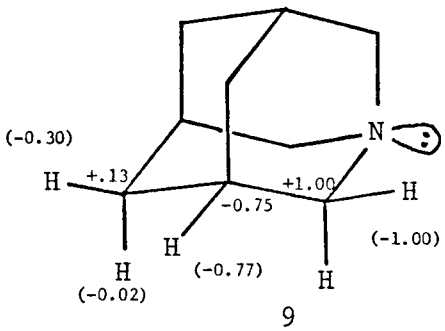

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6 and 9, the dihedral angle between α-H_{ax} and the nitrogen lone pair is about the same (60°) as between α-H_{eq} and the lone pair. In 7, the angle is 60° for α-H_{eq} and 180° for α-H_{ax}. Thus in 6 and 9, the contact shifts are more alike than in 7 where the α-H_{ax} shift is larger, as would be expected from a Karplus type relationship. An even greater difference is shown in the equatorial β protons. In 6 and 9, they have a "W" arrangement (which is known to favor long-range proton coupling) with the unshared electrons and they show a much greater shift than the β-protons in 7 or 8. These steric effects are also shown in the ^{13}C shifts; the β carbons in 6 and 9 shift more than in 8. Based on these results, Morishima proposed that the unpaired electrons from $Ni(acac)_2$ are distributed along the carbon chain more efficiently through a "zig-zag path" than a "folded path" (10, 11, p 19). Similar effects are seen in the $Ni(acac)_2$ shifts of quinoline, isoquinoline,[24] some tropanes,[25]

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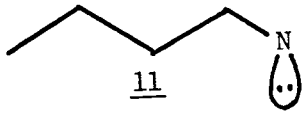

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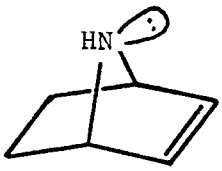
and in the protonation shifts of several cyclic amines.[26] Studies were also made by Morishima on the position of the nitrogen lone pair in Compounds 12 and 13.[27] As with previous work, the assumption is made that $Ni(acac)_2$ complexation does not significantly change the nitrogen lone pair stereochemistry.



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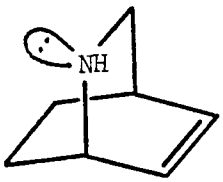

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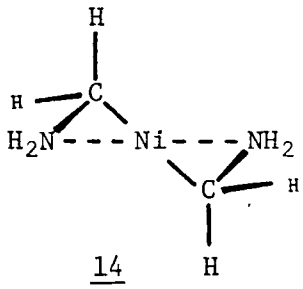
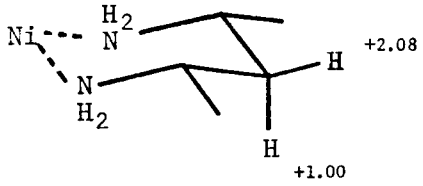
Zamaraev observed the ^1H nmr of diaminoethane in the presence of $NiCl_2$.[28] The 3:1 complex showed separate resonances which were attributed to "axial" and "equatorial" protons of a puckered ring (14). The sterically hindered environment prevents rapid ring flipping.



14

Reilley has made an extensive study of complexes of nickel(II) with diamines.[29,30] The ^1H nmr spectra of these complexes show shifts whose magnitude can also be explained in terms similar to spin-spin coupling. Compounds 15 and 16 are examples. An equation was given relating the shift magnitude to the dihedral angle (Figure 4, p 21).



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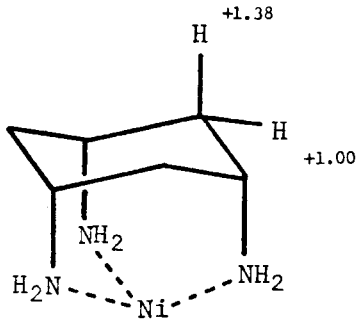

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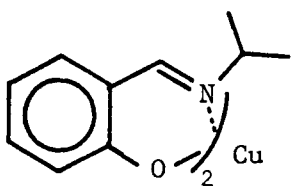
Several other studies are briefly mentioned here. The ^1H nmr spectrum of 17 has been observed.[31] Eaton, in one of the first detailed studies of the nmr spectra of paramagnetic complexes, looked at derivatives of 18.[32] In another early work, Pratt observed several amino acids in the presence of Ni(II) and Co(II) salts.[33] Horrocks studied $Ni(acac)_2$ and $Co(acac)_2$ complexes of pyridine-N-oxide[34] and substituted anilines.[35] Other compounds include piperidine and various pyridines,[36,37] benzylamine and some other simple primary amines,[6] diacids and hydroxyacids,[38] 6-aminobenzonorbornenes (19, p 22),[39] and alkylanilines (20, p 22).[40]



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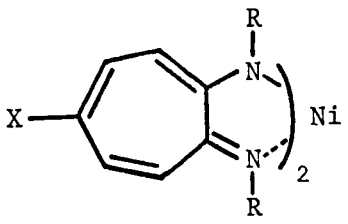

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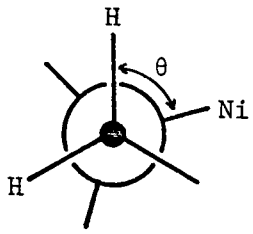
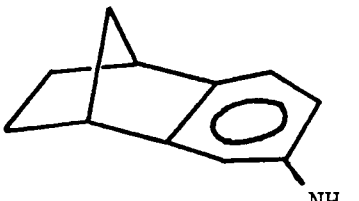


Figure 4. Dihedral angle defined by Reilley.



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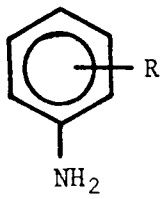

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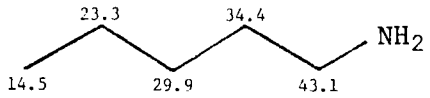
Pseudo-contact interactions also affect T_1. Levy measured ^{13}C T_1's with and without $Cr(acac)_3$ or $Fe(acac)_3$.[41] An r^{-6} relationship between distance and the decrease in T_1 was used to assign resonances or determine metal location. Other uses of these "relaxation reagents" [$Cr(acac)_3$ is the most common] are aiding in the observation of non-protonated carbons, removing the nuclear Overhauser effect (NOE) for quantitative ^{13}C analysis, and suppressing unfavorable negative NOE's (for example ^{15}N).[41,42] Some cautions concerning the use of these compounds have also been made.[43]

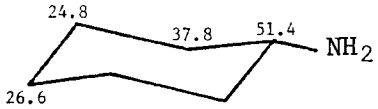
The work which is most closely related to this work is that of Doddrell.[5] $Cu(acac)_2$ was used to assign ^{13}C nmr resonances in some cyclohexylamines by observing the relative amounts of line broadening in each compound. The results are shown in Figure 5 (p 23). As expected from previous work, $Cu(acac)_2$ broadened, but did not shift, the nmr lines and the broadening was greatest for the β carbons. These results are consistent with a predominantly contact interaction. For 21, 22, 27, and 28 (p 23) inspection of chemical shifts and line

21



2 > 1 > 3 >> 4 ≃ 5

22



2 > 1 > 3 > 4

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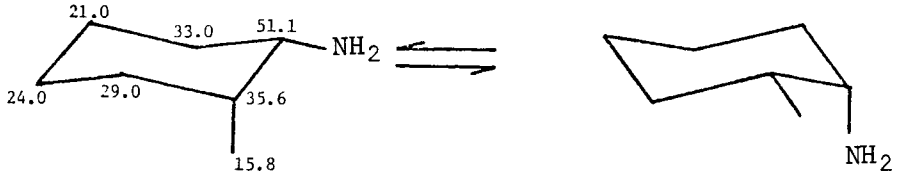
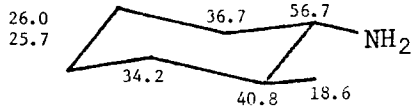


2 ≃ 6 > 1 > 3 ≃ 5 ≃ Me > 4

24



2 > 1 ≃ 6 > 3 >> 4 ≃ 5 ≃ Me

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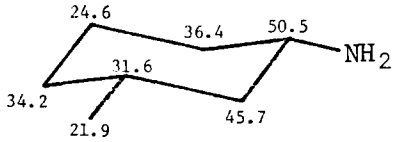

2 ≃ 6 > 1 > 3 ≃ 5 > Me > 4

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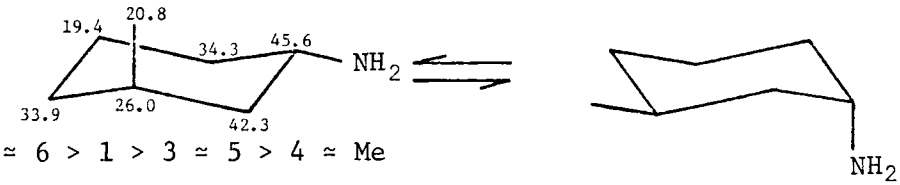

2 ≃ 6 > 1 > 3 ≃ 5 > 4 ≃ Me

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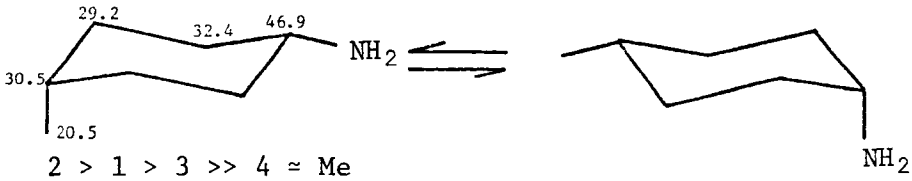
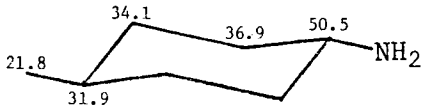


2 > 1 > 3 >> 4 ≃ Me

28



2 > 1 > 3 >> 4 ≃ Me

Figure 5. Amines studied by Doddrell.

intensities leads to unambigious assignments. In all cases, the pattern for line broadening was $\beta > \alpha > \gamma >$ all others. Application of this pattern to 23 (p 23) results in a straightforward assignment of carbons 3, 4, and 5. It also differentiates between C-4 and C-6 in 25 and 26 (p 23). In 25, the methyl group is broadened more than C-4 even though both are δ carbons. As with the examples of Morishima, a "W" arrangement of the amino and methyl groups allows more efficient transfer of the effects of the unpaired electron. In 24 (p 23), steric interference caused the $Cu(acac)_2$ to favor the side away from the methyl group. This explains why C-2 is broadened more than C-6 and C-3 more than C-5. It was not possible to distinguish between C-4 and C-5 in 24 (p 23). The assignments made in this manner agree with those of a later study which used chemical shift data only.[44]

Doddrell obtained his line broadening data by running a series of nmr spectra for each compound and observing the "rate" at which each line broadened with increasing amounts of $Cu(acac)_2$. Detailed data were given for 22 and 24 (p 23), which are shown in Table I (p 25). While not defined, the "concentrations" given are assumed to be the mole ratio of $Cu(acac)_2$ to amine. Cyclohexane was used as an internal linewidth standard.

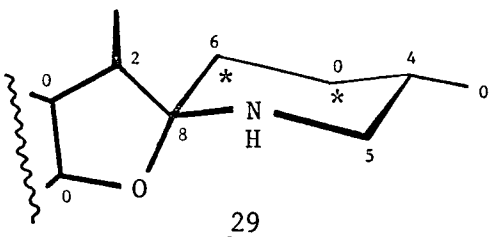
An example of Doddrell's method being used to assign ^{13}C resonances in a complex molecule is provided by Wenkert.[45] Partial

TABLE I

C-13 LINE BROADENING DATA FROM DODDRELL'S WORK

Amine	$Cu(acac)_2$ Concentration	^{13}C Linewidth ΔW (Hz)						
		1 α	2 β	3 γ	4 δ	5 γ	6 β	Me γ
Cyclohexylamine (22)	2×10^{-7}	0.0	0.5	0.0	0.0	0.0	0.5	-
	2×10^{-6}	0.0	1.0	0.0	0.0	0.0	1.0	-
	2×10^{-5}	0.0	2.0	0.0	0.0	0.0	2.0	-
	2×10^{-4}	1.0	3.5	0.0	0.0	0.0	3.5	-
	1×10^{-3}	4.0	6.0	0.0	0.0	0.0	6.0	-
	2×10^{-2}	9.0	15.0	1.0	0.0	1.0	15.0	-
trans-2-methyl-cyclohexylamine (24)	4×10^{-5}	0.0	2.0	0.0	0.0	0.0	0.0	0.0
	1×10^{-4}	0.5	2.5	0.0	0.0	0.0	0.0	0.0
	3×10^{-4}	0.5	8.5	0.5	0.0	0.0	1.0	0.0
	2×10^{-3}	4.5		0.5	0.0	0.0	3.0	0.0
	9×10^{-3}			4.0	0.0	0.0	4.0	0.0

structure 29 shows the amount of line broadening in Hz with 0.11 equivalents of $Cu(acac)_2$. The carbons of interest are shown with asterisks. Larger amounts of $Cu(acac)_2$ were needed than in Doddrell's examples which is indicative of a sterically hindered amino group.



29

CHAPTER IV

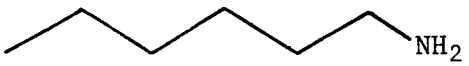
RESULTS AND DISCUSSION

A. Overview

A method was desired of distinguishing between epimeric amines in rigid systems based on the ^{13}C nmr line broadening effect of $Cu(acac)_2$ The most straightforward numerical value for the amount of line broadening is the slope of the line obtained by plotting the increase in linewidth versus the mole ratio of $Cu(acac)_2$ to amine. Hopefully, after examination of a set of model compounds, a characteristic range of values would be apparent for both axial and equatorial cyclohexylamines. Based on previous results the differences would be greatest for the γ carbons. The following discussion begins with a brief account of how the data were obtained followed by the data in tabular and graphical form. The next parts discuss some unexpected problems and the experiments designed to determine their cause. The last part concerns the application of the data to the stereochemical problem mentioned above.

B. Data

Line broadening data were obtained on amines 22 and 30-42 (Figure 6, p 28). The $Cu(acac)_2$ to amine ratio ranged from about 10^{-5} to 10^{-2}. Typical concentrations were approximately 0.5 g of the amine in 3 ml of chloroform-d and $Cu(acac)_2$ in chloroform-d such that one µl gave a $Cu(acac)_2$ to amine ratio of 10^{-5}. The $Cu(acac)_2$ was added



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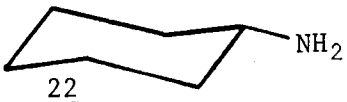

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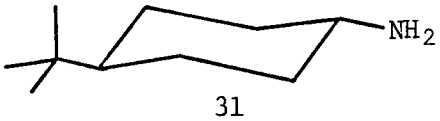

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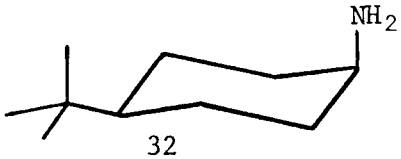

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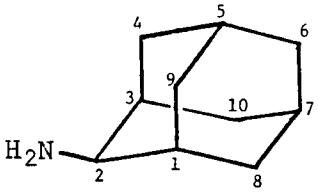

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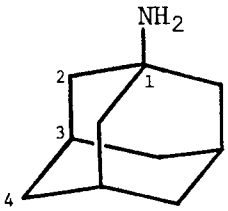

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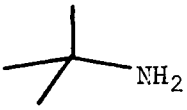

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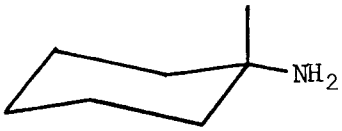

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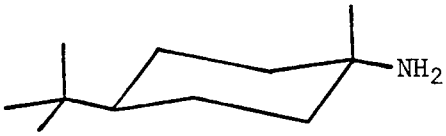

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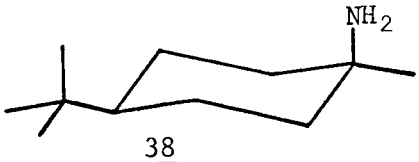

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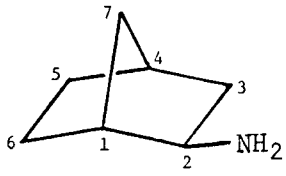

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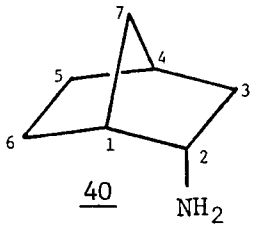

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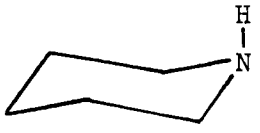

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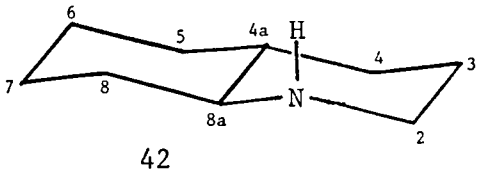

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Figure 6. Amines used in this work.

with a microliter syringe and the quantities were chosen in a logarithmic manner to "evenly" cover about three decades. A typical "run" of 10-15 spectra took about 10 hours. The linewidths were calculated using a routine in the Nicolet NTCFT computer program. The data show the increase in linewidth, ΔW, which was found by subtracting the linewidth without $Cu(acac)_2$ from the spectra with $Cu(acac)_2$ and then applying a correction based on the change in linewidth of an internal standard (dioxane or cyclohexane). The data for compounds 22 and 30-42 (p 28) are shown in Tables II-IV (pp 30-32), Figures 7-17 (pp 33-42), Tables V and VI (pp 43 and 44), Figures 18-20 (pp 45-47), Table VII (p 48), Figure 21 (p 49), Tables VIII and IX (pp 50 and 51), Figures 22 and 23 (pp 52 and 53), Tables X and XI (pp 54 and 55), Figures 24-26 (pp 56-58), Tables XII and XIII (pp 59 and 60), and Figures 27-30 (pp 61-64). Figure 8 (p 34) and Figures 14 and 15 (p 40) [and the figure on p 75] give an indication of the reproducibility of the data. The repeated data in these figures were not used in the later calculations.

C. Increase in Linewidth with Time

On several occasions, samples containing $Cu(acac)_2$ showed significant increases in linewidth on standing overnight. Since most of these samples contained high copper concentrations i.e., the last sample in a run) experiments were done to investigate the effect of time on linewidth at a lower $Cu(acac)_2$ concentration. The results are shown in Figure 31 (p 65), which plots the β carbon linewidth of cyclohexylamine 22 versus time. All samples contained 0.8 g cyclohexylamine, 2 ml of solvent, and a 2.00×10^{-4} mole ratio of $Cu(acac)_2$. The other information is given in Table XIV (p 66). The data in Figure 31 (p 65) show a

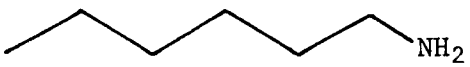

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TABLE II

C-13 LINE BROADENING DATA FOR n-HEXYLAMINE 30

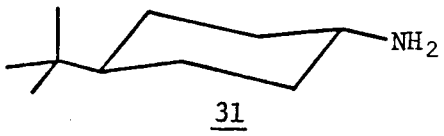
Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)					
	1 α	2 β	3 γ	4 δ	5 ε	6 ζ
1×10^{-5}	.38	1.61	.03	.02	-.02	-.01
1×10^{-4}	3.47	13.04	.16	.03	-.01	.01
3×10^{-4}	8.71	24.19	.33	.04	.02	.00
1×10^{-3}	22.60		.81	.06	.00	.03
3×10^{-3}			1.76	.10	.02	.01
1×10^{-2}			3.74	.16	.02	.03
3×10^{-2}			5.58	.36	.17	.08
1×10^{-1}				.63	.28	.05

22

TABLE III

C-13 LINE BROADENING DATA FOR CYCLOHEXYLAMINE 22

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)			
	1 α	2 β	3 γ	4 δ
1×10^{-5}	.10	.53	.03	.02
2×10^{-5}	.22	.98	.02	.00
5×10^{-5}	.50	2.23	.08	.01
1×10^{-4}	.89	4.32	.15	.01
2×10^{-4}	1.51	7.10	.30	.10
5×10^{-4}	2.88	12.54	.49	.13
1×10^{-3}	4.20	19.06	.61	.00
2×10^{-3}	8.03	36.75	1.01	.03
5×10^{-3}	13.43	50.56	1.65	.06
1×10^{-2}	21.84		2.52	.03
2×10^{-2}			3.55	.18
3×10^{-2}			4.66	.25



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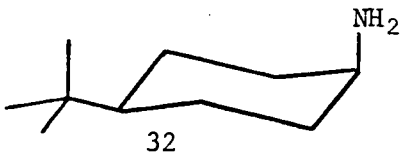

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TABLE IV

C-13 LINE BROADENING DATA FOR 4-t-BUTYLCYCLOHEXYLAMINES 31 AND 32

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)					
	31			32		
	1 α	2 β	3 γ	1 α	2 β	3 γ
1.0×10^{-6}	.01	.03	.01	.02	.04	.01
1.0×10^{-5}	.12	.14	.01	.09	.11	.00
3.0×10^{-5}	.82	1.05	.04	.66	.85	.03
4.0×10^{-5}	.59	1.17	.05	.42	.99	.04
5.0×10^{-5}	1.24	4.44	.14	.88	3.71	.04
6.0×10^{-5}	1.76	7.62	.23	1.55	6.49	.02
7.0×10^{-5}	2.43	10.37	.28	1.64	8.43	.04
8.0×10^{-5}	2.60	11.18	.33	2.25	9.20	.05
1.0×10^{-4}	3.24	14.54	.40	1.99	12.08	.02
1.3×10^{-4}	4.07	19.04	.52	3.87	16.07	.02
1.7×10^{-4}	6.70	24.88	.73	5.81	31.71	.05
2.3×10^{-4}	8.67	42.51	.82	7.97		.04
3.0×10^{-4}	11.22		1.14	8.90		.08
4.0×10^{-4}	13.45		1.54			.07
6.0×10^{-4}	22.05		2.52			
9.0×10^{-4}			6.53			.09
1.3×10^{-3}						.10
2.0×10^{-3}						.22
4.0×10^{-3}						.32
7.0×10^{-3}						.49
1.2×10^{-2}						.87

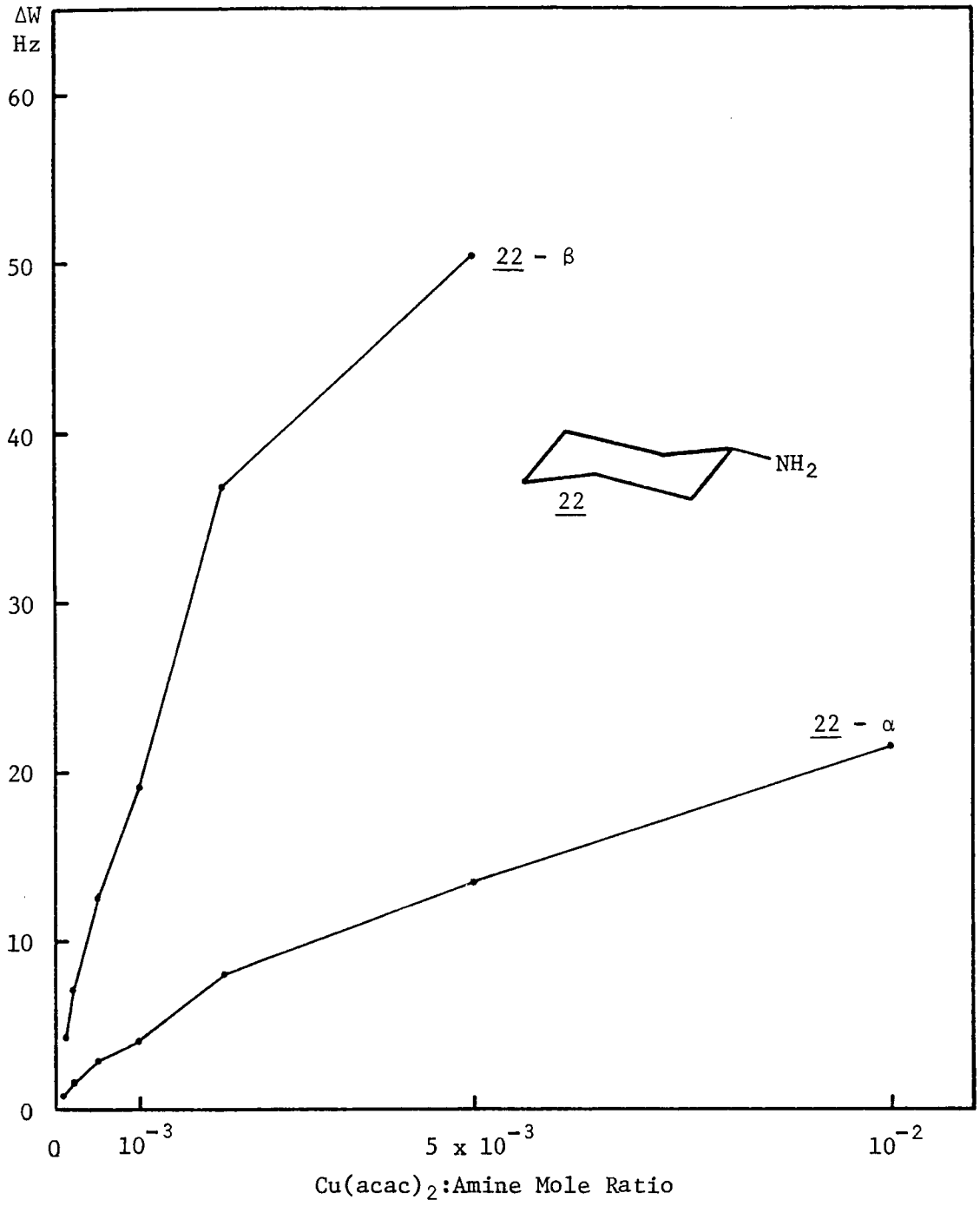


Figure 7. Data for the α and β carbons of cyclohexylamine 22.

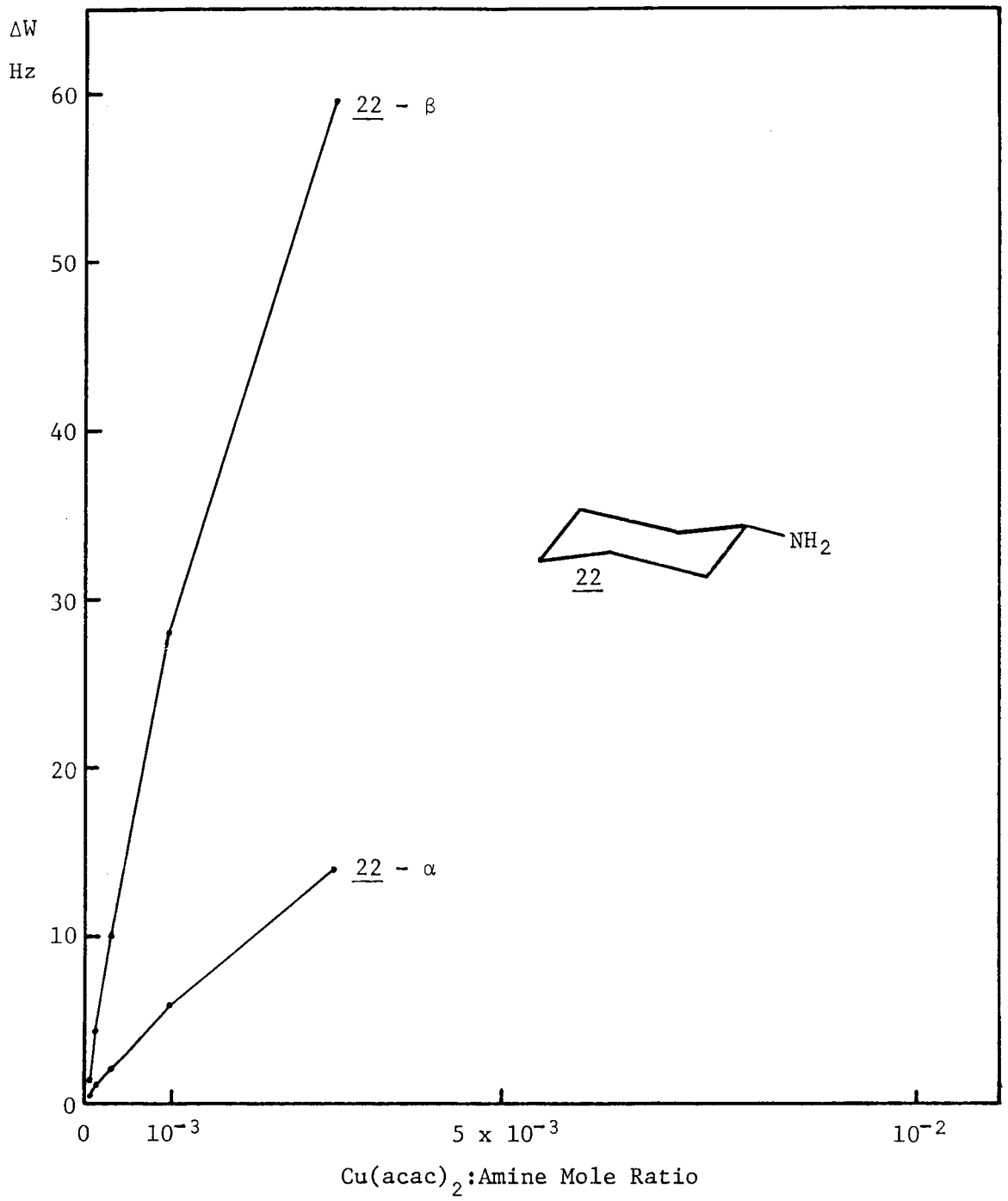


Figure 8. Data for the α and β carbons of cyclohexylamine 22 (repeat).

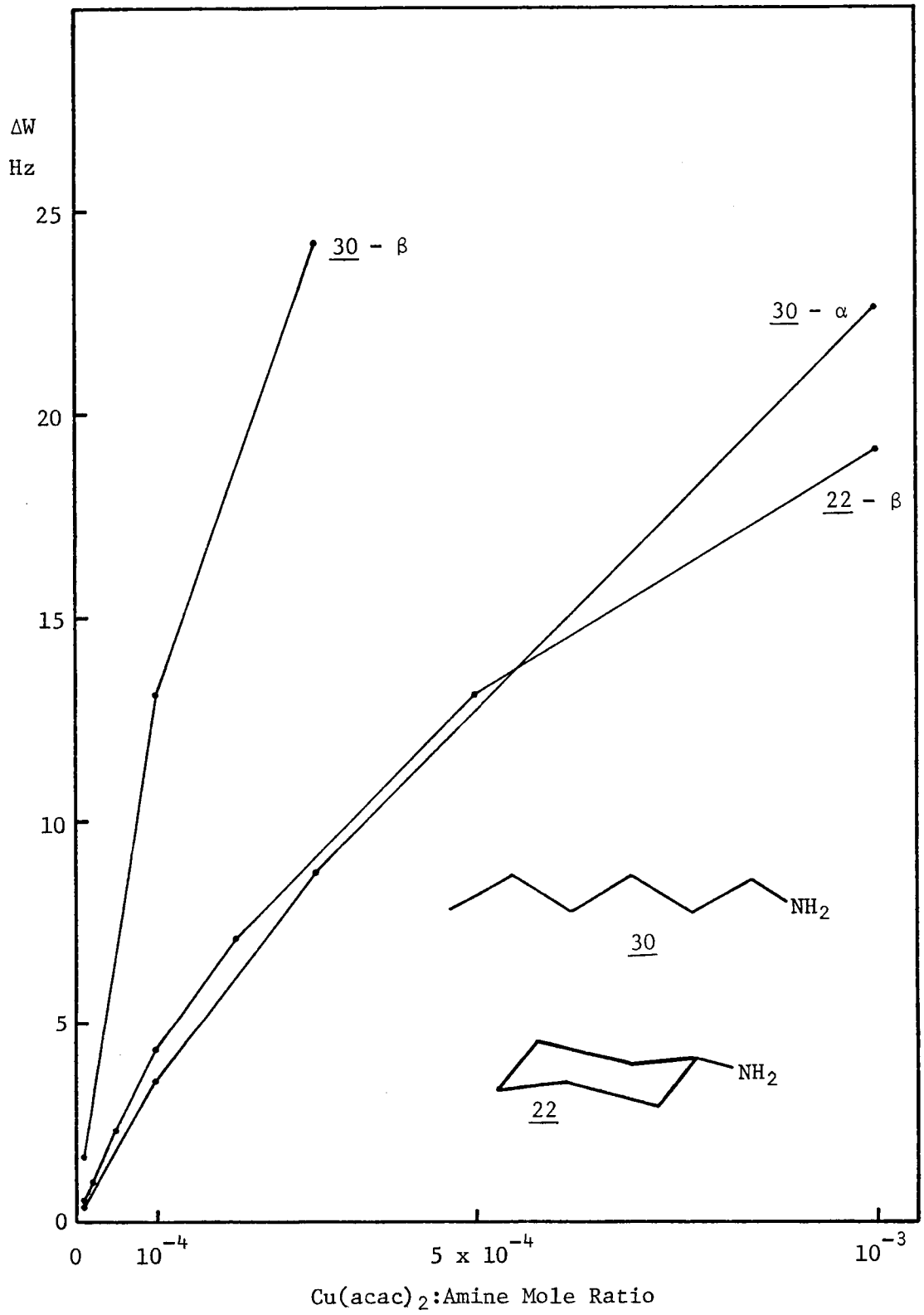


Figure 9. Data for the α carbon of cyclohexylamine 22 and the α and β carbons of n-hexylamine 30.

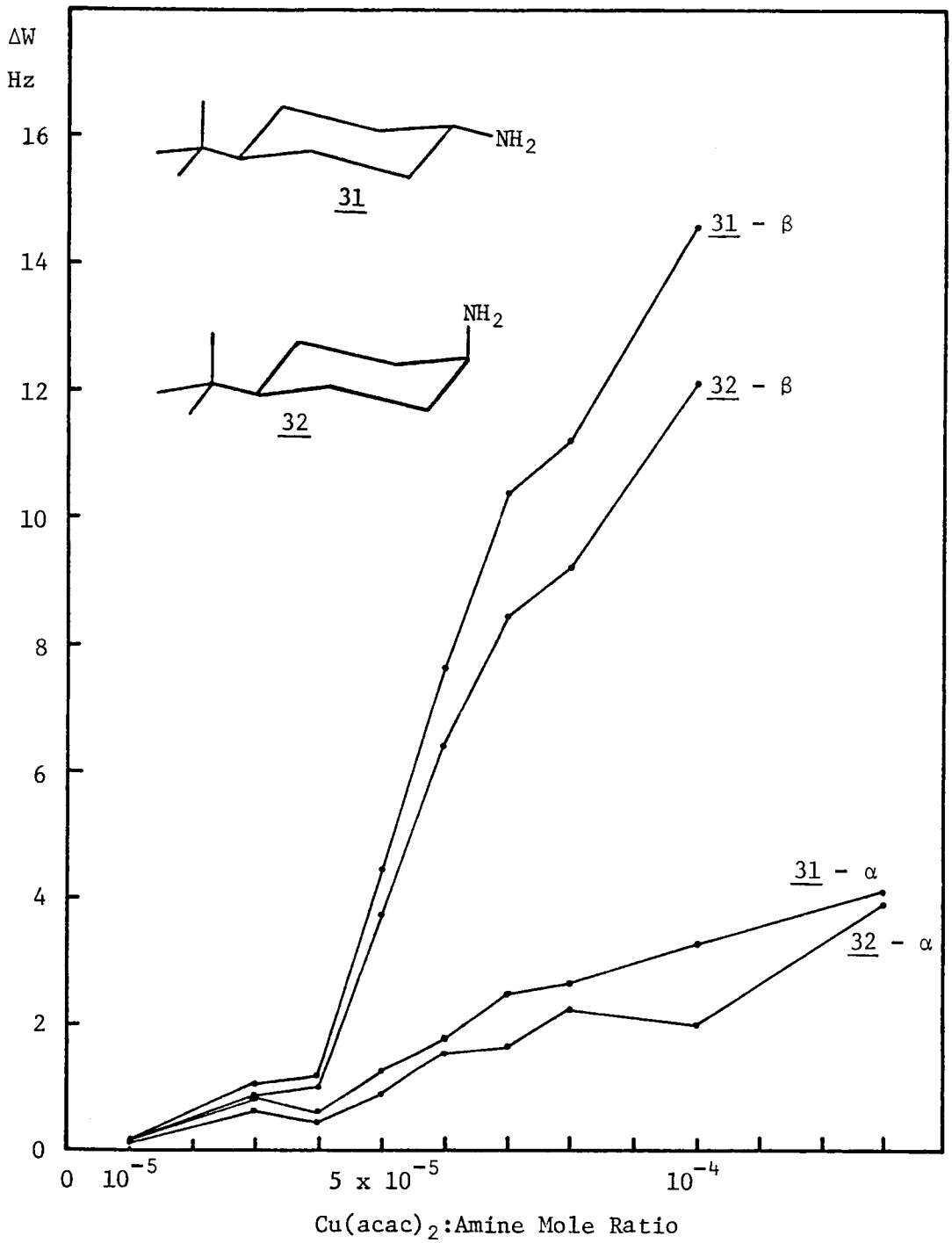


Figure 10. Data for the α and β carbons of 4-t-butylcyclohexylamines 31 and 32 (first part).

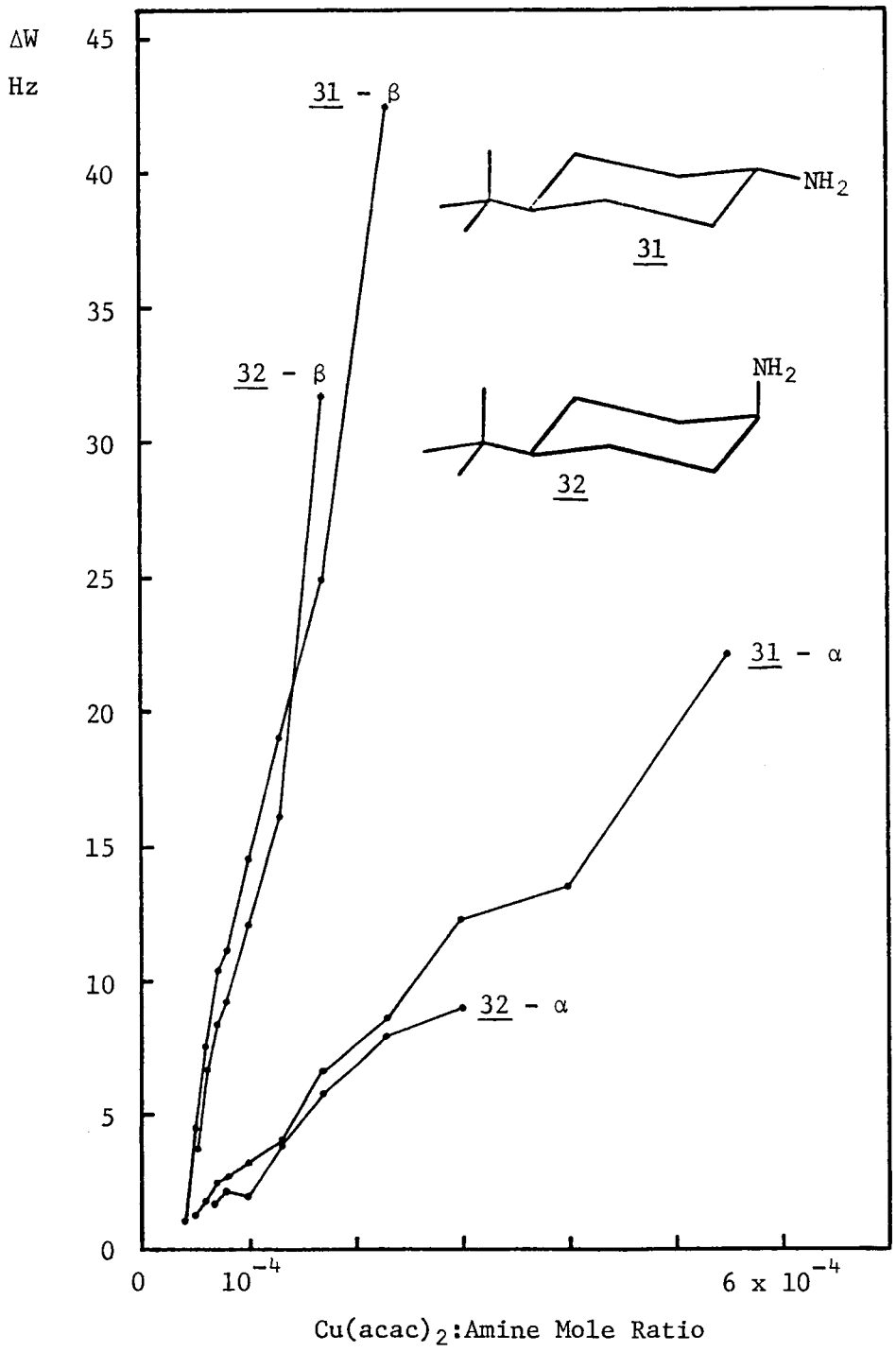


Figure 11. Data for the α and β carbons of 4-t-butylcyclohexylamines 31 and 32 (second part).

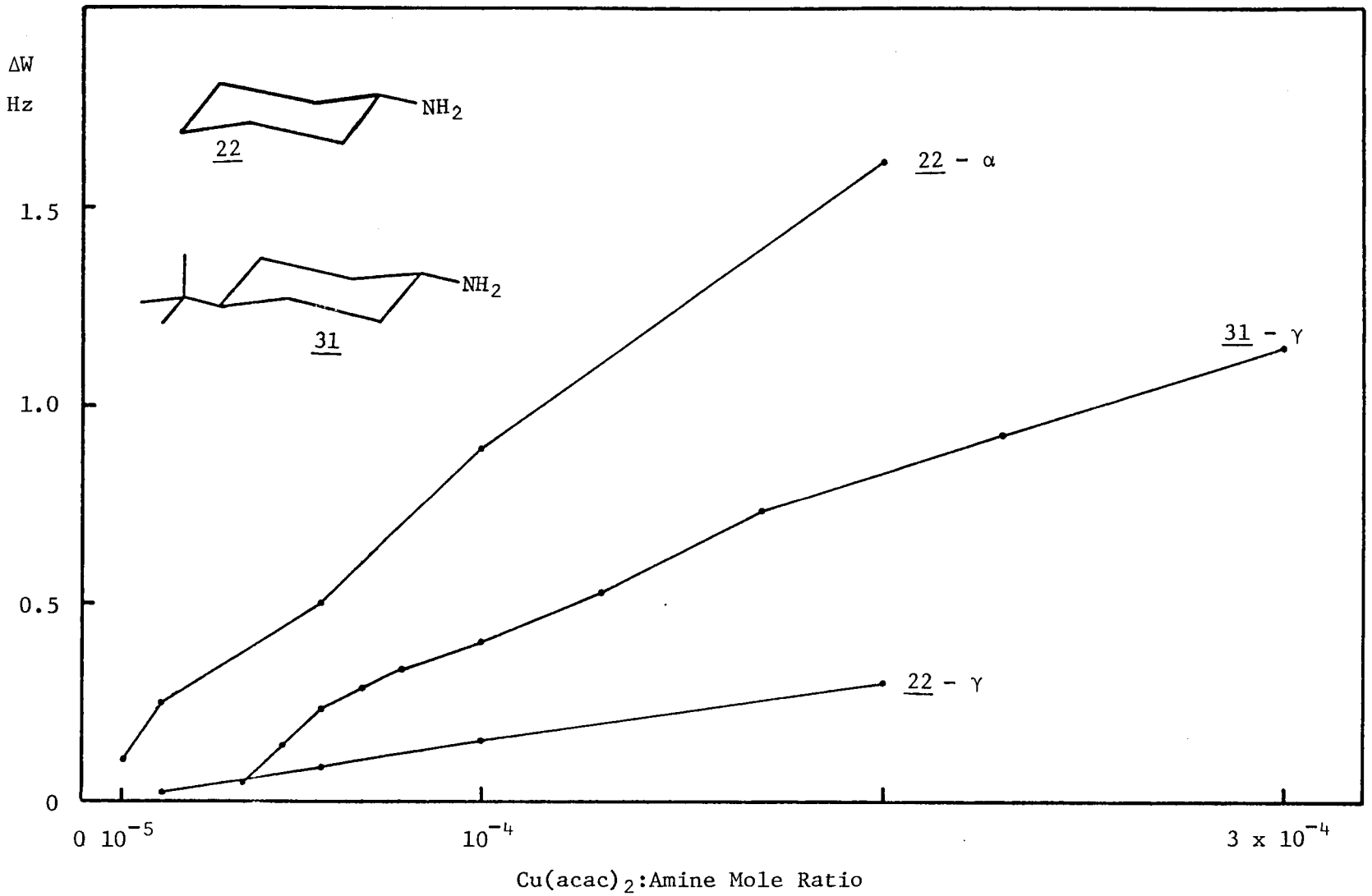


Figure 12. Data for the α and γ carbons of cyclohexylamine 22 and the γ carbon of trans-4-t-butyl-cyclohexylamine 31.

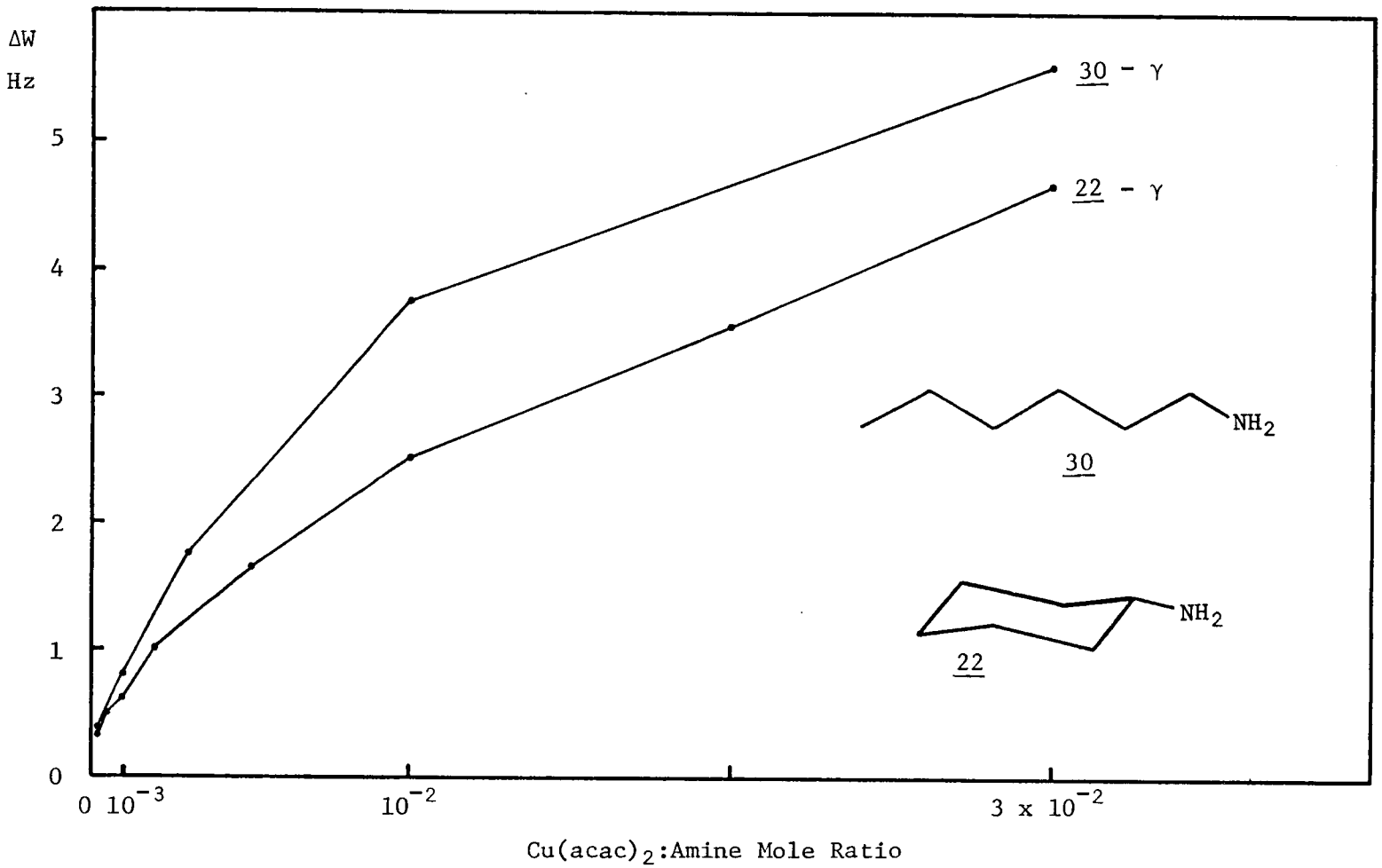


Figure 13. Data for the γ carbons of cyclohexylamine 22 and n-hexylamine 30.

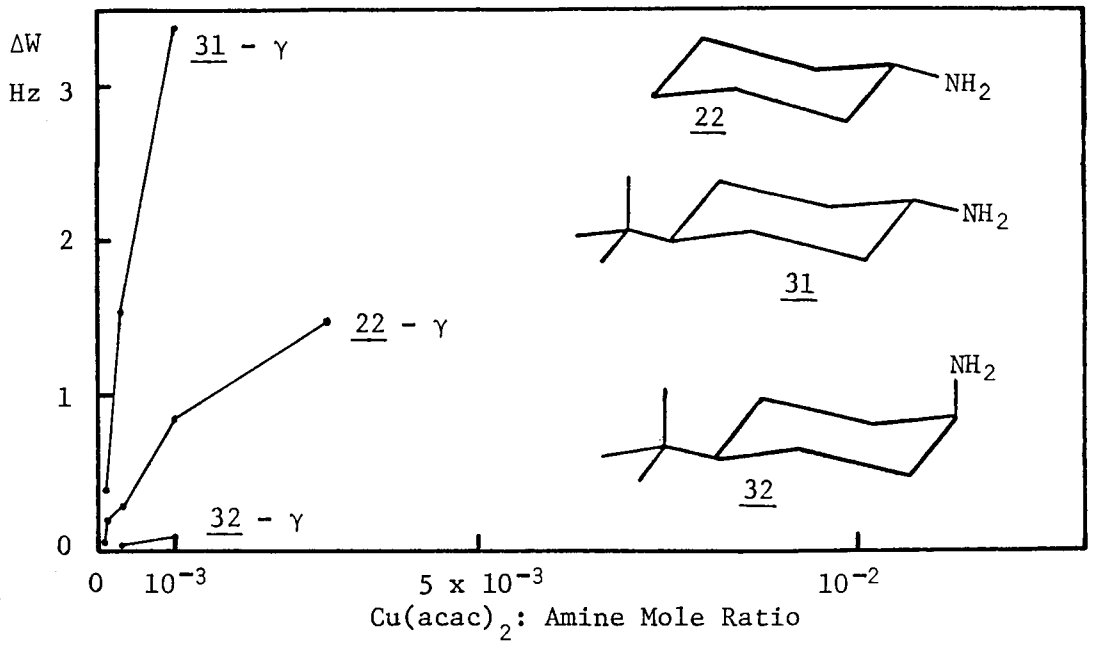


Figure 14. Data for the γ carbons of cyclohexylamine 22 and 4-t-butylcyclohexylamines 31 and 32 (repeat).

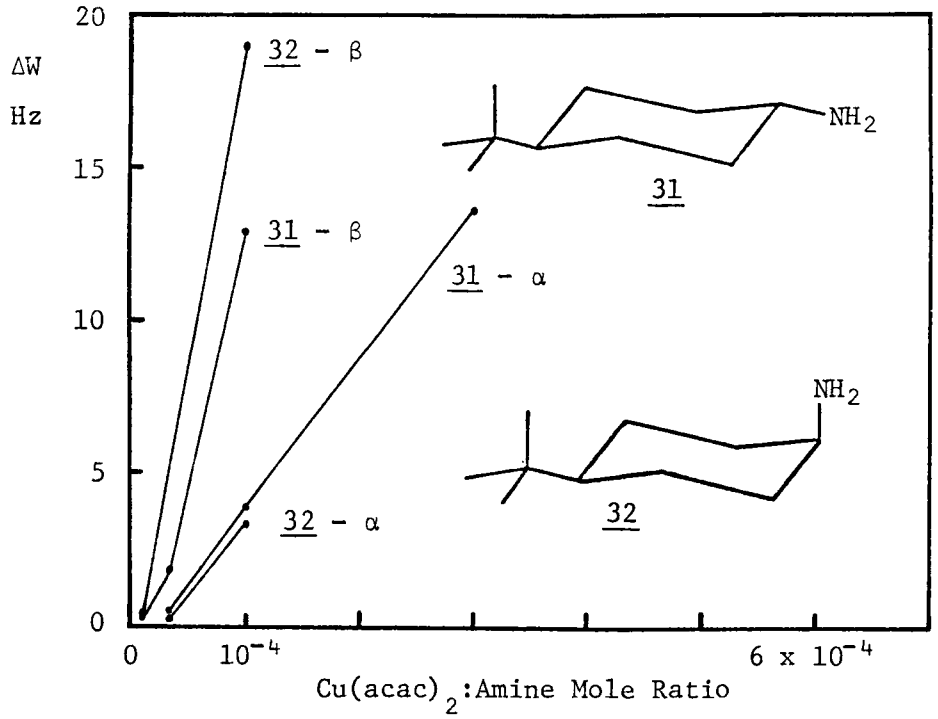


Figure 15. Data for the α and β carbons of 4-t-butylcyclohexylamines 31 and 32 (repeat).

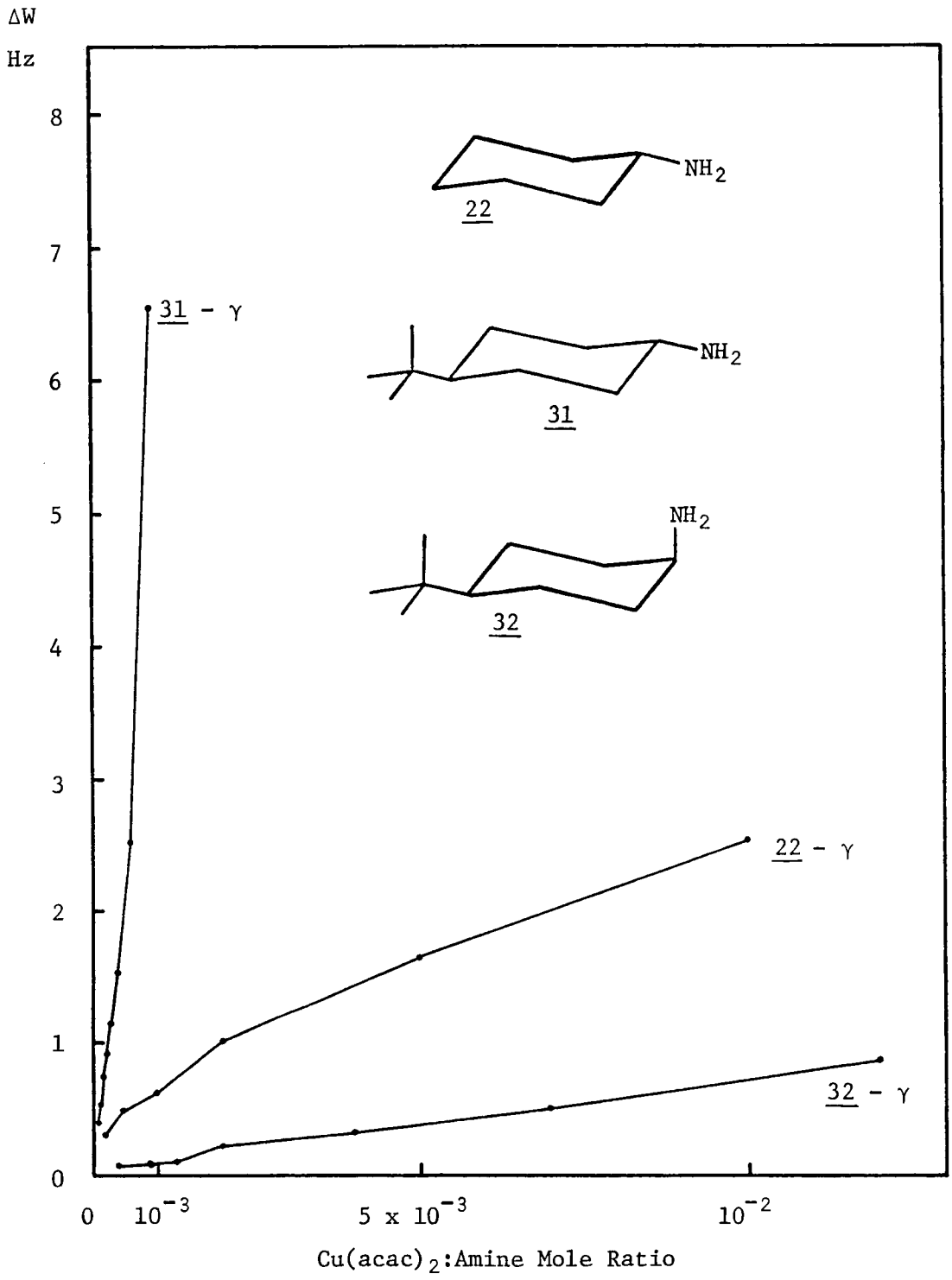


Figure 16. Data for the γ carbons of cyclohexylamine 22 and 4-t-butylcyclohexylamines 31 and 32.

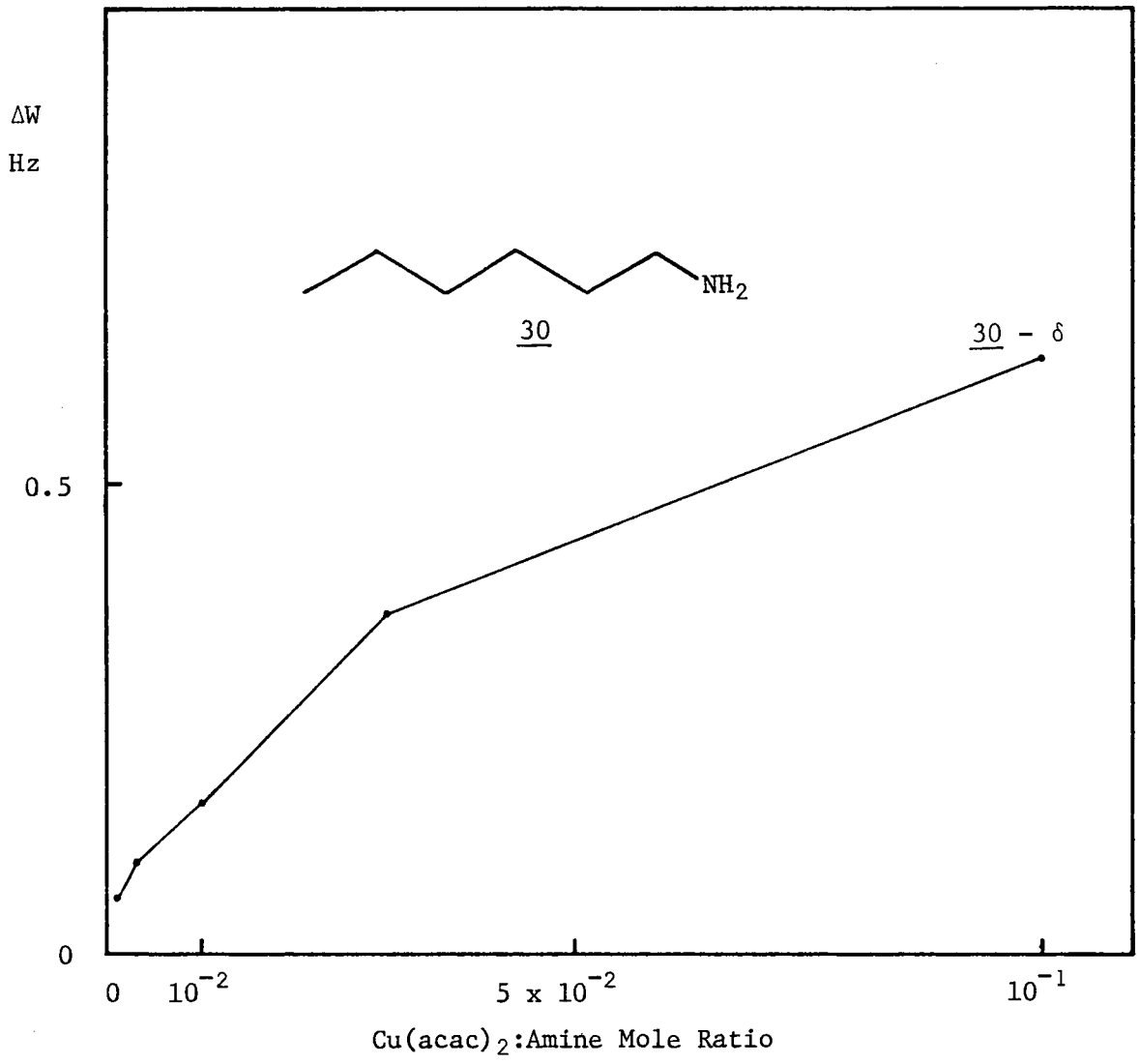
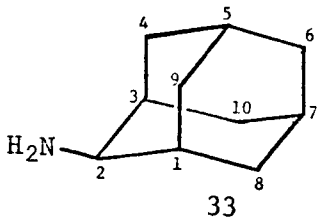


Figure 17. Data for the δ carbon of n-hexylamine 30.

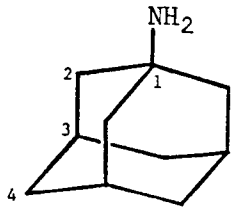


33

TABLE V

C-13 LINE BROADENING DATA FOR 2-ADAMANTYLAMINE 33

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)						
	2 α	1 β	8 γ	9 γ	7 δ	5 δ	6 ε
1×10^{-5}	.47	1.05	-.01	-.03	-.01	-.01	-.02
2×10^{-5}	1.02	2.59	.07	.03	.05	.04	.04
5×10^{-5}	1.85	6.49	.15	.05	.15	.14	.09
1×10^{-4}	3.14	11.79	.21	-.08	.08	.15	.14
2×10^{-4}	6.00	22.73	.37	.02	.06	.09	.12
5×10^{-4}	13.73		.90	.10	.12	.14	.14
1×10^{-3}	19.29		1.69	.13	.09	.04	.13
2×10^{-3}			3.38	.28	.12	.11	.20
5×10^{-3}				.61	.15	.16	.37
1×10^{-2}				.97	.25	.24	.34
2×10^{-2}				1.48	.33	.33	.27



34

TABLE VI

C-13 LINE BROADENING DATA FOR 1-ADAMANTYLAMINE 34

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)			
	1 α	2 β	3 δ	4 δ
1×10^{-5}	-.33	.02	-.05	.02
2×10^{-5}	-.07	.19	-.02	.06
5×10^{-5}	-.25	.35	-.05	.02
1×10^{-4}	-.14	.71	.00	.07
2×10^{-4}	.02	1.34	.00	.11
5×10^{-4}	.23	2.23	.02	.15
1×10^{-3}	.65	3.36	.01	.18
2×10^{-3}	1.14	5.00	.02	.24
5×10^{-3}	3.11	8.86	-.02	.32
1×10^{-2}			.07	.68
2×10^{-2}			.00	.80
4×10^{-2}			.06	

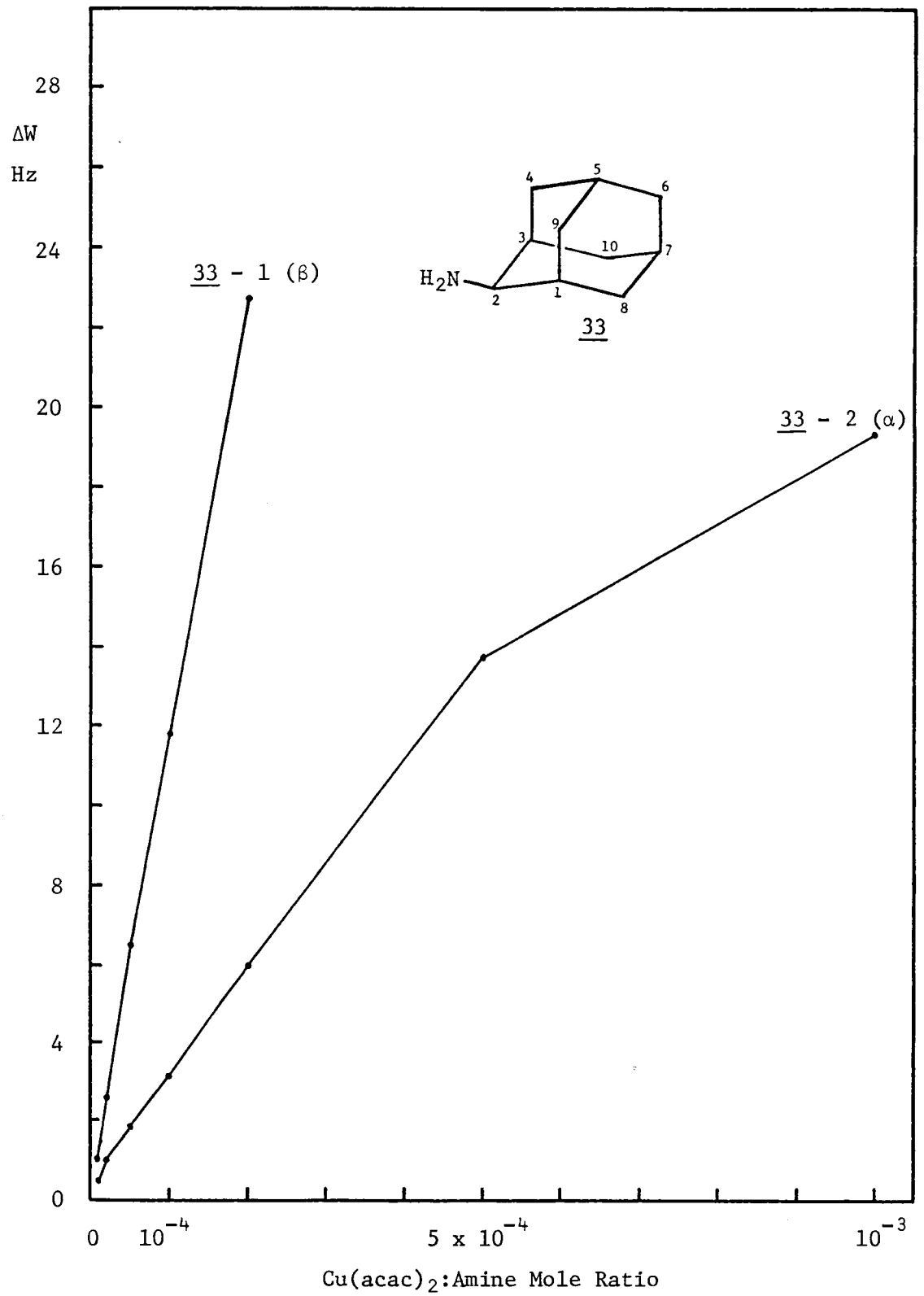


Figure 18. Data for carbons 1 and 2 of 2-adamantylamine 33.

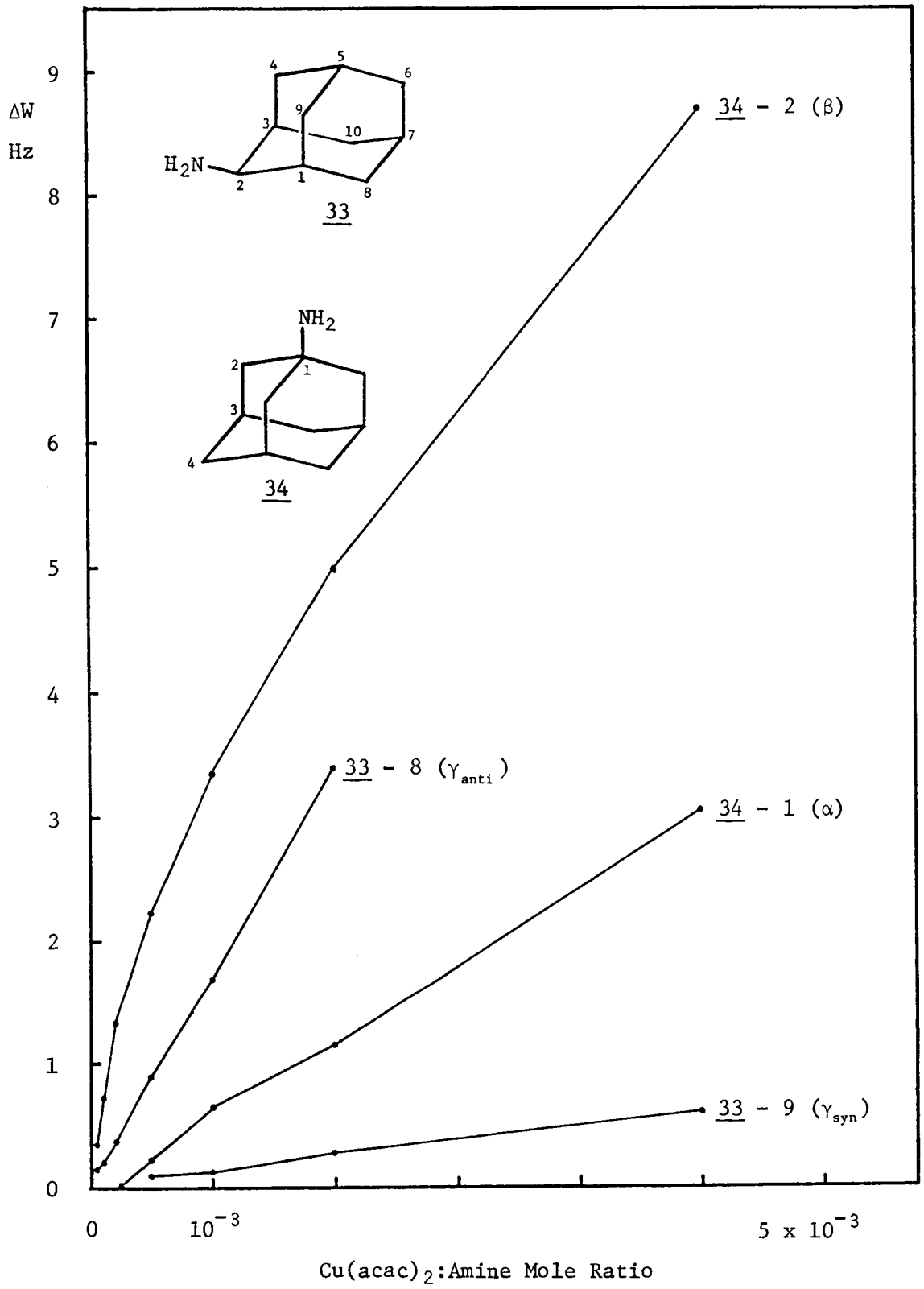


Figure 19. Data for carbons 8 and 9 of 2-adamantylamine 33 and carbons 1 and 2 of 1-adamantylamine 34.

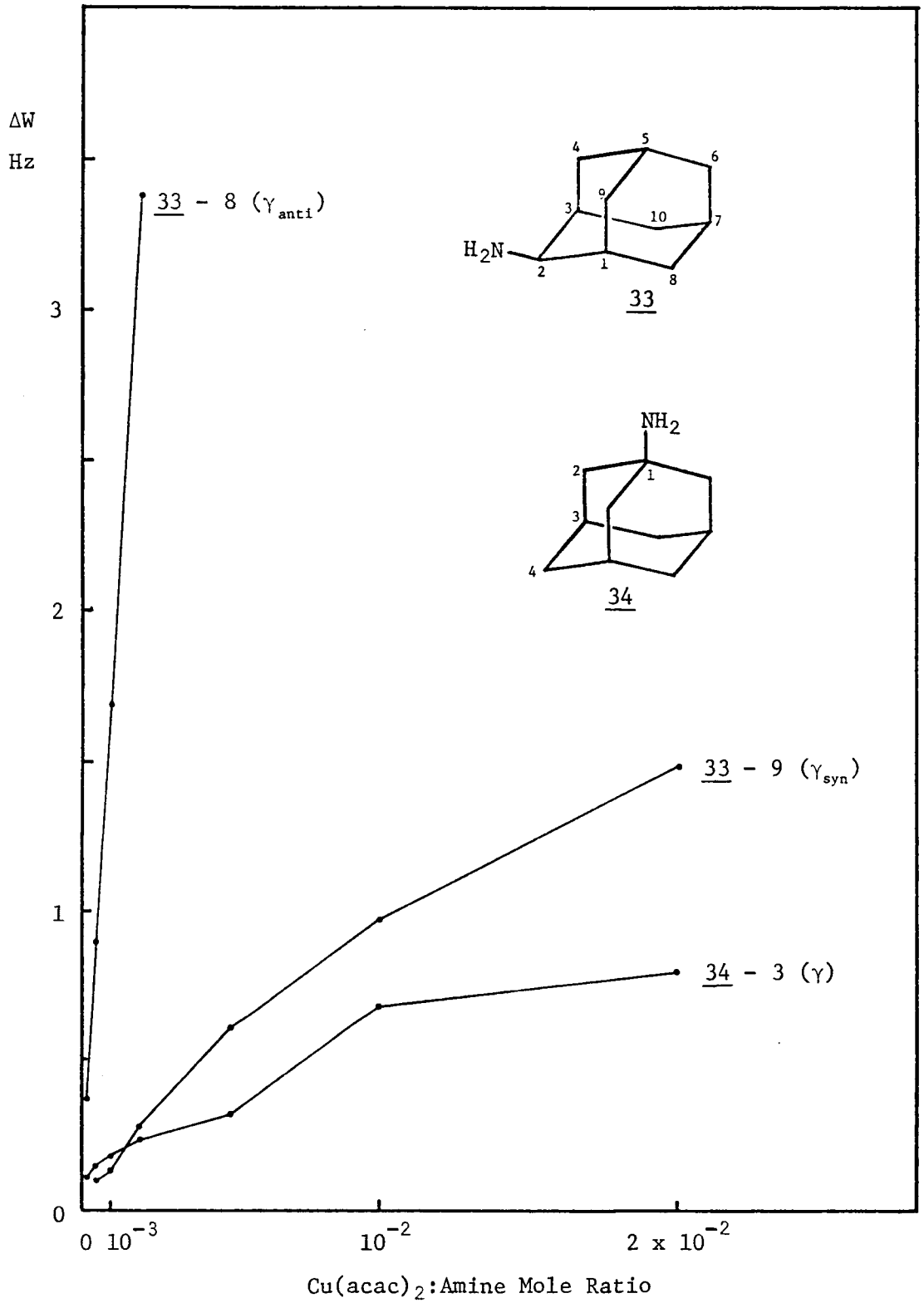
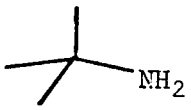


Figure 20. Data for carbons 8 and 9 of 2-adamantylamine 33 and carbon 3 of 1-adamantylamine 34.



35

TABLE VII

C-13 LINE BROADENING DATA FOR t-BUTYLAMINE 35

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)	
	1 α	2 β
1×10^{-5}	-.03	-.02
3×10^{-5}	-.02	.12
1×10^{-4}	.05	.51
3×10^{-4}	.09	1.12
1×10^{-3}	.22	2.50
3×10^{-3}	.50	5.41
1×10^{-2}	1.63	11.87

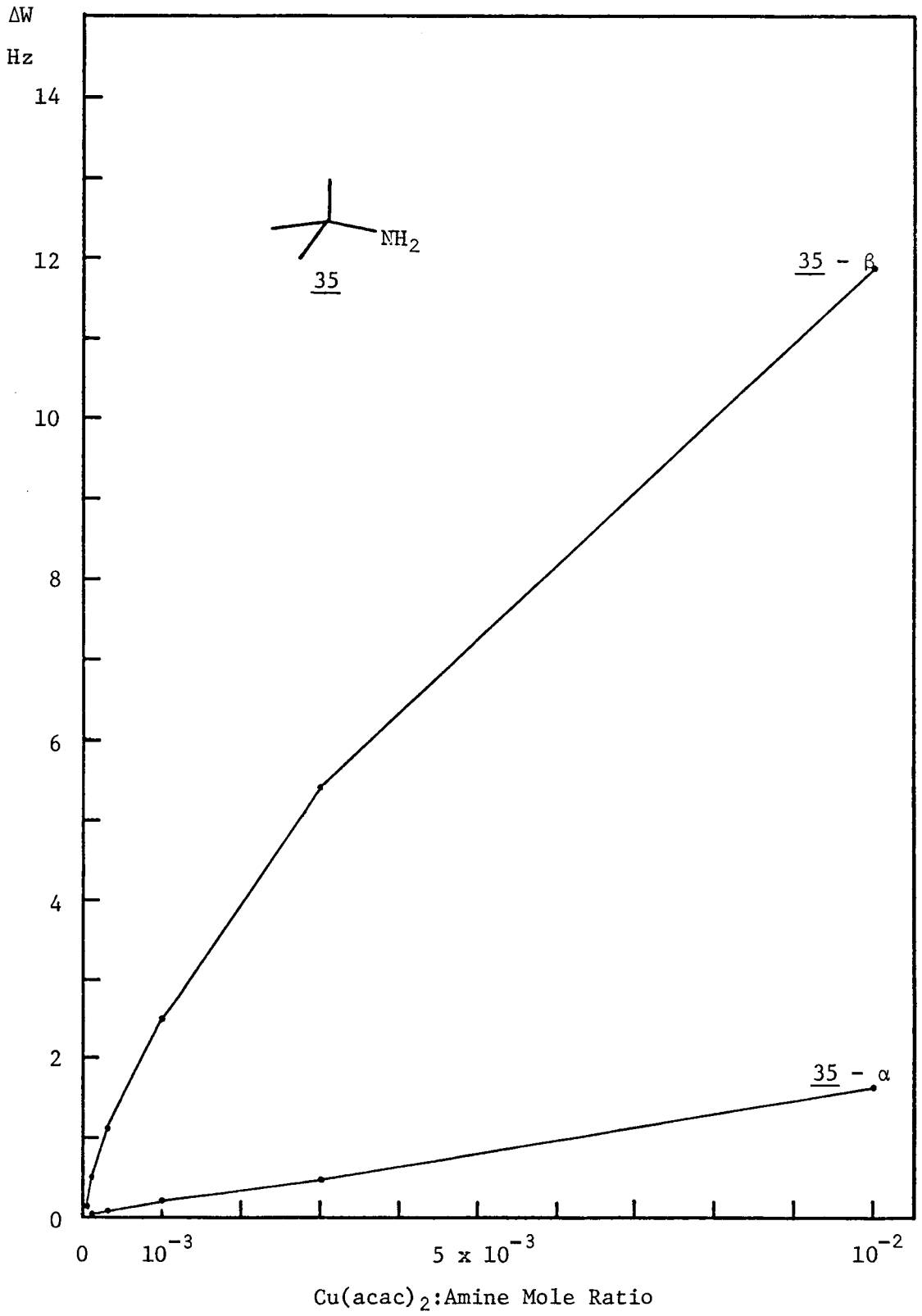


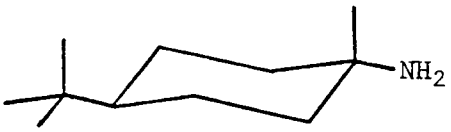
Figure 21. Data for the α and β carbons of t-butylamine 35.

36

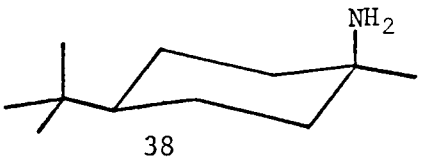
TABLE VIII

C-13 LINE BROADENING DATA FOR 1-METHYLCYCLOHEXYLAMINE 36

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)				
	1 α	2 β	3 γ	4 δ	Me β
1×10^{-5}	.08	.01	-.02	.01	.11
3×10^{-5}	.09	.03	-.01	.03	.04
1×10^{-4}	.08	.25	.01	.05	.14
3×10^{-4}	.12	.75	.03	.03	.29
1×10^{-3}	.26	2.21	.09	.05	.84
3×10^{-3}	.51	5.23	.15	-.01	1.76
1×10^{-2}	1.40	12.72	.41	.02	4.57
3×10^{-2}	3.30	31.51	.88	.01	



37



38

TABLE IX

C-13 LINE BROADENING DATA FOR
1-METHYL-4-t-BUTYLCYCLOHEXYLAMINES 37 AND 38

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)							
	Equatorial Amine 37				Axial Amine 38			
	1 α	2 β	3 γ	Me β	1[a] α	2 β	3 γ	Me[a] β
1×10^{-5}	.09	-.03	-.05	-.05		.25	-.03	
1×10^{-4}	.08	.25	-.01	.03		.54	.01	
1×10^{-3}	.08	1.42	-.03	.09		2.53	.13	
1×10^{-2}	.16	5.63	.01	.45		11.57	.43	
1×10^{-1}	1.41	33.5	.08	2.19			1.83	

a. Not calculated.

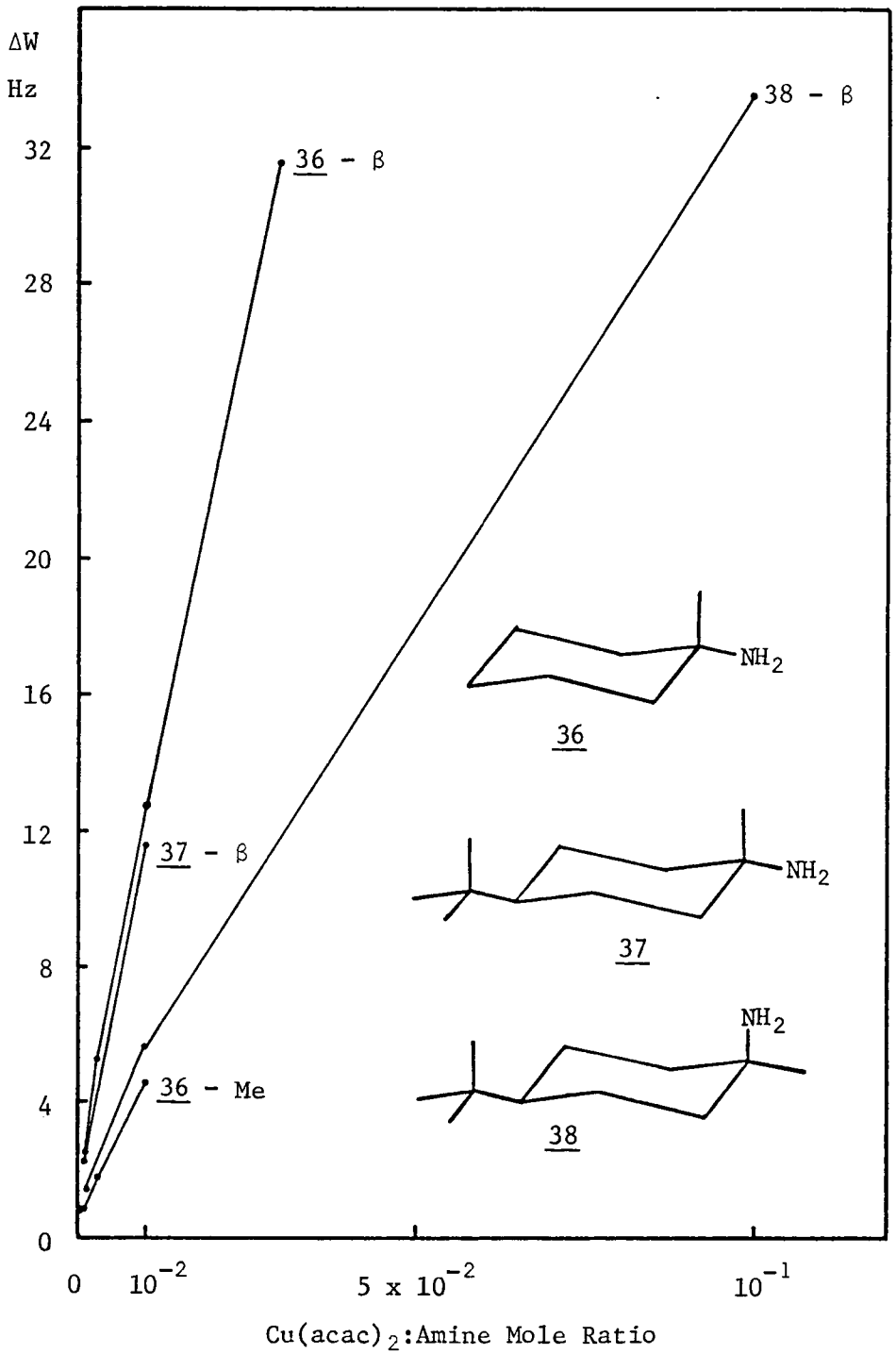


Figure 22. Data for the Me and β carbons of 1-methylcyclohexylamine 36 and the β carbons of 1-methyl-4-t-butylcyclohexylamines 37 and 38.

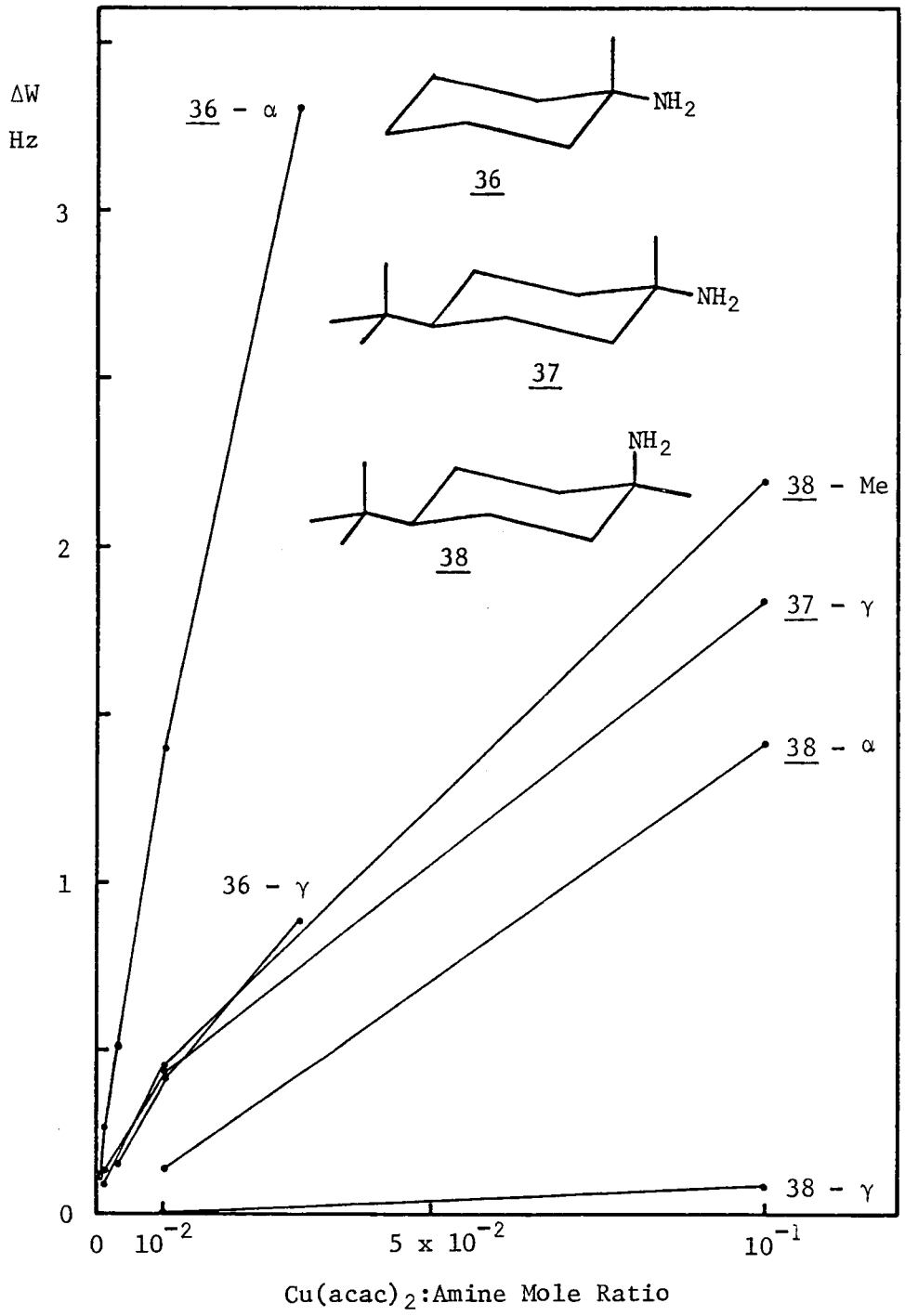
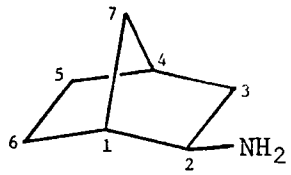


Figure 23. Data for the α and γ carbons of 1-methylcyclohexylamine 36 and α, β, and Me carbons of 1-methyl-4-t-butylcyclohexylamines 37 and 38.

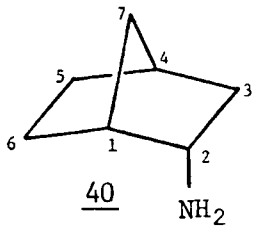


39

TABLE X

C-13 LINE BROADENING DATA FOR exo-NORBORNYLAMINE 39

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)						
	2 α	1 β	3 β	4 γ	7 γ	6 γ	5 δ
1×10^{-6}	.10	.32	.13	.02	.03	.00	.00
3×10^{-6}	.10	.48	.25	-.03	-.01	-.01	-.04
1×10^{-5}	.27	1.23	.62	.03	.01	-.01	.00
2×10^{-5}	.50	2.24	1.50	.03	.02	.01	.03
5×10^{-5}	1.13	5.45	3.42	-.06	-.01	.04	.00
1×10^{-4}	2.09	11.32	7.42	.01	.02	.08	-.01
2×10^{-4}	4.19	24.38	13.75	.03	.08	.21	-.01
5×10^{-4}	9.32			.01	.15	.67	.03
1×10^{-3}	17.36			.04	.21	.80	.03
2×10^{-3}	32.35			.10	.36	1.37	.02
5×10^{-3}				.16	.53	2.35	.07
1×10^{-2}				.28	.87	3.52	.15
2×10^{-2}				.35	1.04	4.49	.17



40

TABLE XI

C-13 LINE BROADENING DATA FOR endo-NORBORNYLAMINE 40

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)						
	2 α	1 β	3 β	7 γ	4 γ	6 γ	5 γ
1×10^{-6}	.01	-.02	-.12	.00	-.01	-.02	.01
3×10^{-6}	.03	.05	-.21	.01	.02	-.05	.02
1×10^{-5}	.06	.15	-.10	.02	-.02	-.02	.01
3×10^{-5}	1.14	4.24	1.13	.01	-.01	-.04	-.03
6×10^{-5}	2.46	10.07	3.04	.03	.02	.00	.01
1×10^{-4}	4.44	16.63	5.69	.05	-.02	.00	-.02
2×10^{-4}	8.12	41.89	12.83	.13	.04	.03	-.03
5×10^{-4}	16.60		51.78	.38	.04	.16	.01
1×10^{-3}	37.62			.69	.12	.26	.02
2×10^{-3}				1.30	.35	.54	.14
5×10^{-3}				2.81	.71	1.09	.17
1×10^{-2}				6.03	1.14	1.65	.22
2×10^{-2}				8.10	1.95	2.15	.29

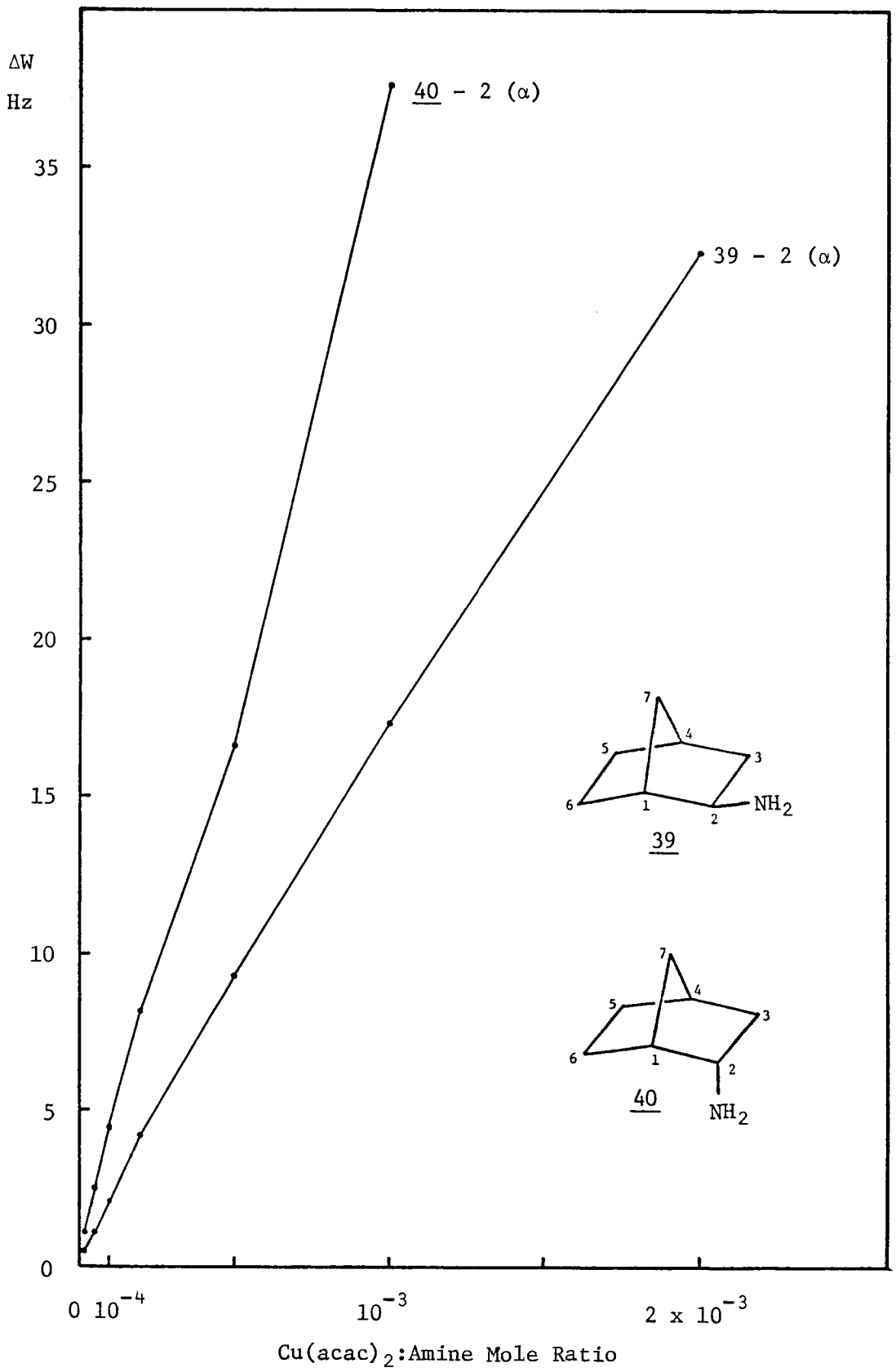


Figure 24. Data for the α carbons of norbornylamines 39 and 40.

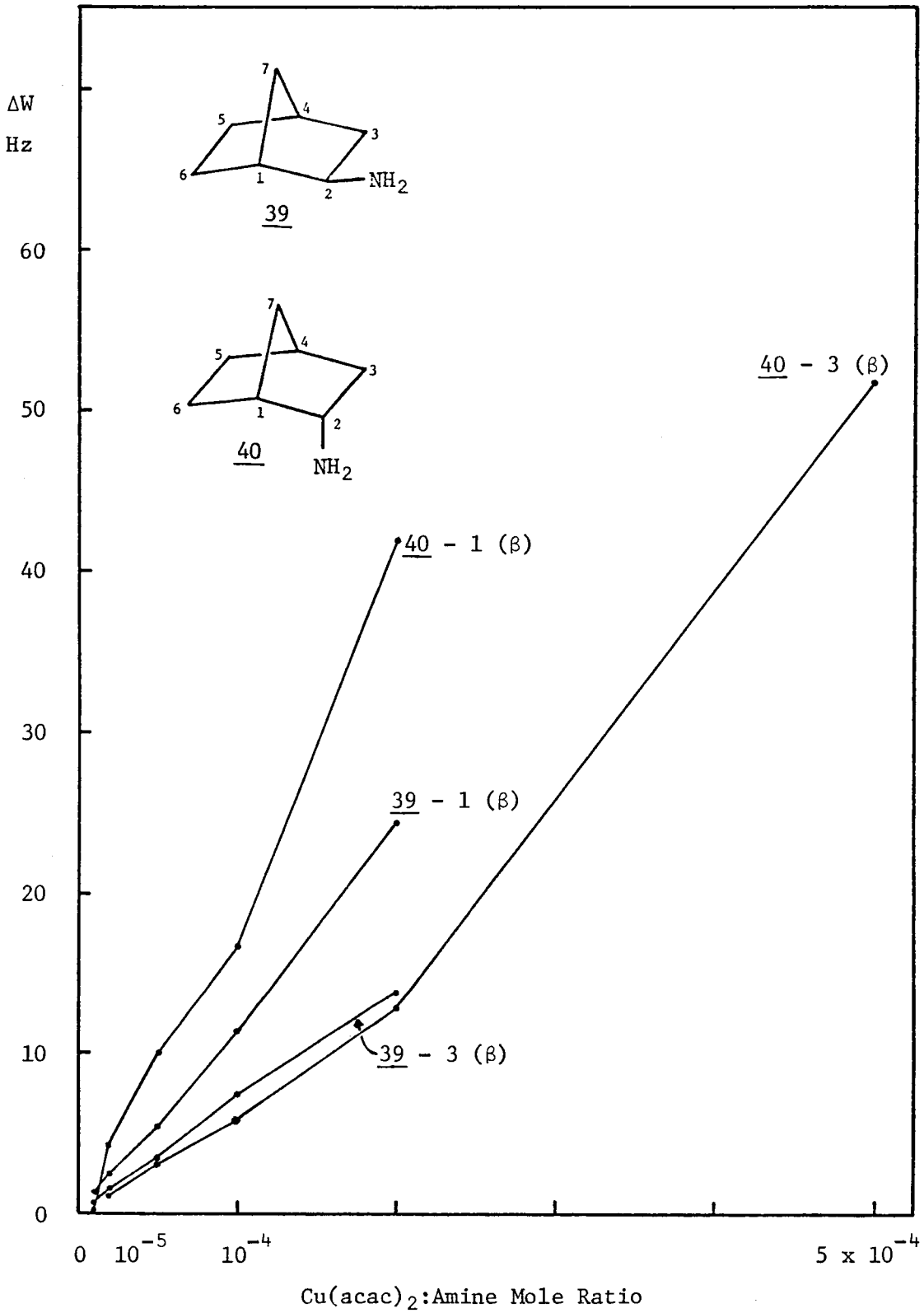


Figure 25. Data for the β carbons of norbornylamines 39 and 40.

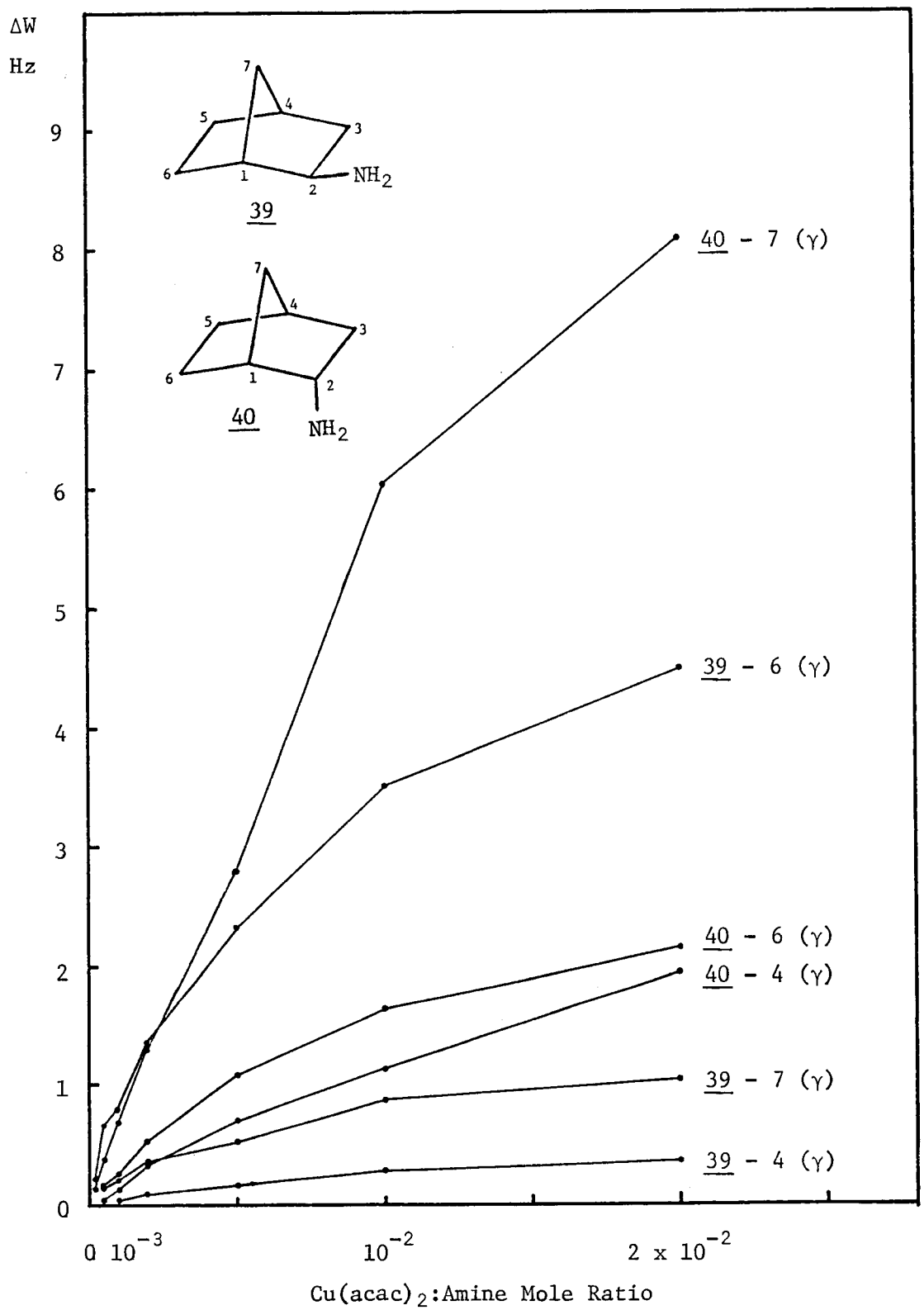
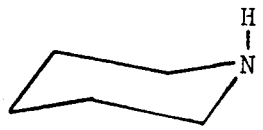


Figure 26. Data for the γ carbons of norbornylamines 39 and 40.

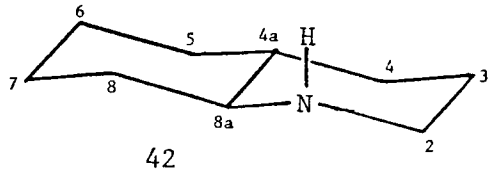


41

TABLE XII

C-13 LINE BROADENING DATE FOR PIPERIDINE 41

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)		
	2 α	3 β	4 γ
1×10^{-5}	.35	.70	.00
3×10^{-5}	.92	2.14	-.01
1×10^{-4}	4.43	10.86	.05
3×10^{-4}	8.16	22.12	.09
1×10^{-3}	13.61	52.69	.29
3×10^{-3}	29.57		.54
1×10^{-2}			1.13



42

TABLE XIII

C-13 LINE BROADENING DATA FOR DECAHYDROQUINOLINE 42

Mole Ratio $Cu(acac)_2$: Amine	^{13}C Linewidth ΔW (Hz)								
	8a α	2 α	4a β	8 β	3 β	5 γ	4 γ	7 γ	6 δ
1×10^{-5}	.11	.49	.63	.03	.51	.17	.20	.00	.00
2×10^{-5}	.39	.80	1.16	.13	1.05	.30	.18	.02	.00
5×10^{-5}	1.01	2.19	2.87	.33	2.21	.82	.43	.05	.02
1×10^{-4}	2.00	4.03	6.32	.54	5.04	1.14	.71	.10	.00
2×10^{-4}	4.30	6.81	9.34	1.13	9.25	2.72	1.36	.23	.03
5×10^{-4}	7.72	13.07	17.61	1.95	14.82			.31	.03
1×10^{-3}	13.67	22.92		3.45	20.44			.53	.03
2×10^{-3}	18.99			4.83				.69	.04
5×10^{-3}	22.25			8.88				1.20	.08

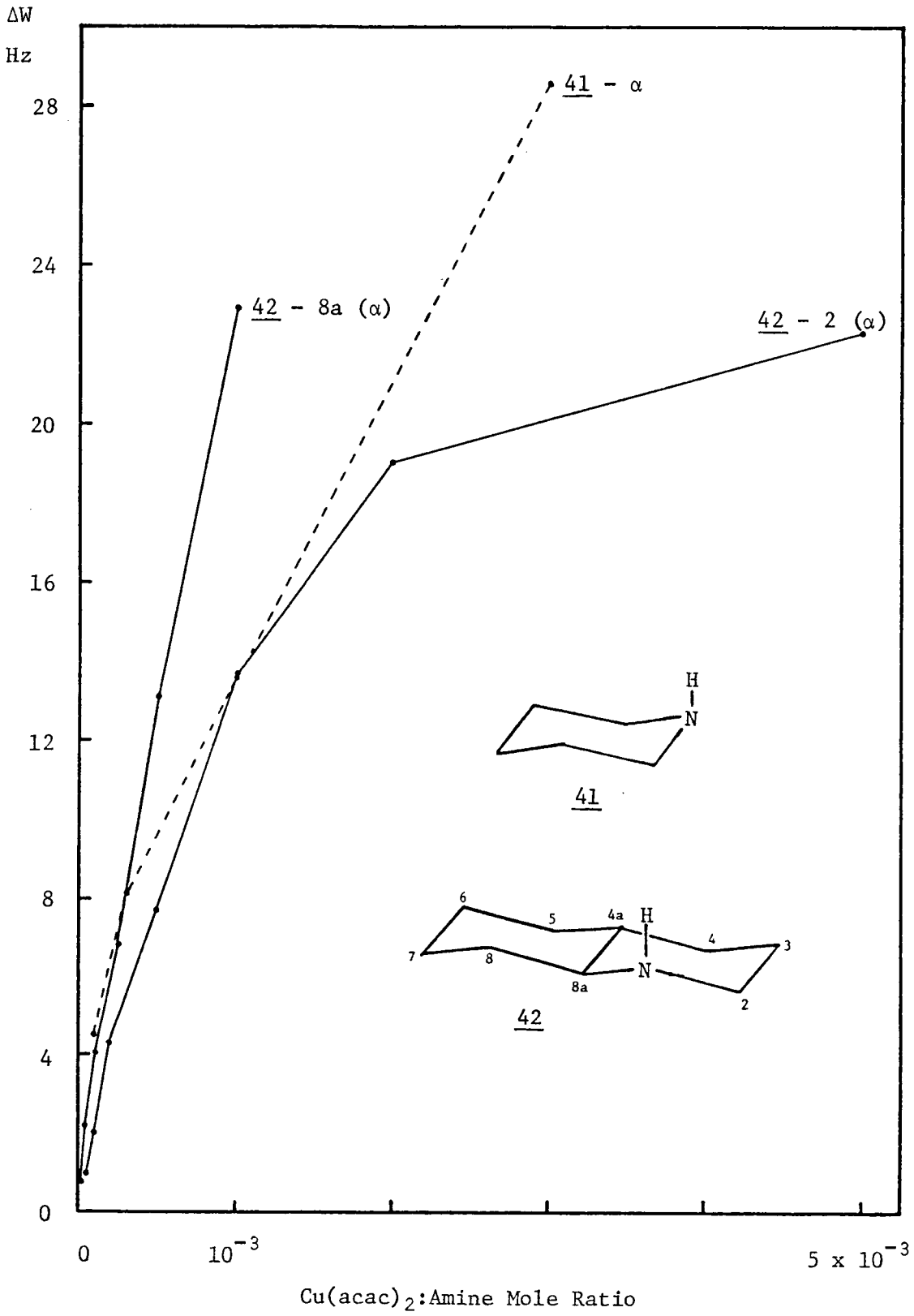


Figure 27. Data for the α carbon of piperidine 41 and carbons 2 and 8a of decahydroquinoline 42.

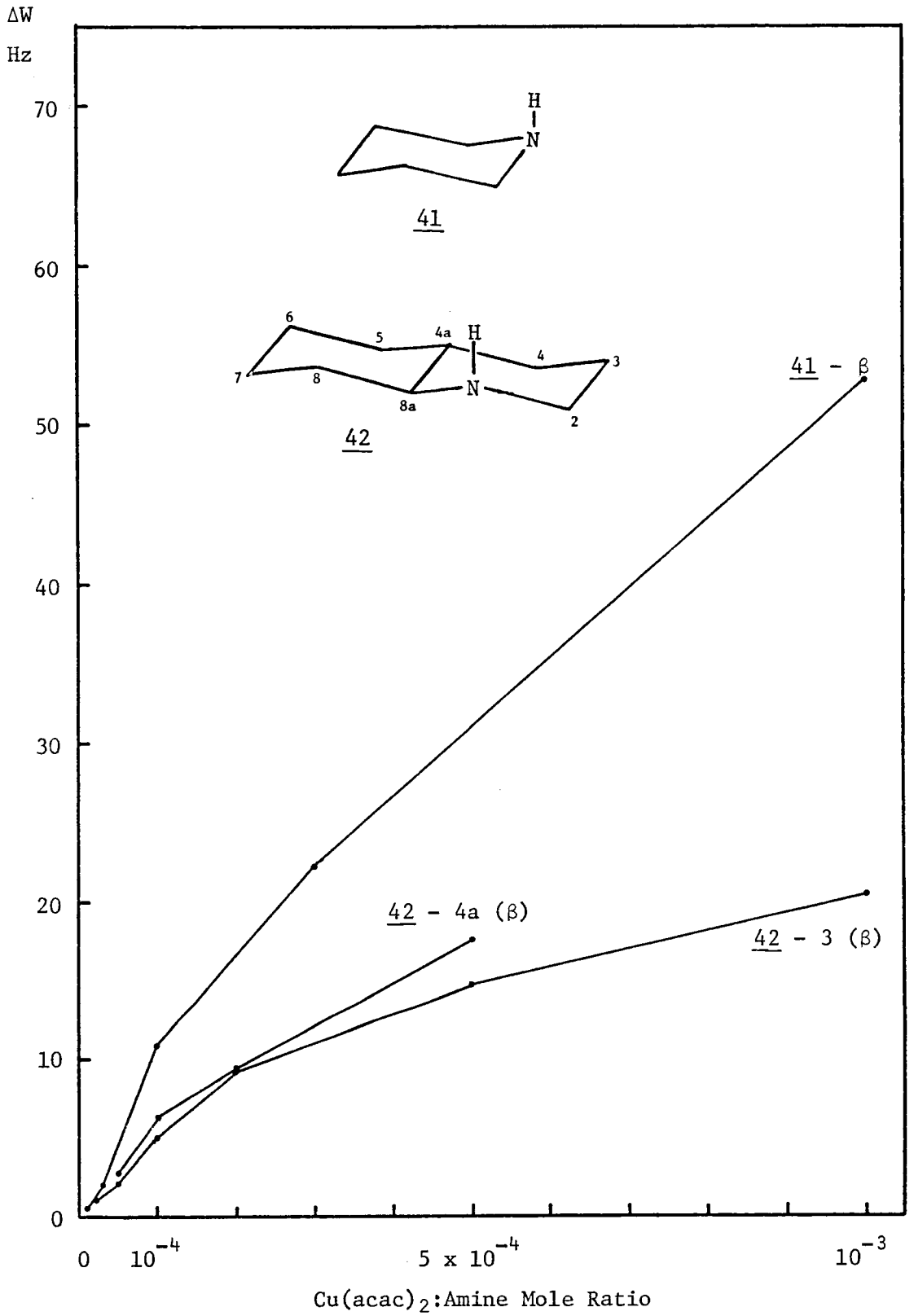


Figure 28. Data for the β carbon of piperidine 41 and carbons 3 and 4a of decahydroquinoline 42.

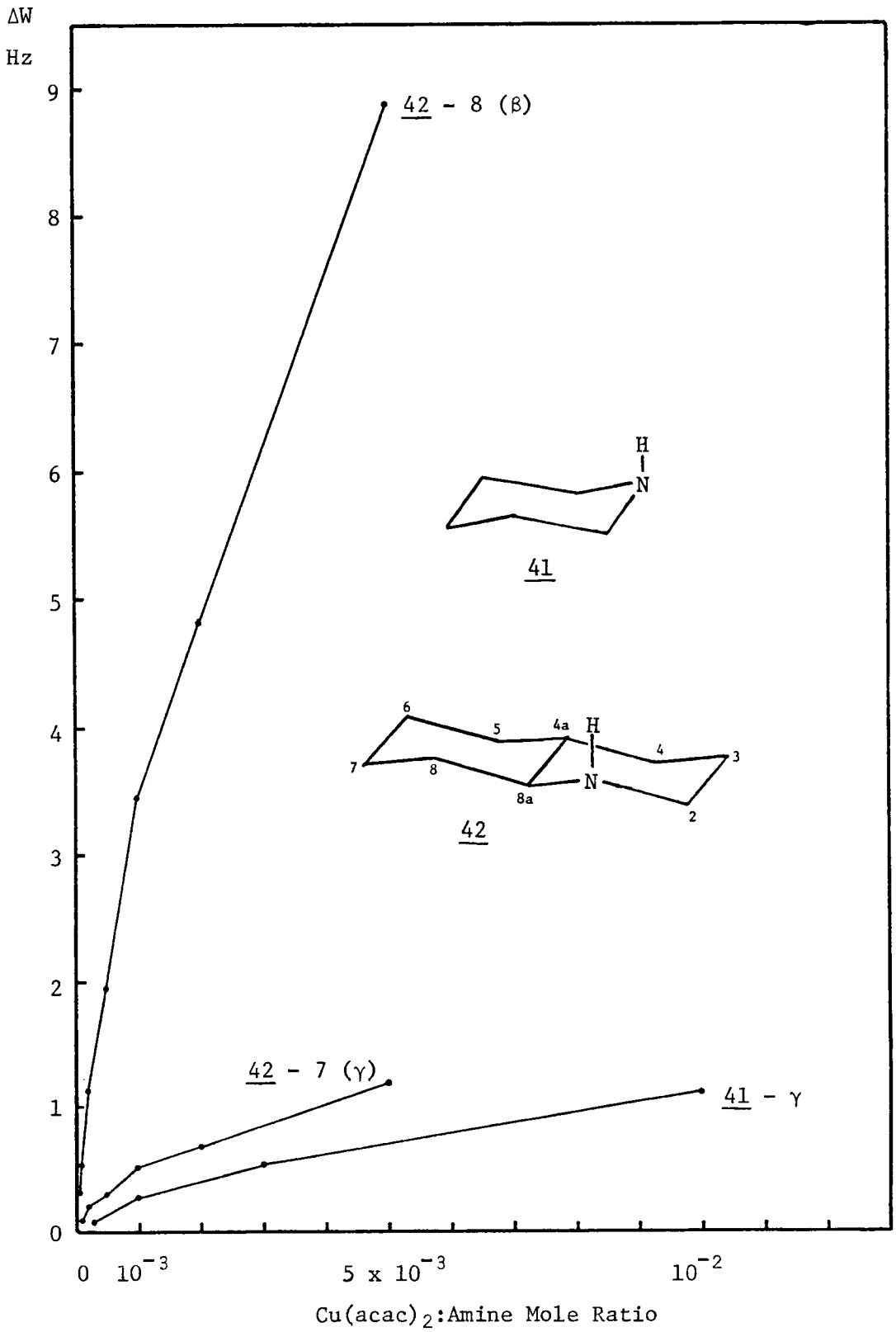


Figure 29. Data for the γ carbon of piperidine 41 and carbons 7 and 8 of decahydroquinoline 42.

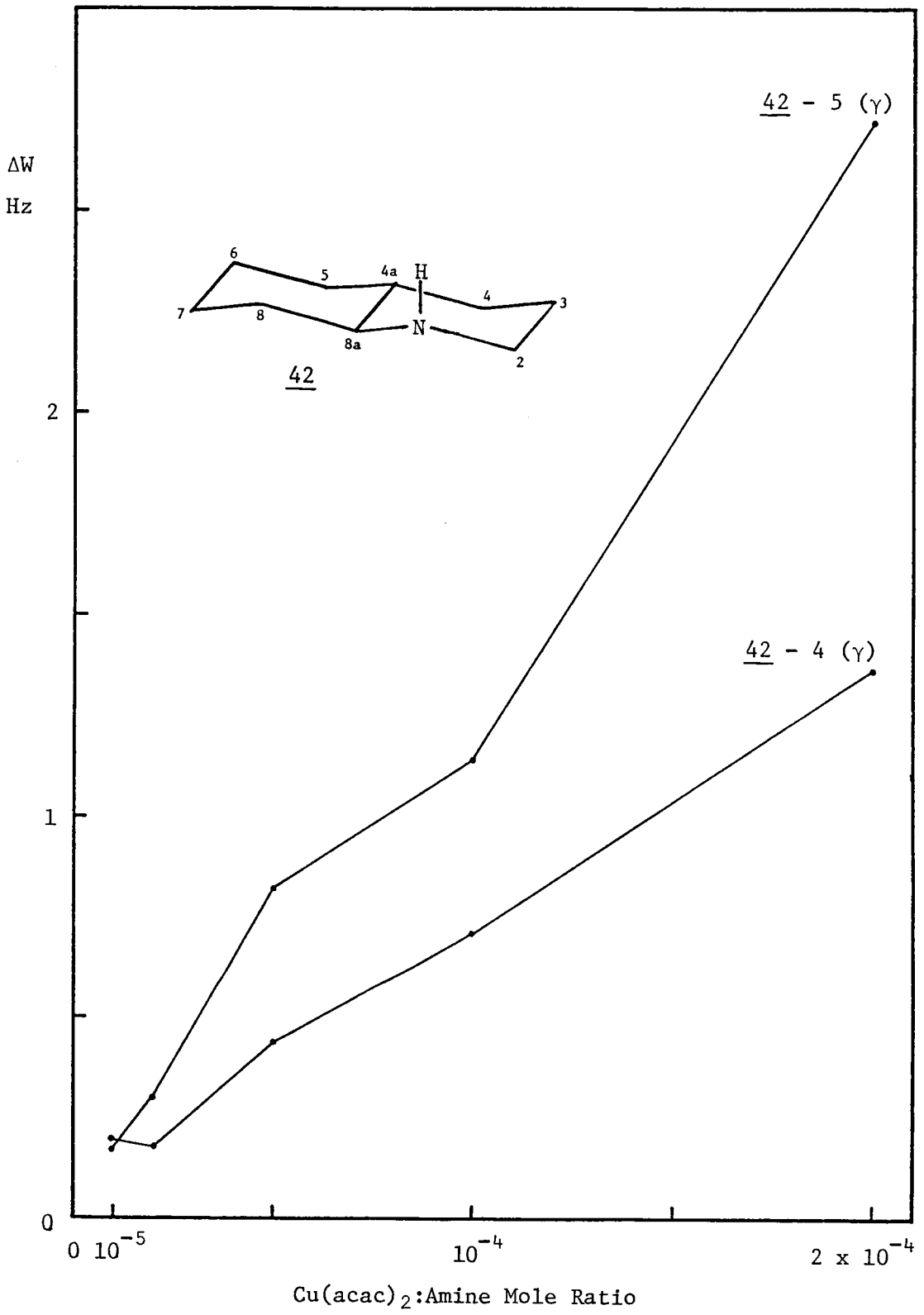


Figure 30. Data for carbons 4 and 5 of decahydroquinoline 42.

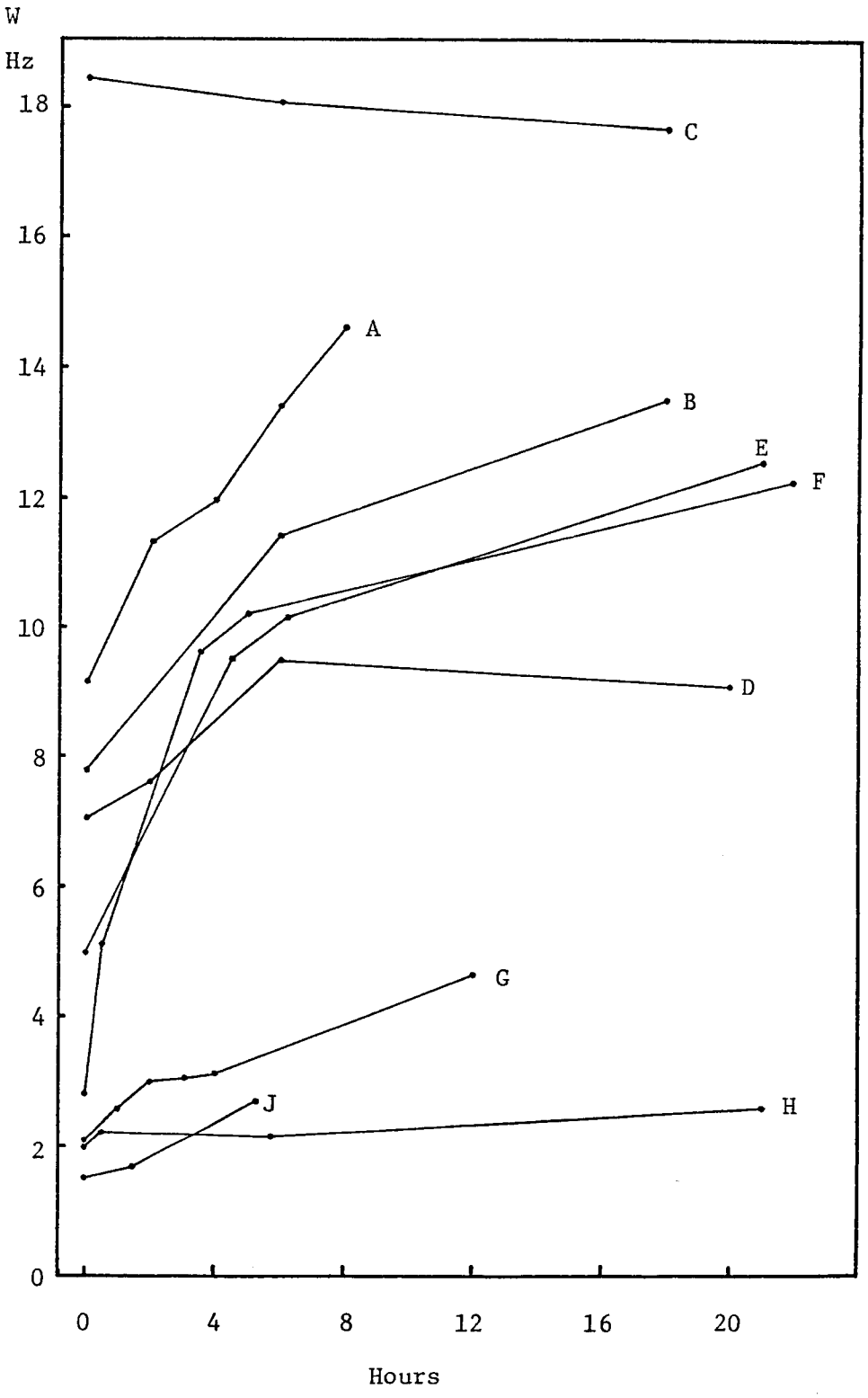


Figure 31. C-13 linewidths of the β carbon of cyclohexylamine 22 as a function of time.

See Table XIV (p 66) for key to letters.

TABLE XIV

INFORMATION FOR FIGURE 29 (P 65)

Run	Solvent	Dioxane[a] Used?	Degassed?
A	$CDCl_3$	Yes	No
B	$CDCl_3$	No	No[b]
C	$CDCl_3$	Yes	Yes[c]
D	C_6H_6	Yes	No
E	$CDCl_3$	No	No
F	$CDCl_3$	No	No
G	C_6H_6	No	Yes
H	C_6H_6	No	No
J	C_6H_6	No	No[d]

a. Internal linewidth standard.

b. Sample sat for two days before $Cu(acac)_2$ was added.

c. Sample sat for two days before $Cu(acac)_2$ was added and it became yellow.

d. Methylene chloride used for the $Cu(acac)_2$ solution.

large amount of scatter, much more than the expected uncertainty in the calculation of the linewidth. Also, it is clear the linewidths increase with time, the chloroform solutions (A, B, E, and F in Figure 31, p 65) more than the benzene solutions (G, H, and J in Figure 31, p 65). The presence of dioxane or the degassing of the solution appears to have no effect. One sample (C in Figure 31, p 65), which showed visible signs of reaction prior to addition of the $Cu(acac)_2$, gave dramatically different results. Since the linewidth increases appeared to be smaller when using benzene as a solvent and recognizing that amines can react with halogenated compounds, an experiment was done to observe the effect of a small amount of halogenated solvent. The results are shown in Table XV (p 68). A brief explanation of what was done is needed. Since $Cu(acac)_2$ is only sparingly soluble in common solvents other than chloroform and methylene chloride (when no amine is present) the $Cu(acac)_2$ was added as a solid or a saturated solution in cyclohexylamine. The reason for the second method was to investigate whether the amine-copper complex was undergoing some type of change with time which resulted in the formation of a species that was more effective in broadening nmr lines than the original complex. Some possible changes might be rearrangement of the geometry of the ligands or partial replacement of the acetylacetone by amine. In order to produce any potential changes, $Cu(acac)_2$ was added to an excess of cyclohexylamine and heated at 60° overnight. The resulting green solution was used as the source of $Cu(acac)_2$ and is referred to in Table XV (p 68) as "heated $Cu(acac)_2$." For all the samples

TABLE XV

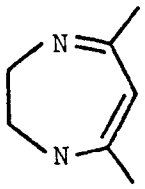
EFFECT OF METHYLENE CHLORIDE ON THE C-13 NMR LINEWIDTHS OF CYCLOHEXYLAMINE:$Cu(ACAC)_2$ AS A FUNCTION OF TIME

Sample	Time (Hours)	^{13}C Linewidth Hz[a]		
		1 α	2 β	3 γ
Heated $Cu(acac)_2$ No CH_2Cl_2	0	1.56	4.11	.81
	12	1.62	4.14	.80
	24	1.73	4.30	.94
Heated $Cu(acac)_2$ 50 µl CH_2Cl_2	0	1.44	3.89	.82
	12	2.07	6.25	.96
	24	2.23	7.81	1.03
Fresh $Cu(acac)_2$ No CH_2Cl_2	0	1.16	2.41	.74
	12	1.25	2.70	.77
	24	1.23	2.76	.80
Fresh $Cu(acac)_2$ 50 µl CH_2Cl_2	0	1.28	2.70	.76
	12	1.88	5.63	.87
	24	2.08	7.22	.89

a. The δ carbon was used as an internal linewidth standard. The solvent was benzene.

in Table XV (p 68), the concentration of $Cu(acac)_2$ is not known since the amount of solid needed was very small (~0.2 mg) and the "solubility" of $Cu(acac)_2$ in cyclohexylamine was not determined. However, the quantities were chosen so that the line broadening approximated that shown for a 2×10^{-4} mole ratio of $Cu(acac)_2$. The results (Table XV, p 68) show that very small amounts of methylene chloride are sufficient to cause changes in linewidths large enough to be significant during the course of a normal run. Chloroform would be expected to be even more reactive. The samples without methylene chloride show small increases in linewidth which are probably not significant. The prior "equilibration" of $Cu(acac)_2$ with cyclohexylamine appears to have no effect. Thus, the linewidth increases with time that were observed while obtaining the main body of data are apparently due to a reaction of the amine with a halogenated solvent.

The difficulties caused by halogenated solvents in the presence of amines do have precedent. An early report by Davies[46] says that no reaction was obtained with trimethylamine and chloroform or carbon tetrachloride and a reaction occurred with bromoform only in the presence of oxygen. Collins[47] and Foster[48] note that some simple primary and tertiary amines react readily with carbon tetrachloride forming the amine hydrochlorides. However, several reports[49,50] of the facile reaction of chloroform with amines at room temperature were later shown to be caused by bromo compounds in the chloroform.[49] Compound 43 (p 70) gives a hydrochloride with chloroform.[51] The problems encountered in

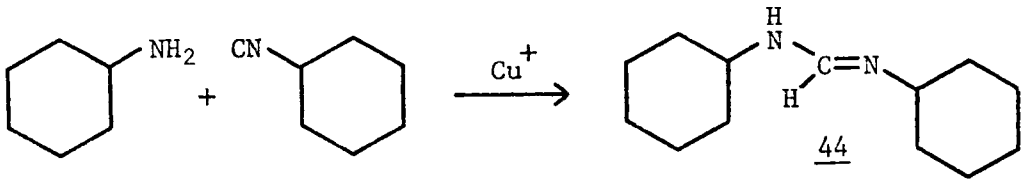


43

the present work are due to copper's being an effective catalyst for the reaction of amines with halogenated compounds. Cromwell reported that cupric acetate catalyzed the reaction of piperidine with carbon tetrachloride.[52] More impressively, the same mixture boiled after addition of copper foil. Similar results were obtained in this laboratory using $Cu(acac)_2$. The copper foil catalyzed reaction of other primary amines with carbon tetrachloride has been reported.[53] Chloroform was said to react much more slowly. The most complete study is that of Smith, who examined the catalytic effect of cupric acetate on the reaction of carbon tetrachloride with a wide variety of amines.[54] Depending upon the amine and the conditions of the reaction, the following compounds were detected: amine hydrochloride, chloroform, N-alkyl imine, ammonium chloride, isocyanide, cyanide, urea, formamide, phosgene, and primary amine (from secondary amines). The rate and course of the reaction was influenced by oxygen. A mechanism involving radicals was proposed.

While it is not clear what changes occur in the nmr samples which cause the amount of line broadening to increase, Smith's work shows that the system, if similar to carbon tetrachloride, is very complex and it could be expected that changes in the copper species could occur. Of

the compounds detected by Smith, the only one investigated in this laboratory was the isocyanide. Upon standing for 5 days, a mixture of chloroform and cyclohexylamine containing copper sulfate became dark brown and produced a revolting odor. Considering the observations of Beichl[53] and Smith,[54] the formation of an isocyanide was suspected, and peaks corresponding to cyclohexylisocyanide were observed in the ^{13}C nmr of the reaction mixture. Isocyanides form complexes with Cu(I) and Cu(II); however under most conditions isocyanides reduce Cu(II) to Cu(I).[55] The ^{13}C nmr spectra of isocyanides and their Cu(I) complexes have been studied.[56] Horrocks examined the proton nmr shifts caused by $Ni(acac)_2$ and $Co(acac)_2$ for some isocyanides and noted that spurious results were obtained if the samples were allowed to stand before use.[57] Copper(I) also catalyzes a reaction between isocyanides and amines (Equation 9).[58] The product may be capable of complexing copper, but no evidence was found for compounds such as 44 in the nmr samples.



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(9)

In view of the information mentioned above, a brief study was made of the effect of cyclohexylisocyanide on the nmr linewidths of cyclohexylamine in the presence of $Cu(acac)_2$. The results are shown in Table XVI (p 72). The solvent was benzene and the $Cu(acac)_2$ and cyclohexylisocyanide were added as chloroform-d solutions. The data show

TABLE XVI

EFFECT OF CYCLOHEXYLISOCYANIDE ON THE C-13 NMR LINEWIDTHS OF CYCLOHEXYLAMINE:$Cu(ACAC)_2$[a]

Amount of Cyclohexyl-isocyanide[b]	Time (Hours)	^{13}C Linewidths Hz		
		1 α	2 β	3 γ
0	0.0	1.08	1.91	.72
0	0.5	1.16	2.32	.65
1×10^{-2}	1.0	1.44	3.72	.56
1×10^{-2}	1.5	1.36	3.88	.58
5×10^{-2}	2.0	1.54	4.70	.84
5×10^{-2}	2.5	1.11	3.59	.51
5×10^{-2}	48	(<.9)[c]	.83	(<.9)[c]

a. This is a series of runs on the same sample. The mole ratio of $Cu(acac)_2$ was 2×10^{-4}. Linewidths are uncorrected.

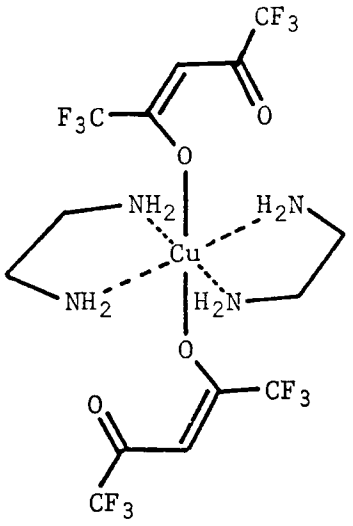
b. Mole ratio to cyclohexylamine.

c. Not calculated, but relative peak heights were the same as in uncomplexed spectra.

the addition of isocyanide causes an immediate increase in linewidth (above that expected from the chloroform); however, a decrease in linewidth then occurs which eventually results in the linewidth's returning to the normal [no $Cu(acac)_2$] value. This is accompanied by a disappearance of the blue color of the copper complex. This result is similar to the observation made for the sample of endo-norbornylamine (40, p 28) which, after two weeks, lost the blue color and gave a ^{13}C nmr spectrum with normal linewidths. A difficulty in associating the linewidth increases with the formation of isocyanides is that Smith did not observe isocyanides in the reaction of secondary amines with carbon tetrachloride. In this study, piperidine (41, p 28) and decahydroquinoline (42, p 28) were similar to the primary amines in their increase in linewidth with time.

Some other observations have been made which relate to the above discussion. Graddon noted that copper complexes of α-substituted β-diketones decomposed on standing with pyridine in a not completely characterized reaction which involved cleavage of the diketone.[59] Fackler reported that he could not cause $Ni(acac)_2$ to form the corresponding Schiff base by heating with a primary amine.[60] An example of a copper complex with unusual geometry (45, p 74) has been found by Bush;[61] however, both the copper(hexafluoroacetylacetonate)$_2$ and the ethylenediamine are quite different from the compounds in this work.

In summary, the use of $Cu(acac)_2$ to produce ^{13}C nmr line broadening in amines is complicated by the catalytic effect of the $Cu(acac)_2$



45

on the reaction of amines with halogenated solvents. Even the small amounts used to dissolve the $Cu(acac)_2$ should be avoided. While the nature of these changes has not been determined, the reaction is known to be fairly complex, and in the case of cyclohexylamine one of the known products, cyclohexylisocyanide, has been shown capable of causing some of the same changes when added to an amine-$Cu(acac)_2$ solution.

D. Nonlinear Plots

Another problem which was encountered was that the plots of nmr linewidth versus mole ratio of added $Cu(acac)_2$ did not always give straight lines: the slope being less at high $Cu(acac)_2$ concentrations. This is not the result of the time delay between the first and last runs since a run in which all the samples were made fresh showed the same results (Figure 32, p 75). While the cause of this phenomenon has not been determined, several possibilities (and the reasons for their rejection) are discussed below.

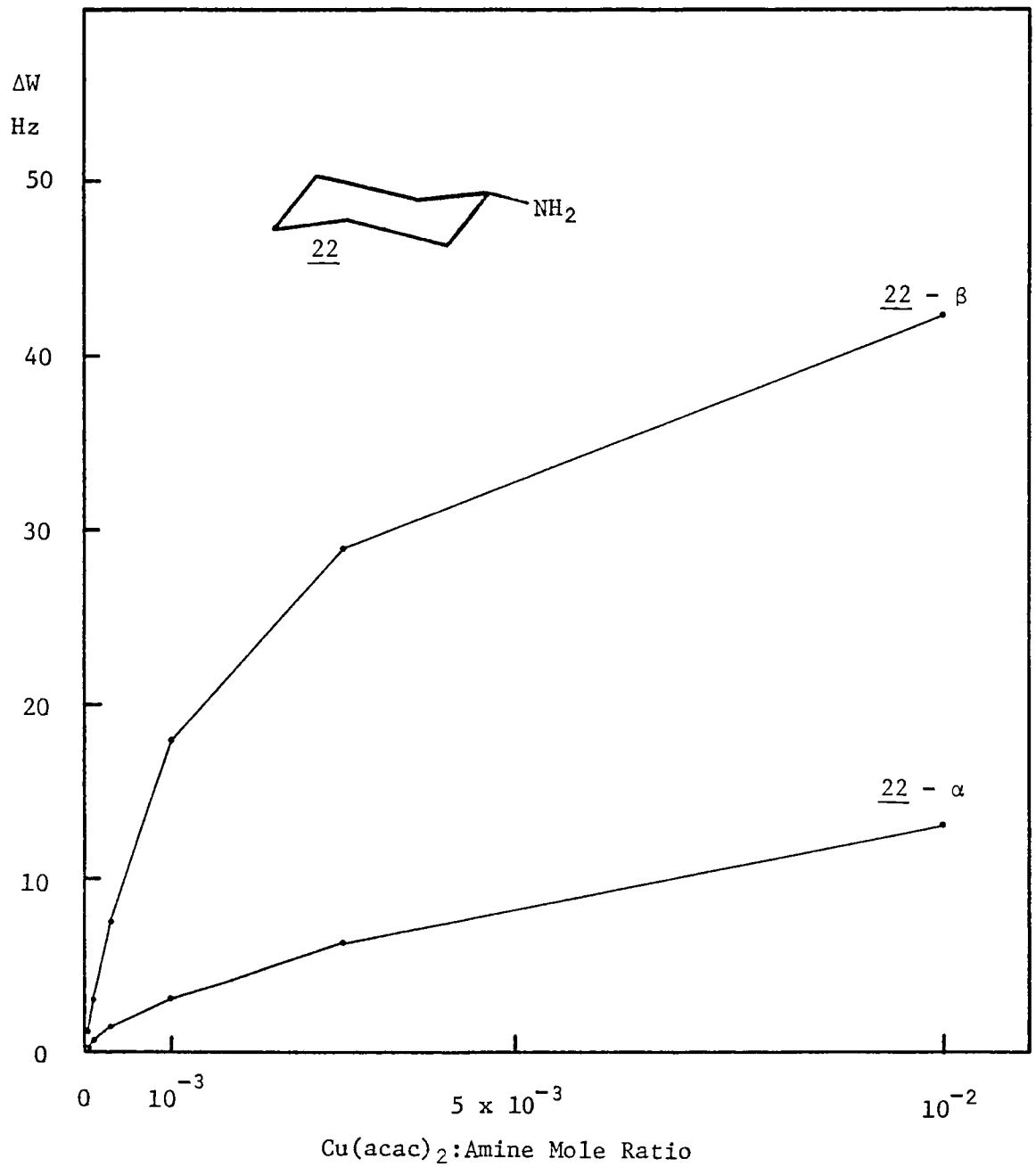


Figure 32. Linewidths of the α and β carbons of cyclohexylamine 22 with each sample made individually.

Of the main studies of paramagnetic shifts mentioned in Chapter III, only two examples are found of nonlinear shift vs. concentration plots. Morishima showed a graph of quinoline proton shifts with $Ni(acac)_2$ in which some of the lines have a short, slightly curved section before becoming linear at higher concentrations.[24] No comment is made. In one of the few examples using $Cu(acac)_2$, Hayamizu obtained a significantly nonlinear plot of the β carbon shift of pyridine (Figure 33, p 77). However, the plots of linewidth vs. concentration apparently were normal.[37] A suggestion was made that this nonlinearity might be due to a $Cu(acac)_2$ dimer. (As mentioned later, this is unlikely.) These anomalies may actually be more common since most of the papers do not include graphs of the data. Since most of the paramagnetic shift data for amines have been obtained by observing a range of metal to amine ratios of ten or less, the possibility existed that nonlinear plots might be found if a larger range were examined. The cyclohexylamine-$Ni(acac)_2$ system was examined over the metal-amine ratio of 10^{-4} to 10^{-2} and no significant deviations from nonlinearity were observed for either the linewidth or shift.

$Cu(acac)_2$ does not have as strong a tendency to form 1:2 metal-amine complexes as $Ni(acac)_2$ or $Co(acac)_2$.[62] Thus, the possibility was considered that the curvature of the lines was due to changes in the relative amounts of 1:1 and 1:2 complexes in the nmr solutions. Numerous studies have been made of the adducts formed from metal diketonates and amines, as solids as well as in solution.[62] In the case of copper, the

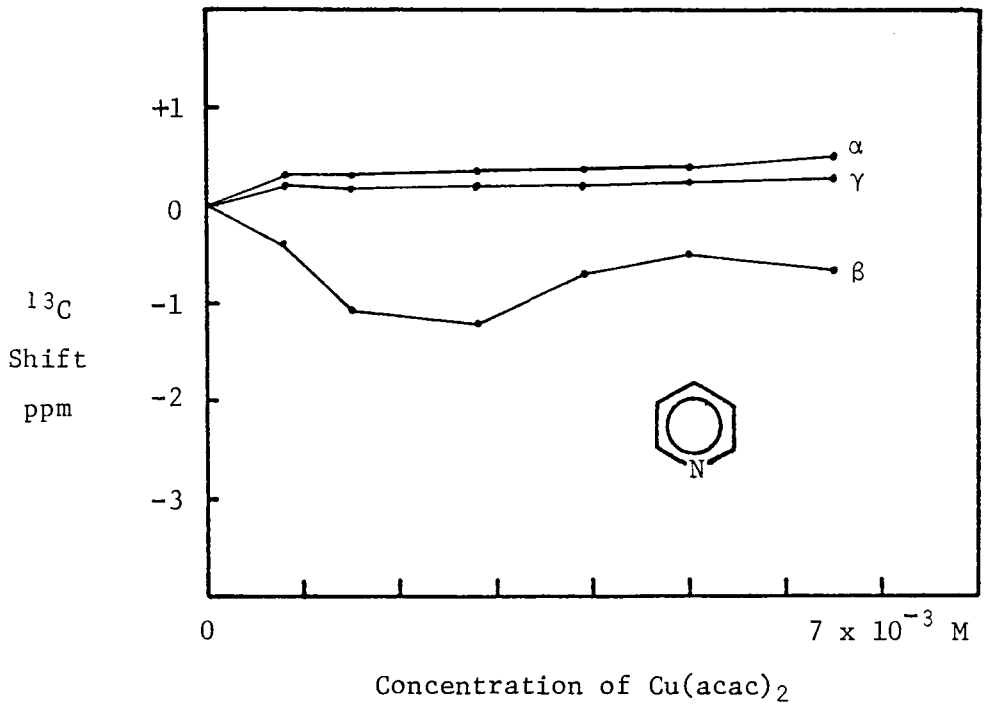


Figure 33. Hayamizu's data.

only evidence for CuL_2-amine$_2$ complexes in solution occurs when L is a compound such a trifluoracetylacetone (tfacac) or hexafluoroacetylacetone (hfacac).[63-65] The strongly electron withdrawing trifluoromethyl group makes these compounds weaker ligands and the resulting CuL_2 is a stronger Lewis acid. A few examples of 1:2 complexes not involving fluorinated ligands are known at very low temperatures,[66] or in the solid state.[67] Many determinations of the equilibrium constant, K_1, for Equation 10 have been made, typically with pyridine and its derivatives.[68,69] For $Cu(acac)_2$ and the amines in this study, K_1 is probably between 100 and 1000 (maybe lower for those amines with no α hydrogens). An estimate of K_2 for Equation 11 is not available for $Cu(acac)_2$. For $Cu(hfacac)_2$ and pyridine[69] $K_1 \simeq 800$ and $K_2 \simeq 10^5$ and

$$CuL_2 + \text{base} \rightleftharpoons CuL_2 \cdot \text{base} \qquad (10)$$

$$CuL_2 \cdot \text{base} + \text{base} \rightleftharpoons CuL_2 \cdot \text{base}_2 \qquad (11)$$

the lack of evidence for $CuL_2 \cdot B$ with nonfluorinated ligands implies a similar large ratio between K_1 and K_2 in such systems. A theoretical argument can be made against changes in the relative amount of $CuL_2 \cdot$base in the concentration region of the nmr samples. Let x be the amount of reaction in Equation 10, y the amount of reaction in Equation 11, R the mole ratio of CuL_2 to B (amine), and the concentration of B equal to one mole/liter. Then

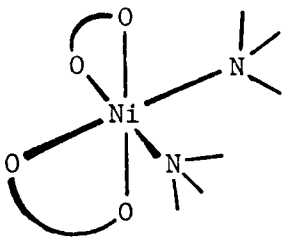
$$K_1 = \frac{x - y}{(1 - x - y)(R - x)} \quad \text{and} \quad K_2 = \frac{y}{(1 - x - y)(x - y)}, \qquad (12)$$

or, since $1 - x - y \simeq 1$ (the maximum CuL_2 concentration is about 0.01 M),

$$K_1 \simeq \frac{x - y}{R - x} \quad \text{and} \quad K_2 \simeq \frac{y}{x - y} = \frac{CuL_2 \cdot B_2}{CuL_2 \cdot B} \quad .$$

Therefore, even if $CuL_2 \cdot B_2$ is present in the nmr samples, the relative amounts of $CuL_2 \cdot B$ and $CuL_2 \cdot B_2$ should not change as CuL_2 is added. If nmr spectra could be observed in the region where $1 - x - y \neq 1$, there would be conflicting trends. The fraction of CuL_2 which forms a complex would decrease, which would make the plots bend down, but the relative amount of $CuL_2 \cdot B$ would increase, bending the plots up. (The latter effect assumes nmr lines are broader in $CuL_2 \cdot B$ than in $CuL_2 \cdot B_2$.) The actual results would depend upon the values of K_1 and K_2.

$Ni(acac)_2$ and $Co(acac)_2$ are trimeric in benzene solution and upon the addition of a limited amount of pyridine, compounds such as $Ni_2(pyridine)(acac)_4$ can be isolated.[62] The addition of excess amine to nickel or cobalt β-diketonates gives only diamine adducts, which can be cis (46) or trans (47). Adducts of simple amines with $Ni(acac)_2$ are



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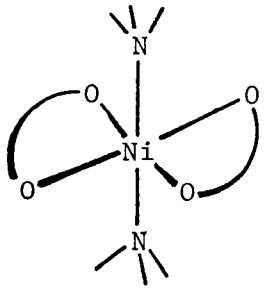

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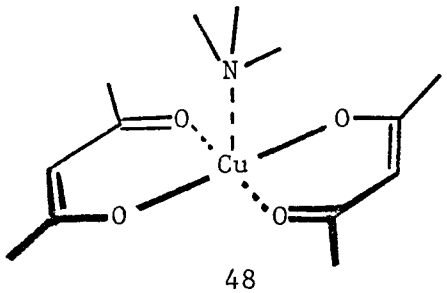
generally trans. With solid $Cu(acac)_2$ only slight intermolecular interactions are found (x-ray) and the uv-vis spectra for the solid and solution are similar. The 1:1 complexes with amines have a square-pyrimidal structure (48, p 80). Unlike nickel and cobalt, no evidence



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has been found for complexes containing more than one $Cu(acac)_2$ unit. Thus, there are no known equilibria other than 10 and 11 (p 78) which might be a cause of the curvature of the line broadening plots.

Another potential source of equilibrium difficulties is the dilution of the nmr solutions as the $Cu(acac)_2$ aliquots were added. For a mole ratio of 3×10^{-2}, the volume would be about twice that with no copper. Using a reasonable value for K_1 and Equation 12 (p 78), it can be shown that the fraction of $Cu(acac)_2$ forming a complex should not change significantly as long as $[B] - x - y \simeq [B]$, where [B] is the concentration of the amine. The results of a dilution experiment are shown in Table XVII (p 81). In order to avoid the problems caused by halogenated solvents, the $Cu(acac)_2$ was added as a solid and the exact mole ratio was not known. There appears to be no general trend in linewidth changes on dilution. The variations which do occur may be due to the significant increase in signal to noise for the more dilute spectra. Since the dilutions in Table XVII (p 81) are far more than in a normal run, any difficulties due to dilution should have been apparent.

TABLE XVII

DILUTION EXPERIMENT

Concentration of Cyclohexylamine (by Volume)[a]	^{13}C Linewidth (Hz)[b]			Number of NMR Acquisitions
	1 α	2 β	3 γ	
.50	1.72	4.33	.87	257
.17 (.50/3)	1.72	3.65	.95	810
.056 (.50/9)	1.62	3.94	.95	3362

a. The solvent was benzene. The $Cu(acac)_2$ mole ratio was about 2×10^{-4}.

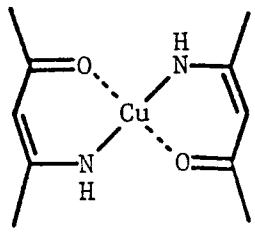
b. The δ carbon was used as an internal standard.

One of the assumptions made in relating linewidth to T_2 was that the exchange of ligands was fast on the nmr time scale (p 13). While there is no evidence that this is incorrect for $Cu(acac)_2$ and amines, it can be shown that even if fast exchange did not occur a linear relationship would still exist between the linewidth and the amount of $Cu(acac)_2(amine)$.[13] The difference in such a case is the linewidth would not represent the true value of $1/T_2$. Kuroda observed the proton nmr of several di- and tripeptides in the presence of Cu(II) as a function of pH.[70] Under certain conditions, the changes in the observed line broadening were due to a minor species with a fast exchange rate rather than the major, more slowly exchanging multidentate Cu(II) complex.

Another possible cause of the nonlinear plots is that the computer linewidth calculation routine could have given incorrect results for wide lines. The computer uses a maximum of 200 data points in its calculation which, under typical conditions, corresponds to a 50 Hz "window" for spectra using 16K of memory, or 100 Hz for 8K spectra, etc. When a wide line was encountered, the linewidth was often calculated using more than one size spectra. Only when the line was "obviously" too wide for the window (i.e. 30 Hz for a 50 Hz window) were questionable results obtained. Otherwise, the calculations would agree. (An example: 31.9 ± 2.8 Hz at 8 K and 32.3 ± 2.9 Hz at 4K.) Also, the calculations agreed with approximate hand measurements on the plotted spectra.

To see if the nonlinear plots were unique to $Cu(acac)_2$, some other copper complexes were studied. The results with cyclohexylamine 22 (p 23)

are shown in Figures 34-37 (pp 84-87). The solvent was benzene, the Cu(4-aminopent-3-en-2-one)$_2$, [Cu(nacac)$_2$] (49) and Cu(trifluoroacetylacetone)$_2$, [Cu(tfacac)$_2$] (50) were dissolved in methylene chloride and the copper dipivaloylmethane, [Cu(dpm)$_2$] (51) was dissolved in benzene.



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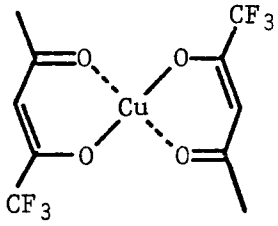

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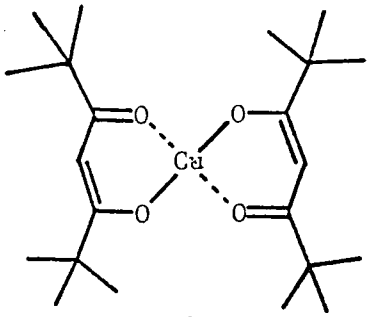

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A wide range of behavior is apparent with no clear relation between some of the observed linewidth changes and steric or electronic properties. The plots range from essentially straight to significantly more curved than with Cu(acac)$_2$.

In addition to broadening the nmr lines of amines, copper complexes also produce shifts; however they are very small compared to Ni(acac)$_2$ or Co(acac)$_2$. Some shift data are shown in Figures 38-43 (pp 88-93). In all cases, the dioxane peak was used as a reference. Unlike the results of amines with other metal complexes, many of the plots of shift vs. mole ratio of copper complex show a distinct curvature. For cyclohexylamine 22 (p 23) with several copper complexes (Figures 38-41, pp 88-91), the magnitude of the shifts and the amount of curvature of the plots correspond very closely with the magnitude and curvature of the line broadening data (Figures 32, 34-37, pp 75, 84-87). In each case the shift magnitude follows the familiar pattern $\beta > \alpha > \gamma$ with the α resonance

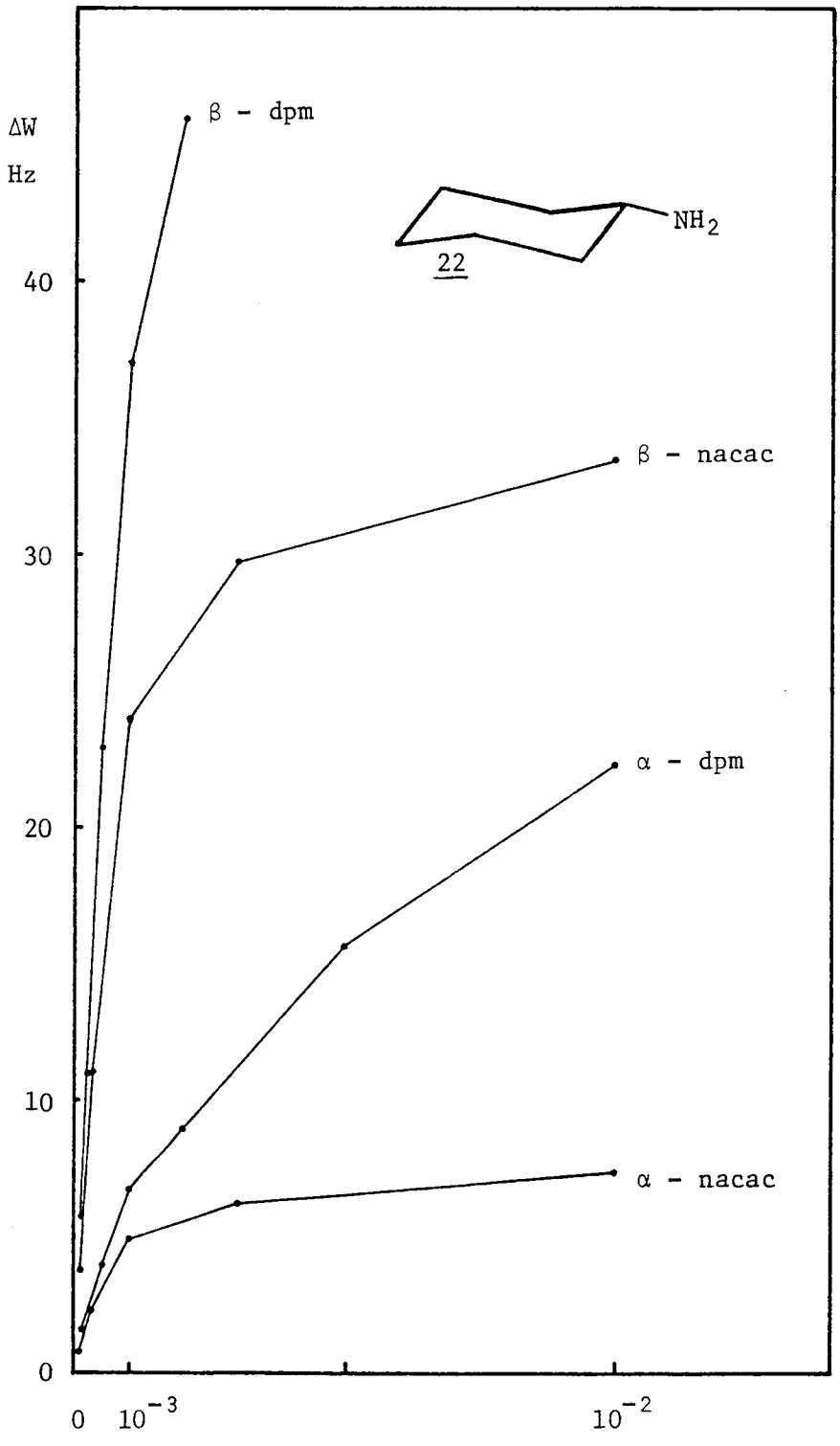


Figure 34. Data for the α and β carbons of cyclohexylamine 22 with $Cu(dpm)_2$ 51 and $Cu(nacac)_2$ 49.

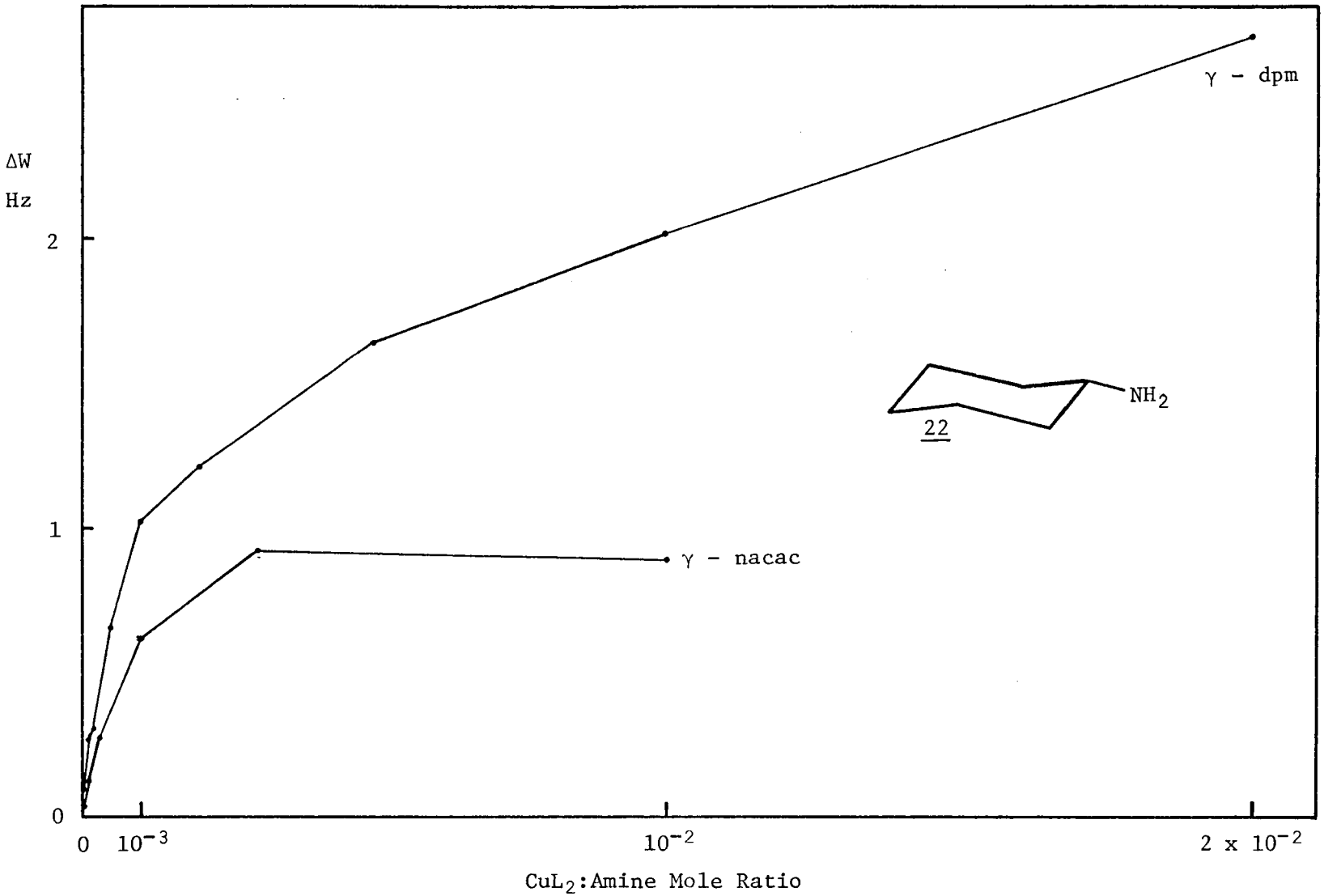


Figure 35. Data for the γ carbon of cyclohexylamine 22 with $Cu(dpm)_2$ 51 and $Cu(nacac)_2$ 49.

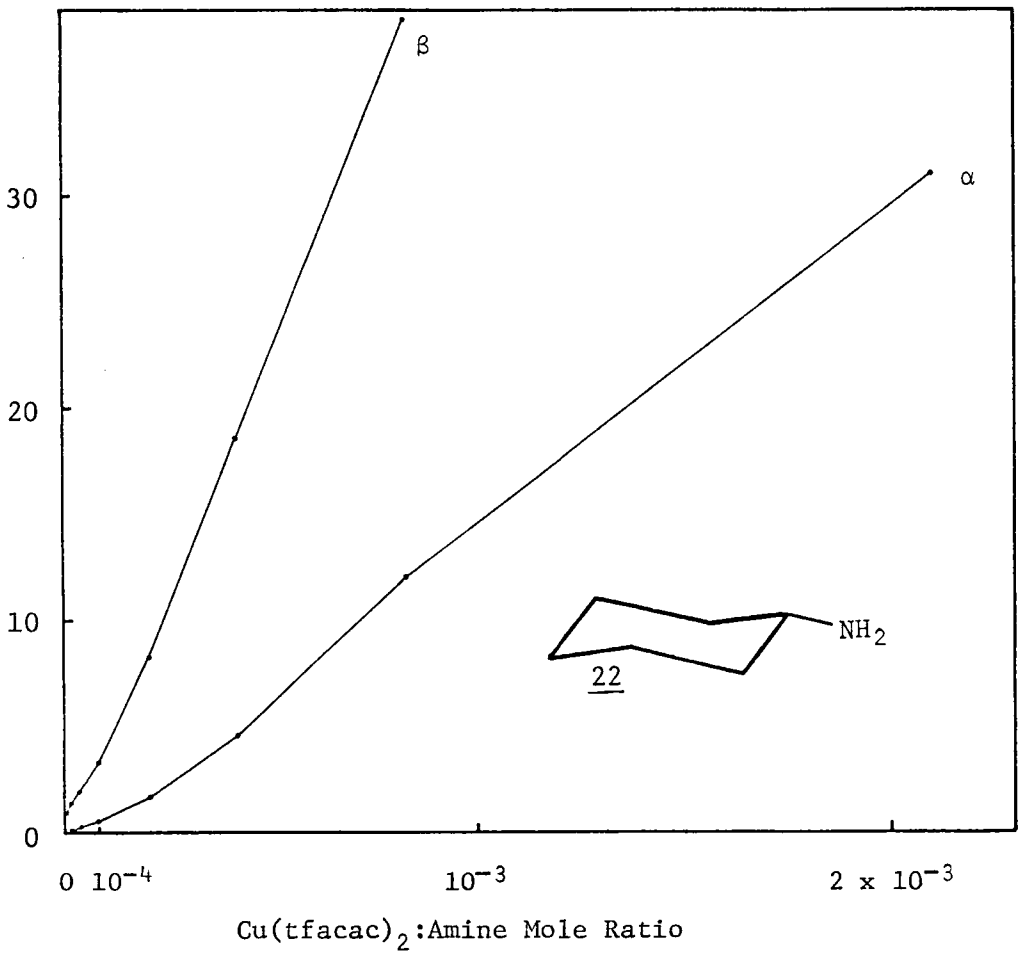


Figure 36. Data for the α and β carbons of cyclohexylamine 22 with $Cu(tfacac)_2$ 50.

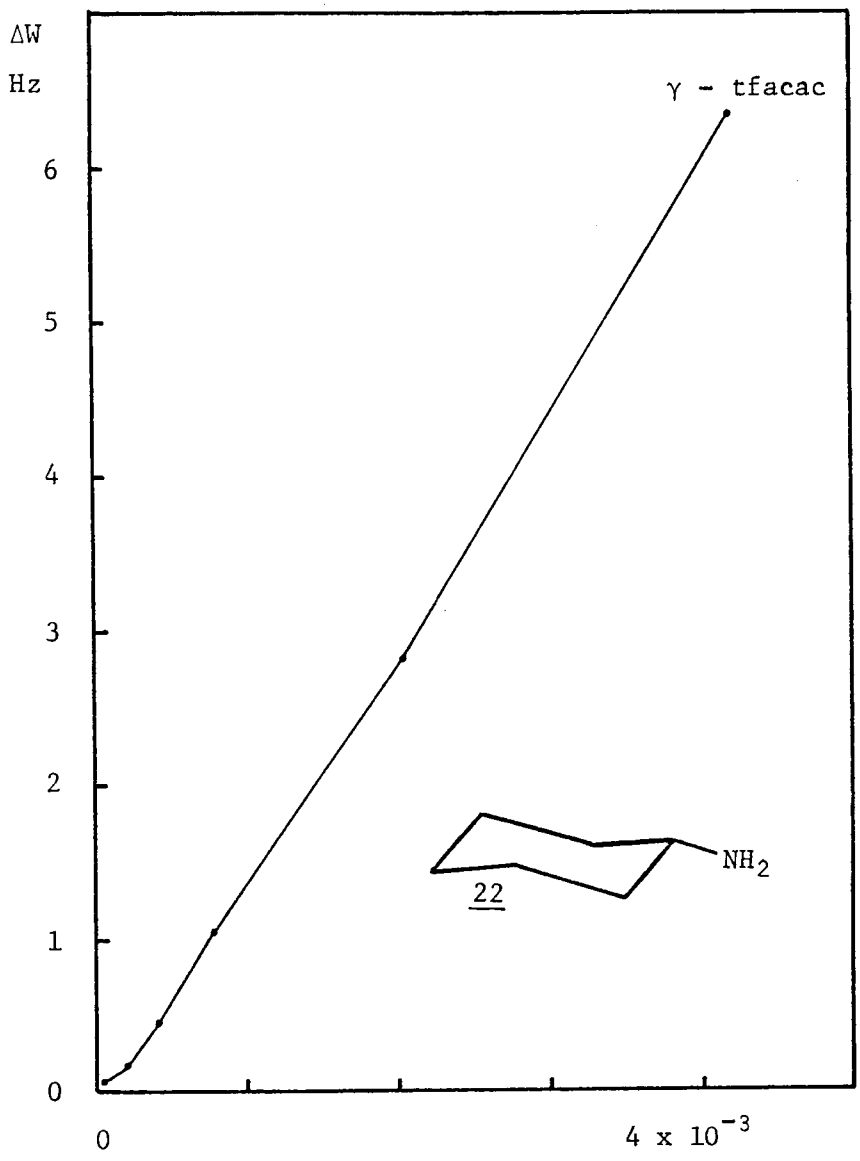


Figure 37. Data for the γ carbon of cyclohexylamine 22 with $Cu(tfacac)_2$ 50.

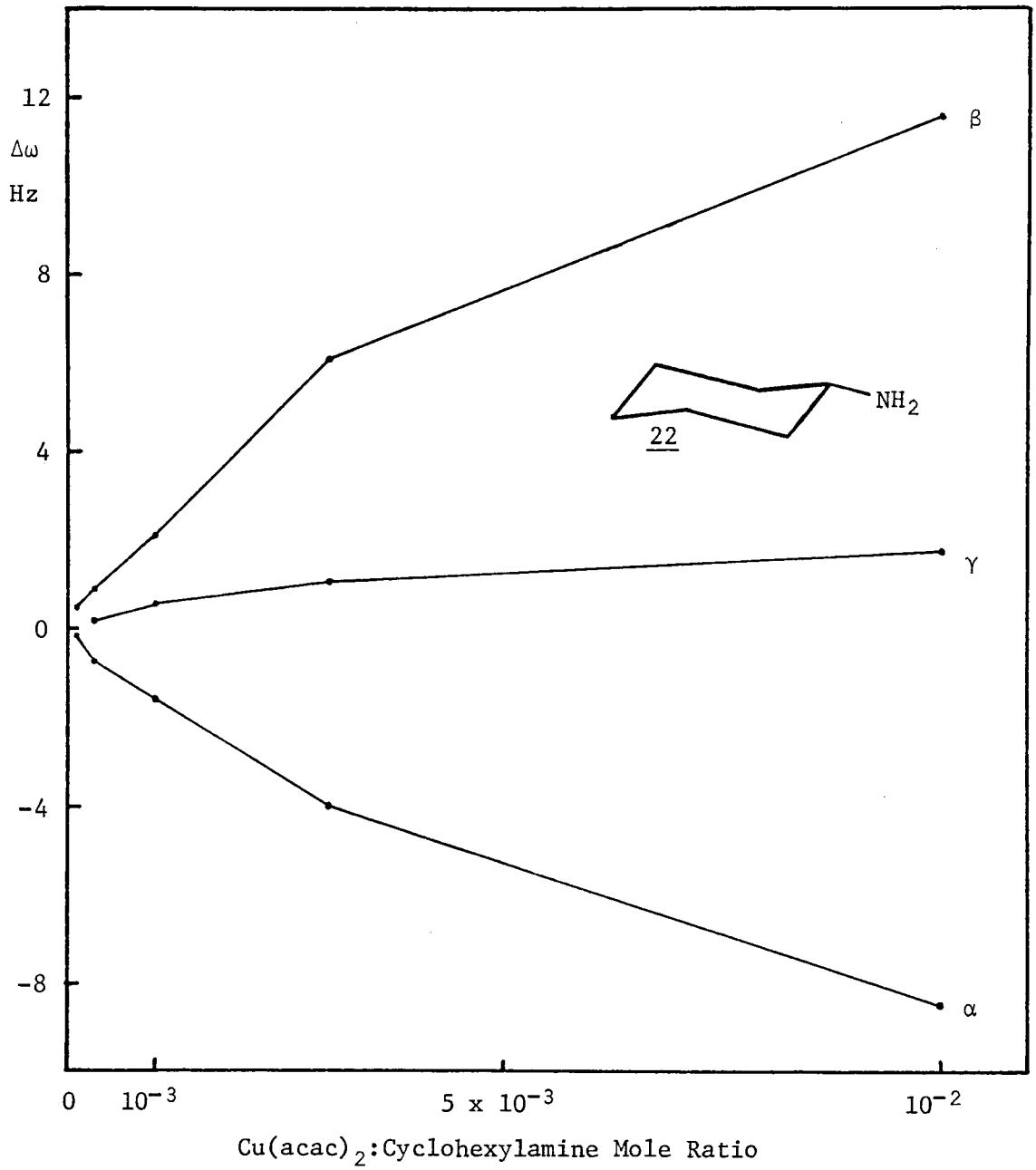


Figure 38. Data for the shifts of cyclohexylamine 22 with $Cu(acac)_2$.

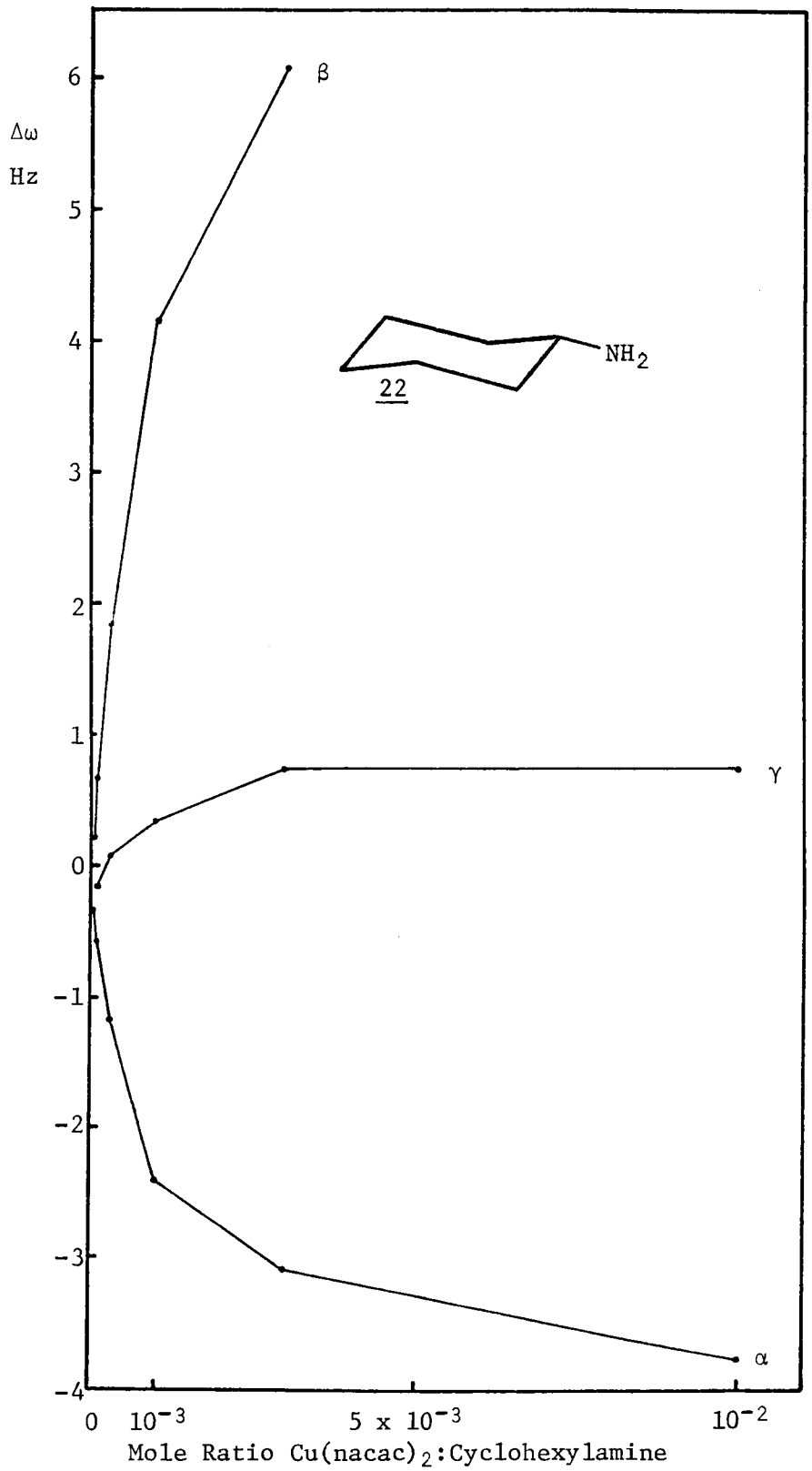


Figure 39. Data for the shifts of cyclohexylamine 22 with $Cu(nacac)_2$ 49.

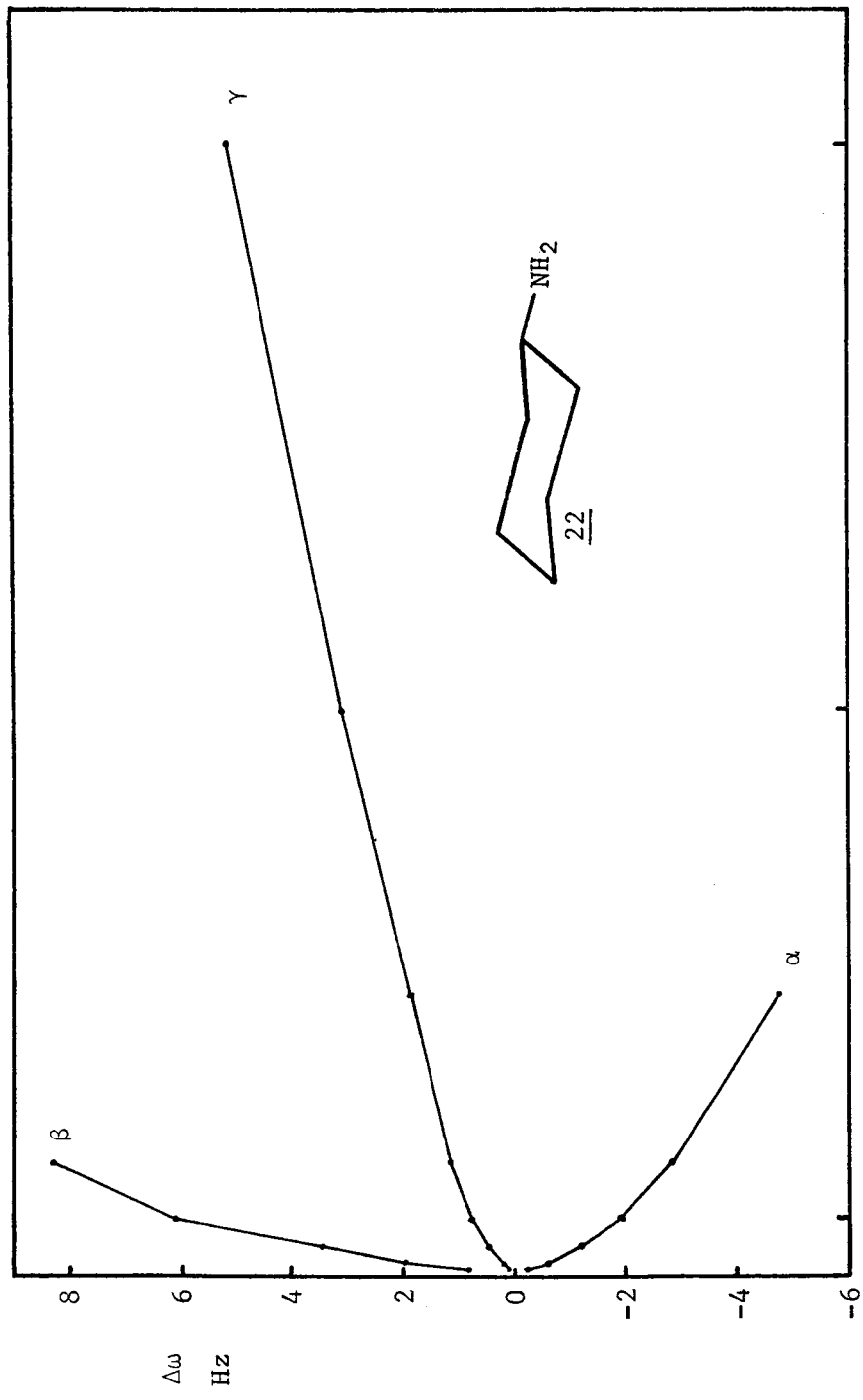


Figure 40. Data for the shifts of cyclohexylamine 22 with $Cu(dpm)_2$ 51.

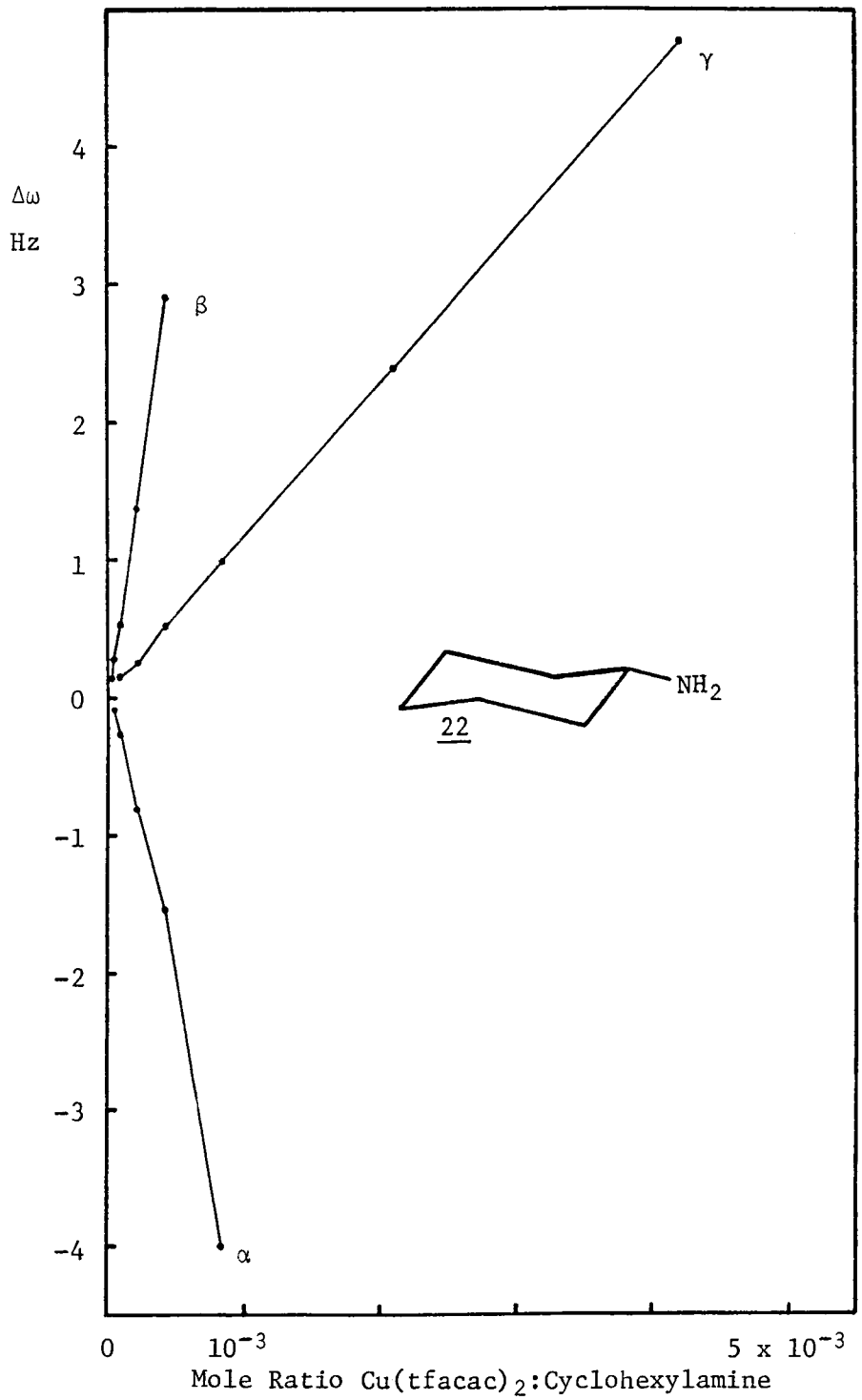


Figure 41. Data for the shifts of cyclohexylamine with $Cu(tfacac)_2$ 50.

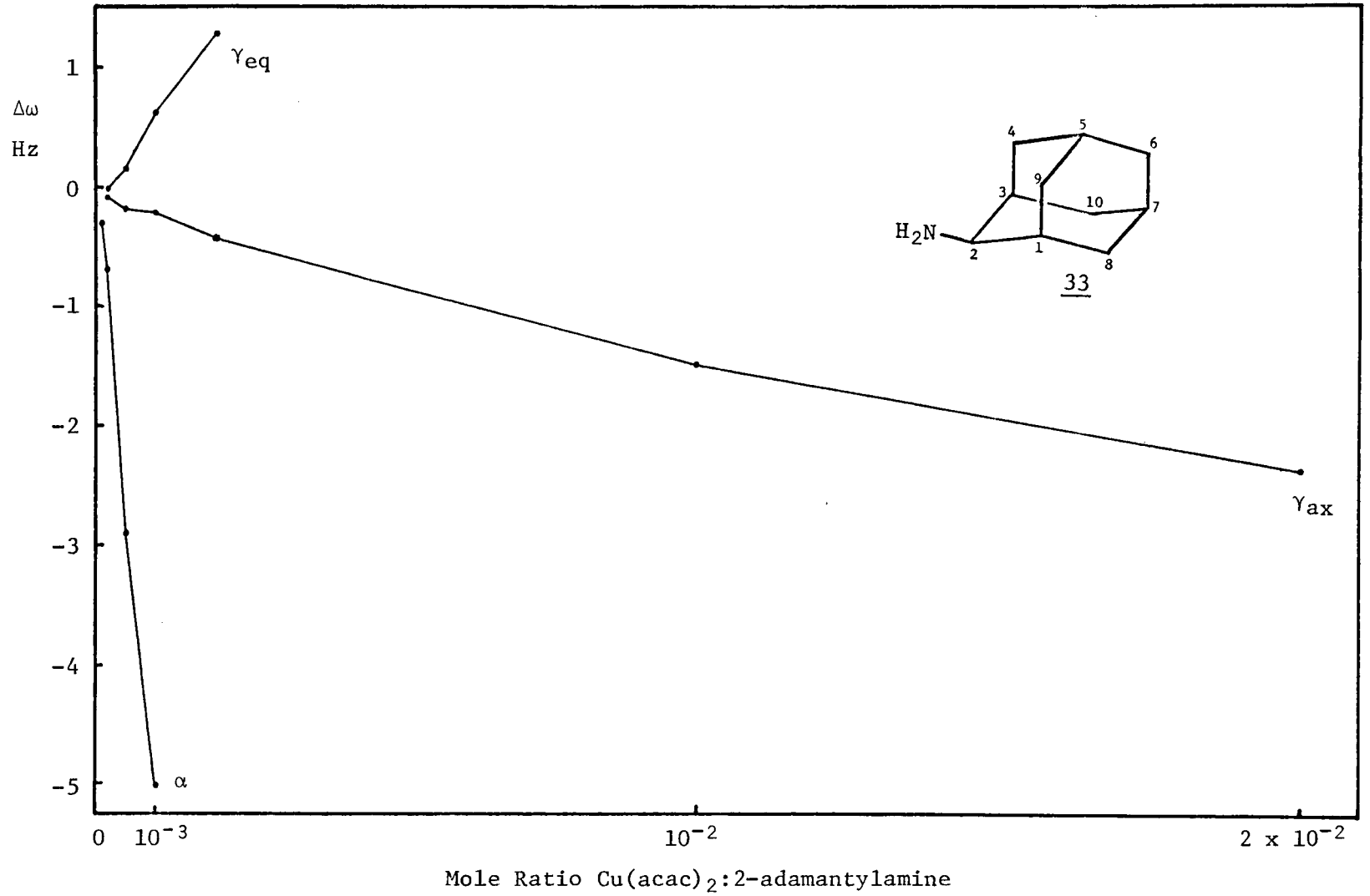


Figure 42. Data for the shifts of the α, γ_{eq}, and γ_{ax} carbons of 2-adamantylamine 33 with $Cu(acac)_2$.

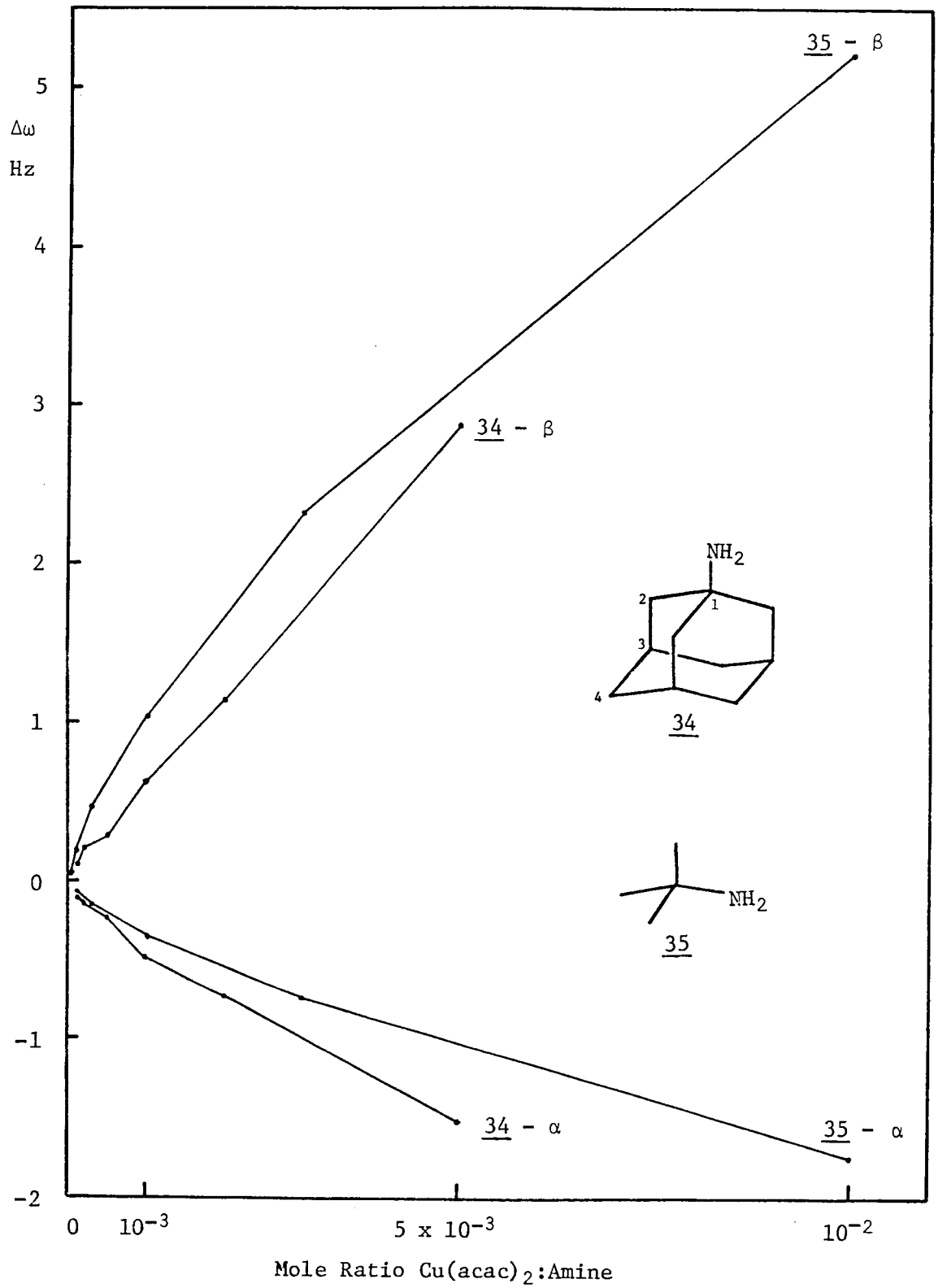


Figure 43. Data for the shifts of the α and β carbons of t-butylamine 35 and 1-adamantylamine 34 with $Cu(acac)_2$.

moving upfield and the β and γ downfield. In contrast, the two different γ resonances of 2-adamantylamine 33 (p 28)(axial and equatorial) shift in opposite directions. This could be due to a pseudo-contact interaction which can show a variation with angle as well as distance. The γ_{eq} shift is larger than the γ_{ax} shift, as with line broadening, but the eq:ax ratio is much smaller for the shifts than for the line broadening (2.5 vs. 13). Similar results are also found for the 4-t-butylcyclohexylamines 31 and 32 (p 28). This difference in ratios implies that a different type of interaction than that causing the line broadening is at least partially responsible for the observed shifts. If this is true, the similarity of the curvature in plots of both the linewidths and shifts suggests a common cause, the most straightforward being some unrecognized equilibrium problem.

Another interesting observation involves the α and β carbons in 1-adamantylamine 34 (p 28) and t-butylamine 35 (p 28): amines on a tertiary carbon. In both cases, the α carbon gives a straight line and the β carbon shows distinct curvature, even though they are plotted over the same concentration range (Figures 19 and 21, pp 46 and 49). While not as clear, carbons 8a (α) and 3 and 4a (β)(Figures 27 and 28, pp 61 and 62) of decahydroquinoline 42 (p 28) show a similar relationship. This implies that the curved lines may be due to an "internal" cause and are not the result of nonproportionality between the amount of $Cu(acac)_2$ added and the amount of complexed amine.

In conclusion, the cause of nonlinearity in the plots of linewidth versus mole ratio of $Cu(acac)_2$ has not been determined. Several suggestions, mainly related to potential equilibrium problems, have been examined and found unlikely. Other evidence (the results with additional copper complexes and the simultaneous presence of curved and straight lines in the same compound) implies that equilibrium problems are not responsible for the observed effects.

E. Stereochemical Aspects of Line Broadening Data

Keeping in mind the difficulties outlined above, a brief discussion is presented of the stereochemical aspects of the line broadening data. The nonlinear plots of linewidth versus mole ratio of $Cu(acac)_2$ make almost any quantitative assignment of their "slope" subject to doubts. Since many of the lines appear to straighten somewhat as they approach zero, the decision was made to use the slope of each line as it approached zero as the "quantitative" value of its slope. This "line fitting" was done by hand. The results are shown in Tables XVIII and XIX (pp 96-99) along with some ratios of slopes for each compound. Other methods of assigning a value to the slope included determining the slope at a point other than zero or determining an average ratio, but these methods did not appear to be as equally applicable to all of the lines. With one exception in decahydroquinoline 42 (p 28), the data agree with Doddrell's work;[5] the order of line broadening in any given compound is $\beta > \alpha > \gamma >$ all others. When an attempt is made to apply

TABLE XVIII

C-13 LINE BROADENING DATA FOR CYCLOHEXYLAMINES

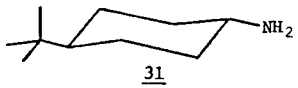
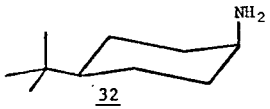
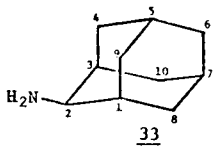
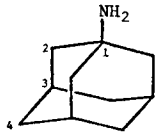
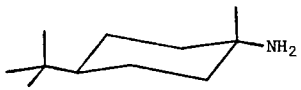
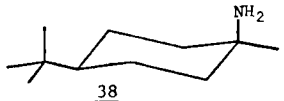
Amine	Slope[a]				Slope Ratios α = 1				Slope Ratios β = 1			
	α	β	γ_{eq}	γ_{ax}	α	β	γ_{eq}	γ_{ax}	α	β	γ_{eq}	γ_{ax}
Group A												
 22	9500	44000	1500		1	4.6	.16		.22	1	.035	
 31	30000	140000	4000		1	4.7	.13		.21	1	.028	
 32	30000	140000		80	1	4.7		.0027	.21	1		.00057
 33	28000	117500	1690	130	1	4.2	.060	.0046	.24	1	.014	.0011

TABLE XVIII (CONTINUED)

Amine	Slope[a]				Slope Ratios α = 1				Slope Ratios β = 1			
	α	β	γ_{eq}	γ_{ax}	α	β	γ_{eq}	γ_{ax}	α	β	γ_{eq}	γ_{ax}
Group B												
 34	610	6650	60		1	11	.10		.092	1	.009	
 36	140	1400 (Me = 500)	40		1	10 (Me = 3.6)	.28		.10	1 (Me = .36)	.028	
 37	30	1400 (Me = 500)	40		1	47 (Me = 17)	1.3		.021	1 (Me = .36)	.028	
 38	14[b]	500 (Me = 40)[b]	.8		1	36 (Me = 2.8)	.057		.028	1 (Me = .08)	.0016	

a. The slope of the line obtained by plotting linewidth (Hz) vs. the mole ratio of added $Cu(acac)_2$. The value shown is the slope as the ratio approached zero.

b. Estimated directly from spectra.

TABLE XIX

C-13 LINE BROADENING DATA

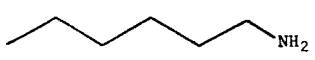
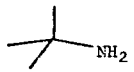
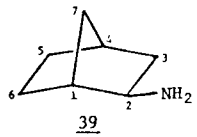
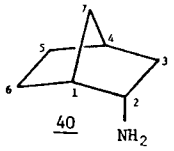
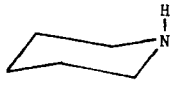
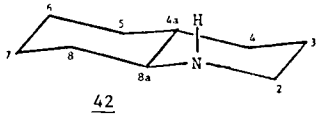
Amine	Carbon Number, Slope, and Slope Ratio(s)[a]							
	α	α	β	β	β	γ	γ	γ
 30	C-1		C-2			C-3		
	40000		100000			1000		
	1		3.5			.025		
	.28		1			.0071		
 35	C-1		C-2					
	175		4500					
	1		25.7					
	.039		1					
 39	C-2		C-1	C-3		C-4	C-6	C-7
	20000		120000	65000		50	615	185
	1		6.0	3.25		.0025	.031	.0092

TABLE XIX (CONTINUED)

Amine	Carbon Number, Slope, and Slope Ratio(s)[a]							
	α	α	β	β	β	γ	γ	γ
 40	C-2		C-1	C-3		C-4	C-6	C-7
	40000		200000	65000		185	275	615
	1		5.0	1.6		.0046	.0069	.015
 41	C-2		C-3			C-4		
	25000		100000			300		
	1		4.0			.012		
	.25		1			.003		
 42	C-2	C-8a	C-3	C-4a	C-8	C-4	C-5	C-7
	14000	25000	45000	60000	4000	7000	13500	600
	1	1.8	3.2	4.3	.28	.50	.96	.043
	.56	1	1.8	2.4	.16	.28	.54	.024

a. The slope of the line obtained by plotting linewidth (Hz) vs. the mole ratio of added $Cu(acac)_2$. The value shown is the slope as the ratio approached zero.

this pattern to all of the amines collectively, it becomes apparent that they fall naturally into two groups, A and B (Table XVIII, p 96), based on whether or not the amino group is on a tertiary carbon. For the compounds with the amino group on a tertiary carbon (Group B), the line broadening averages about 100 times less than for the corresponding carbons in the Group A amines. These results correspond to those of Wenkert,[45] who found that the amount of $Cu(acac)_2$ needed to broaden the ^{13}C nmr lines of the sterically hindered amine 29 (p 26) was much greater than that used in the examples of Doddrell.[5]

However, even when divided into the two groups, the wide range of values that are observed prevents any assignment of characteristic values to α or β carbons. It is not clear if the observed variations between similar compounds are real or if they are due to problems mentioned in the previous sections. The greatest interest, from the point of view of stereochemistry, is in the γ carbons. For the cyclohexylamines there is a significant difference in the amount of line broadening of the γ carbons depending on whether the amino group is axial or equatorial. A "W" relationship exists between the equatorial amino groups and the γ carbons and, as expected from the work of Morishima[23], this will allow more effective line broadening than in the axial amines, which have a "folded" relationship. For 4-t-butylcyclohexylamine (31 and 32, p 28) and 1-methyl-4-t-butylcyclohexylamine (37 and 38, p 28), the line broadening of the equatorial amine isomer is 50 times that of the axial isomer and for 2-adamantylamine, the γ_{anti} ("equatorial") carbons

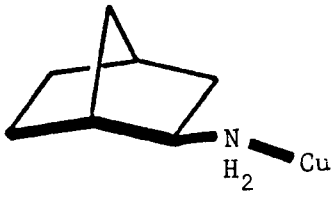
broaden 13 times as much as the γ_{syn} ("axial") carbons. Since 31 and 32 (p 28) were run as mixture, the possibility was considered that selective complexation was responsible for some of the observed differences. An 80:20 trans: cis mixture of 31 and 32 (p 28) was obtained by low temperature recrystalization of the original 65:35 trans:cis mixture. The same line broadening results were obtained for each mixture. Based on this very small sample, a tentative quantitative distinction between "Group A type" axial and equatorial cyclohexylamines would be that for axial amines the γ carbons have a line broadening of less than about 150 Hz/mole $Cu(acac)_2$ and for equatorial amines the γ carbons have a line broadening of more than about 1500 Hz/mole $Cu(acac)_2$. In an attempt to reduce the differences in line broadening between similar amines and/or minimize the differences between Group A and Group B amines, the data were modified by expressing them relative to the α and β carbons in each amine (Table XVIII, p 96). Hopefully, this would cancel out some of the sources of error. When the data are given relative to the α carbon, the β carbons in Group A fall into a relative narrow range but there is no improvement for the γ carbons. Also, there are still significant differences between Group A and B amines. However, when the data are expressed relative to the β carbon, the differences between Group A and Group B are greatly reduced. The values for the γ carbons for either axial or equatorial amines now fall into a range that can be covered by a factor of four. Based on examples in this work, a quantitative description of the amount of line broadening of the

γ carbon in cyclohexylamines, relative to the β carbon line broadening, is about 0.01 or more for equatorial amines and about 0.0015 or less for axial amines. The reason for the difference between Groups A and B in the relative amount of α and β line broadening is not clear; however it may be related to the previous suggestion of Roberts (p 14).[17] The numbers given above should not be considered suitable for application to "unknown" amines without considerable care. However, the data do show w that the original expectations are feasible, particularly if another system were found which did not show the difficulties encountered with $Cu(acac)_2$-chloroform. Better results might be obtained with $Cu(tfacac)_2$ 50 (p 83) since it gave the most linear linewidth plots.

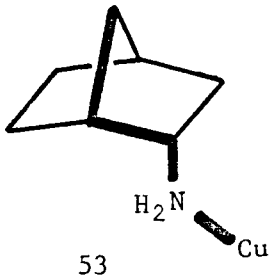
Line broadening data were obtained on some other amines which do not fit into Groups A or B. The only amine studied with two α hydrogens was n-hexylamine 30 (p 28) and the line broadening values obtained are similar to the amines in Group A. The value for the γ carbon lies between those of the γ carbons of the axial and equatorial t-butylcyclohexylamines 31 and 32 (p 28). Similarly, the data obtained for t-butylamine 35 (p 28) correspond to the amines in Group B; however the value for the β carbons is higher than expected considering the values for similarly situated methyl groups in 36, 37 and 38 (p 28).

Good examples of the use of $Cu(acac)_2$ in assigning the ^{13}C nmr resonances of amines are provided by the norbornylamines 39 and 40 (p 28). The line broadening data, along with simple chemical shift considerations and a C-H coupled ^{13}C spectra, permit an unambiguous assignment of all the nmr resonances. In both 39 and 40 (p 28) the

γ carbon which can be in a "W" relationship with the $Cu(acac)_2$ (52 and 53) shows the greatest amount of line broadening. While the differences



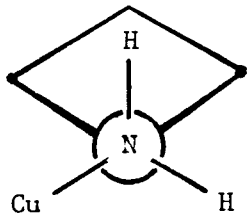
52



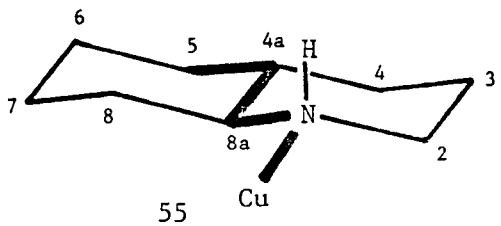
53

are not as significant as with the cyclohexylamines (the "W" is probably not as "good"), this information could allow the complete ^{13}C assignment of 39 and 40 (p 28) without the use of a C-H coupled spectrum.

In trans-decahydroquinoline 42 (p 28) the pattern of line broadening, β > α > γ > all others, has an exception: carbon 8 (β) is broadened less than some of the other α and γ carbons. Also, the line broadening shown by carbon 5 (γ) is much greater than for any other γ carbon in the compounds studied. (The assignments are secure.[71]) These observations can be at least partially ascribed to the completely rigid nature of trans-decahydroquinoline 42 (p 28). In all of the other cyclohexylamines studied, free rotation about the N-C bond is possible. For the equatorial amines there will be two equivalent minimum energy configurations (54, p 104) and thus each γ carbon will be in the ideal "W" relationship less than half of the time. In trans-decahydroquinoline 42 (p 28) the γ carbon 5 is rigidly held in a "W" conformation with the



54



55

N-Cu bond and thus the line broadening is greater (55). Also, the β carbon 8 is in a fixed gauche relationship with the $Cu(acac)_2$ which (assuming a Karplus type interaction) accounts for the unusually small amount of line broadening. Still, some aspects are unexplained. Carbons 4a (β) and 3 (β) show no more line broadening than other β carbons even though they are in the optimum anti relationship. Carbon 4 (γ) shows much more line broadening than expected, especially when compared to the γ carbon of piperidine 41 (p 28) which should be a good model. The relationship of carbons 4 (γ) and 5 (γ) to the nitrogen is similar to that between γ carbons in axial and equatorial cyclohexylamines, but the line broadening ratio observed in trans-decahydroquinoline 42 (p 28) is much smaller. Apparently something besides steric factors is operating which complicates this comparison of a secondary amine with the primary amines.

CHAPTER V

EXPERIMENTAL

Carbon-13 FTNMR spectra were obtained with a Nicolet TT-14 spectrometer operating at 15.08 MHz. Typical parameters were a pulse width of 10 μsec (90° = 14 μsec), spectrum width of 2000 Hz, a one second delay between acquisitions, and 8192 (8K) data points. The number of acquisitions per spectrum was increased from about 500 to 1500 as the lines became broader. Sample temperature was about 35° which reflects the use of broadband proton decoupling. The resulting free induction decays were Fourier transformed with an additional 8K of zero data points which increased the resolution and gave a small increase in signal to noise. No exponential multiplication was used. Chemical shifts were referenced to $CDCl_3$, which was set to 76.9 ppm downfield from TMS. The linewidths at half maximum were calculated with a routine for Lorentzian lines in the Nicolet computer program which could handle a maximum of about 200 data points (50 Hz for a 16K, 2000 Hz spectra). A computer plotted example is shown in Figure 44 (p 106). Dioxane or cyclohexane was used as an internal "linewidth standard."

The nmr samples were run in 10 mm tubes with about 3 ml of total sample volume to prevent interference from vortexing while spinning. Samples contained about 1 g of amine, which was accurately weighed, and this determined the concentration of the solution of copper complex. Typically, one μl of the copper complex solution was made to give a 10^{-4}

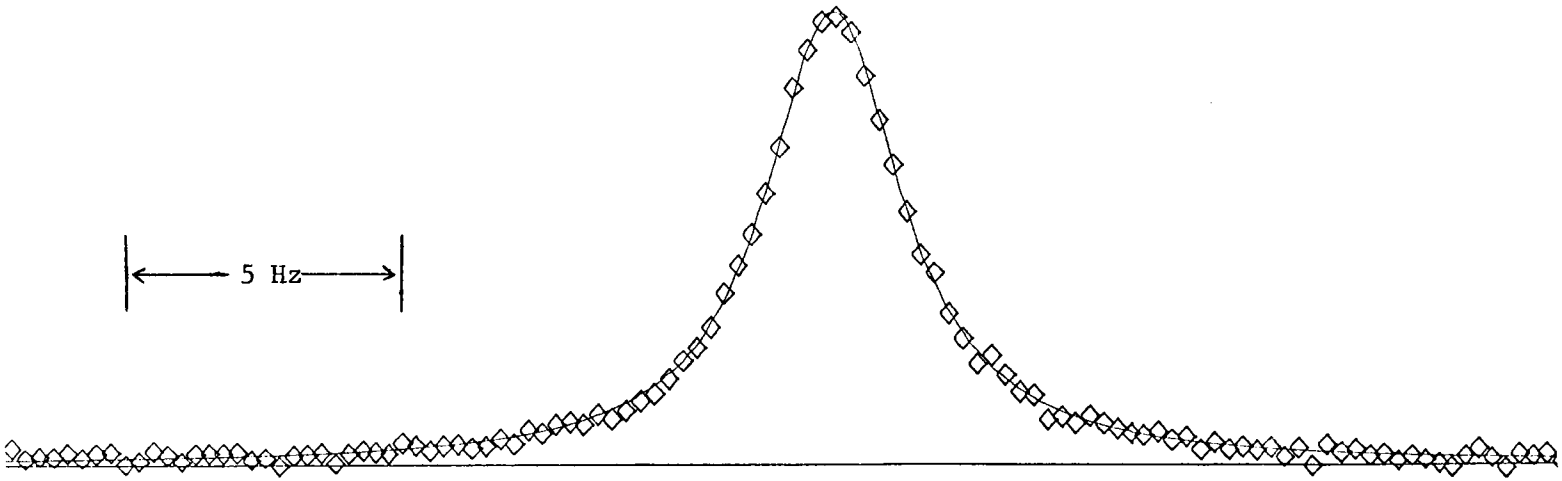


Figure 44. An example of the data obtained for an individual ^{13}C nmr line.

mole ratio of copper to amine. The accuracy of the mole ratio was limited by the syringe. The solvent for the main body of linewidth data (pp 30-64) was chloroform-d. A teflon vortex plug was placed near the top of the nmr tube to minimize contact of the sample with the atmosphere when the cap was removed and the liquids—amine, solvent, and copper solution—were added through a tiny opening in the plug. Decahydroquinoline, endo-norbornylamine, 1- and 2-adamantylamine (42, 40 34, and 33, p 28), which are solids, rapidly formed carbonates and were loaded into the nmr tubes in a dry box. The use of metal containing syringes for the amines, or a metal vortex plug positioner is not recommended as when this was done line broadening was sometimes observed without added $Cu(acac)_2$. The concentration range studied covered a range of about 10^{-5} to 10^{-2} mole ratio of $Cu(acac)_2$ to amine. A typical run is shown in Figure 45 (p 108). Unless described below, the amines (or their HCl salts) are commercially available and were purified by distillation or sublimation.

4-(1,1-Dimethylethyl)cyclohexanamine (31 and 32, p 28).
4-t-butylcyclohexanone was treated with ammonium acetate and sodium cyanoborohydride according to the procedure of Borch to give the amine as a 65:35 trans:cis mixture.[72] A sample enriched in the trans isomer (80:20 trans:cis) was obtained by recrystallization from 30-60 petroleum ether at -78°.

1-Methylcyclohexanamine (36, p 28).
This amine was produced by a Graph-Ritter reaction using 1-methylcyclohexanol.[73] The ^{13}C nmr showed an impurity which may have been 2-methylcyclohexylamine as reported by Haaf.[74]

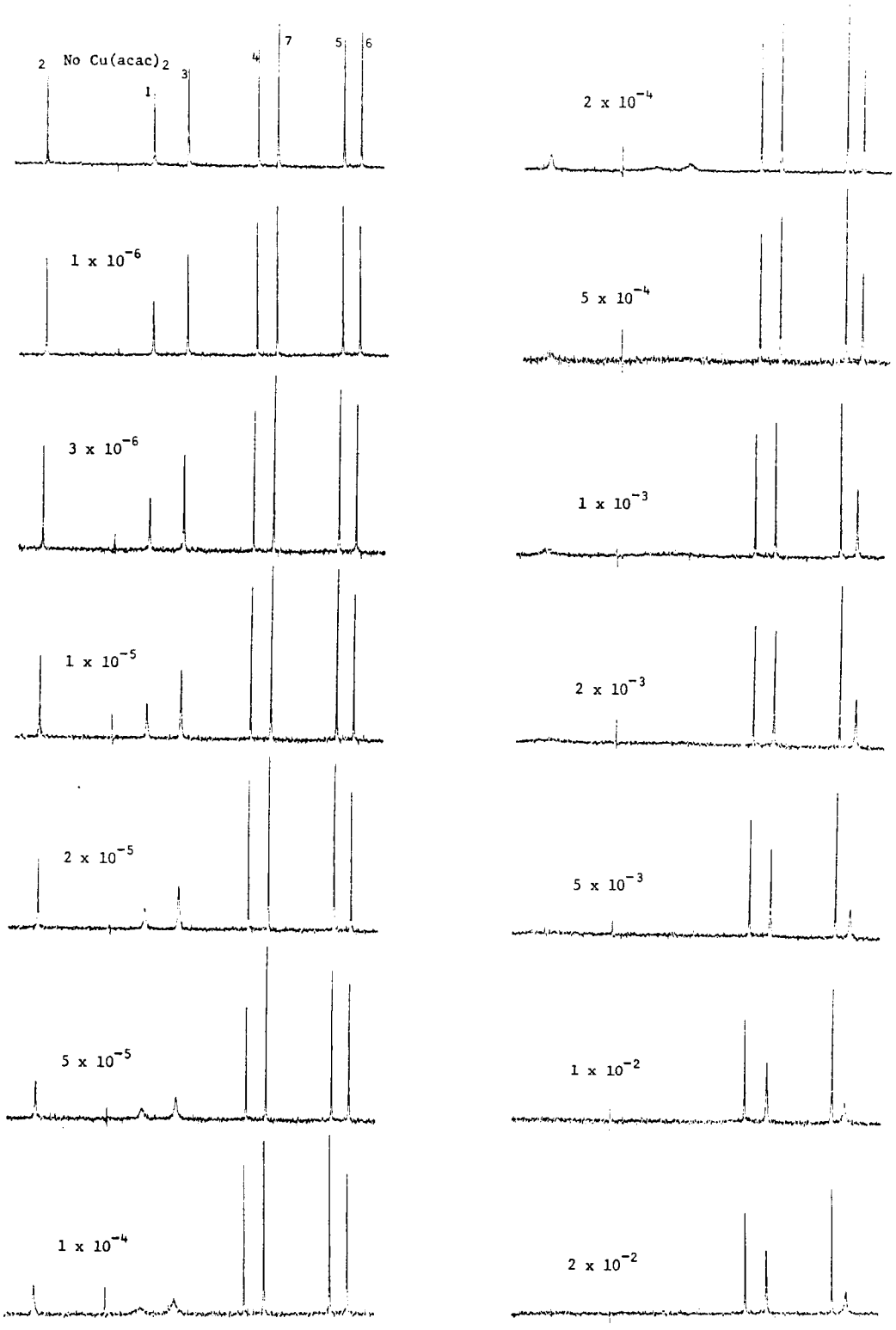


Figure 45. An example of a typical line broadening run.

The mole ratio of $Cu(acac)_2$ to exo-norbornylamine 39 (p 28) is given for each spectra.

4-(1,1-Dimethylethyl)-1-methylcyclohexanamine (37 and 38, p 28). This amine, as a 70:30 axial amine:equatorial amine mixture, was provided from another project in this laboratory.

Tables XX and XXI (pp 110-113) give the ^{13}C chemical shifts of the amines used in this work along with literature data for some other compounds which were useful in assigning the resonances in the spectra of 36, 37 and 38 (p 28) which had not been previously reported. A proton decoupled ^{13}C spectra of cyclohexylisocyanide in chloroform-d was obtained with -NC, δ154.1, triplet, J = 5.1 Hz; C-1, δ51.3, triplet, J = 6.1 Hz; C-2, δ22.4, triplet, J = 0.9 Hz; C-3, δ32.3, singlet; C-4, δ24.6, singlet. The observation of two bond N-C coupling in isocyanides has not been previously reported.[82]

bis(2,4-Pentanedionato-O,O')copper(II).

$Cu(acac)_2$ was available as the dihydrate and was dried by sublimation.

bis(4-Imino-2-pentanonato-N,O)copper(II)(49, p 83).

$Cu(nacac)_2$ was prepared by the procedure of Lacey[83] and sublimed (100°, 10^{-3} mm) to give dark, olive-gray crystals.

General procedure for copper complexes.

Cupric acetate and sodium acetate, in a 1:2.1 mole ratio, were dissolved in water (about 25 ml per gram of copper acetate) and then diluted with an equal volume of ethanol. While stirring, two equivalents of the β-dicarbonyl compound (dissolved in ethanol if it is a solid) were slowly added. Precipitation of the complex usually began at once and stirring was continued until no more increase in precipitate was observed (1-2 hrs). The solid was collected and washed with water, air-

TABLE XX

C-13 CHEMICAL SHIFTS PART 1

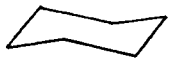
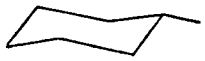
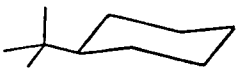
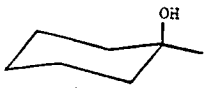
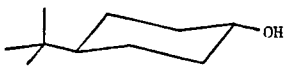
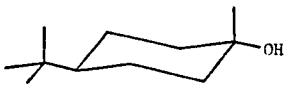
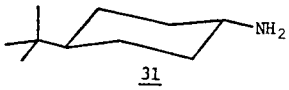
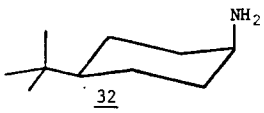
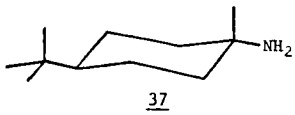
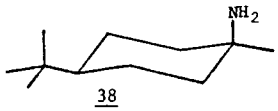
Compound	1	2	3	4	1-Me	C-Me_3	Me_3	References[a]
	27.7	27.7	27.7	27.7				75
	34.1	36.4	27.4	27.4	23.8			75
	26.9	27.4	27.9	48.9		32.6	27.6	76
	27.0	33.0	21.4	48.8	17.5	-	-	75
	32.6	36.0	27.7	48.0	22.8	-	-	75
	69.8	35.8	24.7	26.2				75
	69.6	35.0	23.8	25.1				obs.
	69.8	39.7	22.9	26.0	29.5			77
	69.4	39.6	22.4	25.4	29.2			obs.
	71.0	35.9	25.6	47.2		32.3	27.7	76 (78)
	70.6	35.7	25.4	47.0		32.0	27.4	obs.
	65.8	33.4	20.9	48.1		32.6	27.6	76 (78)
	65.3	33.1	20.7	47.9		32.2	27.2	obs.

TABLE XX (CONTINUED)

Compound	1	2	3	4	1-Me	C-Me_3	Me_3	References[a]
	71.2	41.0	25.1	47.9	25.4	32.5	27.9	77 (76, 79)
	68.9	39.4	22.7	47.7	31.4	32.4	27.8	77 (76, 79)
 22	50.9	37.5	25.7	26.4				75
	49.4	35.9	24.0	24.7				obs.
 36	47.4	39.8	21.8	24.9	28.8			obs.
 31	50.8	37.4	26.3	47.4		32.2	27.6	76
	49.7	36.3	25.1	46.3		31.0	26.4	obs.
 32	45.0	33.9	20.7	48.4		32.4	27.6	76
	43.8	32.8	19.5	47.2		31.2	26.3	obs.
 37	48.2	41.4	23.7	47.2	24.7	31.5	26.8	obs.
 38	47.0	39.7	22.0	47.2	32.3	26.9	31.6	obs.

a. "Obs." indicates observations in this work. Additional references to the same compound are given in parentheses.

TABLE XXI

C-13 CHEMICAL SHIFTS PART 2

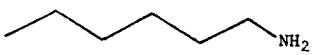
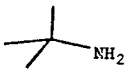
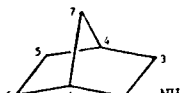
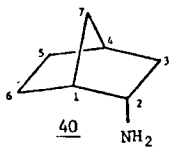
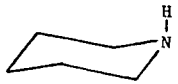
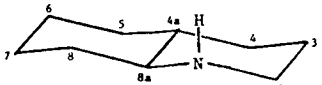
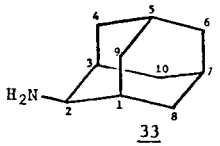
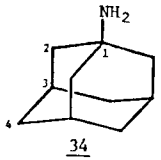
Amine	1	2	3	4	5	6	7	8	8a	References[a]
 30	42.7	34.3	27.0	32.5	23.0	14.3				obs.
 35	47.6	32.9								obs.
 39	45.7	55.4	42.5	36.4	28.9	27.0	34.3			75
	44.2	53.8	41.2	34.9	27.2	25.6	33.1			obs.
 40	43.6	53.4	40.6	38.0	30.7	20.6	39.0			75
	42.2	52.1	39.5	36.6	29.4	19.4	37.8			obs.

TABLE XXI (CONTINUED)

Amine	1	2	3	4	5	6	7	8	8a	References[a]
 41		47.9	27.7	25.9						80
		47.9	27.7	25.6						obs.
 42	43.3[b]	47.3	27.3	32.5	32.6	26.3	25.6	34.0	62.1	71 (80)
	42.7[b]	46.7	26.6	31.8	32.0	25.6	24.9	33.3	61.5	obs.
 33	47.6	47.1	30.3	37.0						81
	47.5	46.9	30.4	36.9						obs.
 34	35.5	55.8	35.5	31.2	27.9[c]	38.6	28.4[c]	38.2		81
	34.2	54.5	34.2	29.7	26.9[c]	37.0	26.4[c]	36.7		obs.

a. "Obs." indicates observations in this work. Additional references to the same compound are given in parentheses.

b. Carbon 4a.

c. Interchangeable, assignment made by comparison to the δ carbons of 31 and 32 (p 28).

dried, and then recrystallized and/or sublimed. While more precipitate could often be obtained by making the filtrate more basic with potassium carbonate or sodium hydroxide, such precipitates were not used due to doubts about their purity or the purity of the starting diketone. The observed melting points of the complexes used in this work are given in Table XXII (p 115).

bis(1,1,1-Trifluoro-2,4-pentanedionato-O-O')copper(II)(50, p 83). $Cu(tfacac)_2$ was sublimed (140°, 10^{-3} mm) to give a very fluffy lavender powder which turned turquoise on contact with ethanol.

bis(2,2,6,6-Tetramethyl-3,5-heptanedionato-O-O')-copper(II)(51, p 83).

$Cu(dpm)_2$ was recrystallized from 100° ligroin to give almost black crystals. Sublimation (140°, 10^{-4} mm) gave a purple powder.

$Cu(acac)_2$ catalyzed reaction of piperidine and carbon tetrachloride.

In a 250-ml flask was dissolved 20 ml of piperidine and 100 mg of $Cu(acac)_2$. To this green solution was added 20 ml of carbon tetrachloride while stirring, and a white precipitate began to form immediately. The temperature and amount of precipiate gradually increased. After 20 minutes the temperature reached 44° and began rising more rapidly and, at 23 minutes, a violent reaction commenced which expelled a portion of the contents of the flask. The maximum temperature was 135°. The residue consisted of a tan solid mixed with a dark,tar-like material.

TABLE XXII

MELTING POINTS OF COPPER COMPLEXS

Compound	Observed Melting Point	Literature Melting Point	Reference
$Cu(acac)_2$	240 dec.	236	84
$Cu(tfacac)_2$ (50 p 83)	196-7	190-2 189	85 86
$Cu(nacac)_2$ (49 p 83)	185-7 dec.	190-2 dec.	87
$Cu(dpm)_2$ (51 p 83)	195-6	197-8	88

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LIST OF REFERENCES

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