Texas A&M University
N-M-R Newsletter

No. 177

June, 1973

(Cont'd inside on p. (i))

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Dr. Bernard L. Shapiro
Department of Chemistry
Texas A&M University
College Station, Texas 77843

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April 12, 1973

Prof. B.L. Shapiro
Department of Chemistry
Texas A & M University

College Station, Texas 77843

Abnormal ^{13}C Shifts in Amines

I have read with interest Dr. J.D.Roberts letter on the "wrong-way" ^{13}C shifts induced in amines by Europium chelates (TAMUNN 171-40, Dec. 1972).

Both Roberts (loc.cit.) and Cushley, Anderson, Lipsky (Chem.Comm. 636, 1972) are unaware of another report on this argument (A.A.Chalmers, K.G.R.Pachler-Tetr.Letters 4033, 1972. ^{1}H and ^{13}C spectra of quinoline in presence of LSR).

Interestingly, the latter Authors find the "wrong-way" ^{13}C shifts for both the β -carbons in quinoline (C-3 and C-10) while Roberts saturated amines show only one β -carbon "wrong-way" shifted.

Chalmers and Pachler data indicate slight but definite differences among the various chelates and lanthanides.The data, furthermore,allow to reconsider their interpretation of the -effect in terms of Contact Shifts (also Cushley, Anderson and Lipsky give credit to contact shifts in their paper).

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In fact, the ^{10}H and ^{13}C Pr/Eu shift ratios deduced from the Chalmers and Pachler data for quinoline are reasonably constant (allowing for the experimental error and omitting the C-3 and C-10 signals in calculating the average). Figures in the Table show that the Pr/Eu shift ratios vompare also reasonably with existing literature data.

This would speak against a contact shift mechanism and seems to favor an explanation of the "β effect" in terms of specific delocalization of σ or π electrons

Sincerely,

Giorgio Montaudo

^{1}H-LIS	Pr/Eu	Reference	^{13}C-LIS	Pr/Eu	Reference
Ld(dpm)$_3$	1.9	1,(vinylpyridine)	Ld (dpm)$_3$	1.7	5, (Bormeol)
Ld (dpm)$_3$	1.4	2,3(Ketones)	Ld (dpm)$_3$	1.4	C. & P.(Quinoline)
Ld (fod)$_3$	1.9	4,(Amides)	Ld(fod)$_3$	1.4	C. & P (Quinoline)
Ld (dpm)$_3$	1.8	C. & P. (Quinoline)			
Ld(fod)$_3$	2.0	C. & P. (Quinoline)			

1) W. De W. Horrocks and J.P.Sipe - J.Amer.Chem.Soc.93, 6800 (1971)

2) P.Kristiansen and T.Ledaal - Tetr.Lett. 4457 (1971).

3) P. Belanger - Chem. Comm. 266 (1971).

4) G.Montaudo - Unpublished.

5) J.Briggs, F.A.Hart, G.P.Moss, E.W.Randall -Chem.Comm.364 (1971).

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May 15, 1973

Title: Cassettes Revisited: Automatic T_1 on Mag Tape; Interrupted Time-Averaging - Bibliography on Applications of ^{13}C NMR in Biochemistry.

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

Dear Barry:

Charlie Peters has exerted his talents again to modify the Freeman-Hill T_1 program (620L version, P/N 20309-M) for Sykes cassette operation. In this version three new commands are added (at the expense of GN, AV, and DL.) These allow the automated collection of data in the normal inversion recovery modes while storing the accumulated FID's on tape for each value of delay time. No worry about fitting spectra on the paper, pens drying up, wrong choice of exponential weighting, etc. After the experiment is finished (overnight or weekend operation would be very convenient) the data can be looked at for optimum choice of weighting function and either called individually by the single-plot command SP followed by spectrum number, or sequentially, using the staggered plot by the command MP (multiple plot). One can take full advantage of the chart dimensions by plotting each spectrum on a different sheet to full expansion (vertical and horizontal) even in the MP mode since there is plenty of time for inserting a new sheet of paper on the recorder during the tape-to-core transfer of data for the next plot. Having the raw data still on tape allows use of different weighting functions on the same raw data to improve signal-to-noise on a broad noisy peak and yet later apply no weighting at all on a stronger, closely-spaced peaks. To select the tape mode of operation the command MT=1 is used. MT=0 gives the unmodified Freeman-Hill version. I shall be glad to supply anyone with the proper list of software changes for the 620-L/Compucorder-100 system.

Another nice application of the cassette that I had recourse to try recently is the continuation of time-averaging after other nucleus interuption. An example of this would be a couple of hours of ^{13}C FT time-averaging, switch to proton for a couple of hours, and switching back to the same sample as before for resumption of time-averaging. There's no problem with frequencies on the XL-100 since the deuterium lock solvent fixes the ^{13}C frequencies also but in general due to small differences in the insert position, etc. there may be small phase errors in any new spectrum. These can be avoided by making sure that the same phase settings are used on the FT module as during the first acquisition. Then a test sample containing the same solvent plus a compound containing peaks across the spectrum is inserted, a few pulses taken and the <u>observe channel phase</u> adjusted for proper phase by repeating the experiment for different observe channel phases. Usually a couple of trys taking less than a couple of minutes will do the job and the signal-averaging can be resumed on the sample of interest after reading in the old data off of the cassette. Of course, this "calibration"

Professor Bernard L. Shapiro May 15, 1973

should have been done before the first acquisition to establish the proper phase settings on the FT module. In certain situations this technique will save data which otherwise would have to be destroyed and also makes possible extremely long averaging (every night for a week, several weekends, etc.) without tying up the instrument during high demand periods.

It may be of interest to those who did not attend the ENC at Boulder that the bibliography of titled references "Applications of ^{13}C nmr in Biochemistry" is available through Varian Instrument Division, Palo Alto (ATTN: ^{13}C NMR). This was a spin-off of a review I put together (same title) which should be appearing about now in Critical Reviews in Biochemistry published by CRC Publishing, 18901 Cranwood Parkway, Cleveland, Ohio 44128. The bibliography covers the literature fairly comprehensively up to March, 1973.

Sincerely yours,

George

George A. Gray
Senior Applications Chemist

GAG/dp

Yale University
SCHOOL OF MEDICINE
NEW HAVEN, CONNECTICUT 06510

SECTION OF PHYSICAL SCIENCES

May 17, 1973

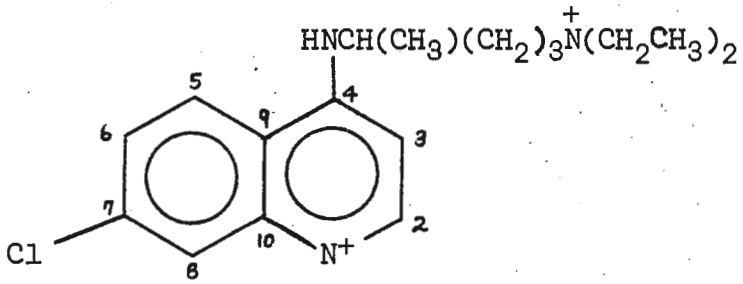
Professor B.L. Shapiro
Department of Chemistry
Texas A and M University
College Station, Texas 77843

Dear Barry:

I must apologize for letting my "subscription" to the TAMU NMR NEWSLETTER lapse to the point where it has taken on a decidedly pink tinge.

TITLE: ^{13}C Study of Antimalarial Binding to DNA.

Perhaps the most interesting data we have obtained lately has resulted from our program which involves studying the interactions of small molecules with biomacromolecules. Specifically, we have studied the problem of binding the antimalarial chloroquine diphosphate (CQDP) to DNA by means of ^{13}C FT NMR.[1]



CQDP

We have been able, thus far, to carry out these experiments using natural abundance CQDP due to the efforts of Ned in getting large amounts of DNA into solution (up to 25 mg/ml).

In the course of this work, we were struck by the dramatic differences seen in the ^{13}C line-widths of the aromatic carbons. The accompanying Figure shows the natural abundance ^{13}C spectrum

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SECTION OF PHYSICAL SCIENCES

of buffered 0.15 M CQDP in the region 99.2 ppm to 161.1 ppm downfield from external hexamethyldisilane (HMDS). (NOTE: Carbons 5,6 and 8 are not specifically assigned as yet, but, since they are all methine carbons and show the effects discussed below to the same extent, their assignments at this point are moot). Upon addition of 0.06 M DNA to the solution, the aromatic carbons broaden significantly due to binding. However, there is a dramatic difference in the line-widths of four of the ^{13}C resonances as compared to the other four, C2 being buried beneath the low field C_6F_6 line. As it turns out, all of the protoned aromatic carbons are approximately 5 times broader than the tertiary carbons (Table). We have shown that the magnitudes of the broadening ($1/T_2^*$) varies with concentration of DNA.

	$1/T_2^*$ (Hz)	
Carbon Number	CQDP	CQDP + DNA
3	4.0	17
4[a]	1.5	3.5
5	3.5	14
6	3.5	17
8	3.5	13
7[a]	2.5	3.5
9[a]	2.5	2.5
10[a]	2.5	3.5

a. Carbons bearing no directly bonded hydrogen.

Clearly, the effects of binding are modulated through the protons.

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SECTION OF PHYSICAL SCIENCES

One possible, but at this point most tenuous, explanation is that the scaler C-H coupling effect on the transverse relaxation rate originally reported by Shoup and VanderHart[2] is operative. Their study was based on the formalism of Gutowsky et al[3] which relates equations of chemical exchange in a simple way to quadrupolar (or fast) relaxation.

We are currently quantifying our results before proposing a mechanism for the observed phenomenon. The T_1 measurements currently underway should shed considerable light on the phenomenon and also the mode of binding of CQDP to DNA.

References

1. This work was reported at the 14th ENC, Boulder, Colo. April 16-18, 1973.

2. R.R. Shoup and D.L. VanderHart, J. Amer. Chem. Soc. 93, 2053 (1971)

3. H.S. Gutowsky, R.L. Vold and E.J. Wells, J. Chem. Phys. 43, 4107 (1965)

Sincerely yours,

Robert J. Cushley

Robert J. Cushley
Associate Professor

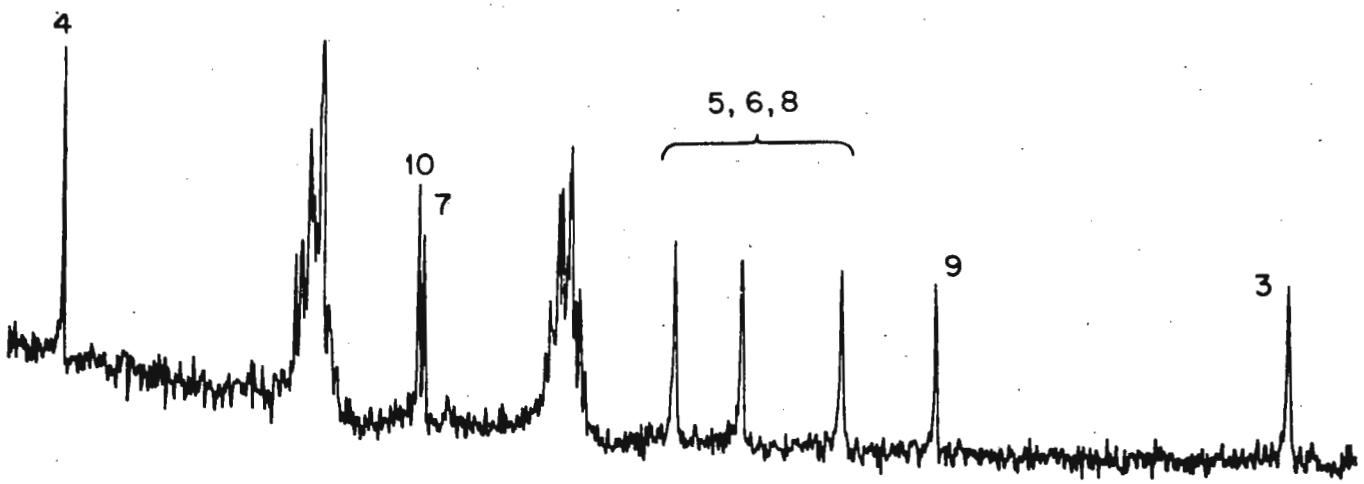
RJC/ak

Edward M. Newman

Edward Newman

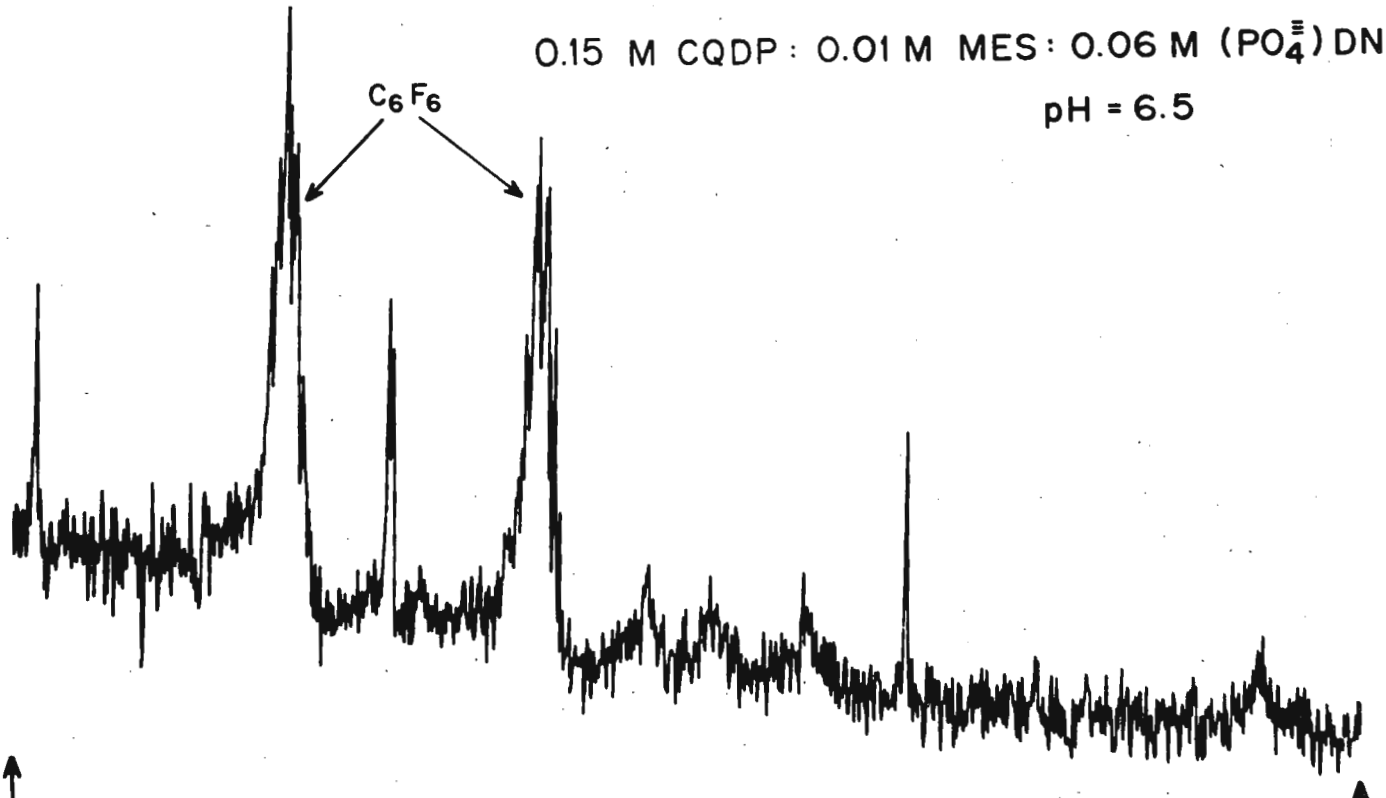
0.15 M CQDP : 0.01 MES pH = 6.5

AROMATIC REGION



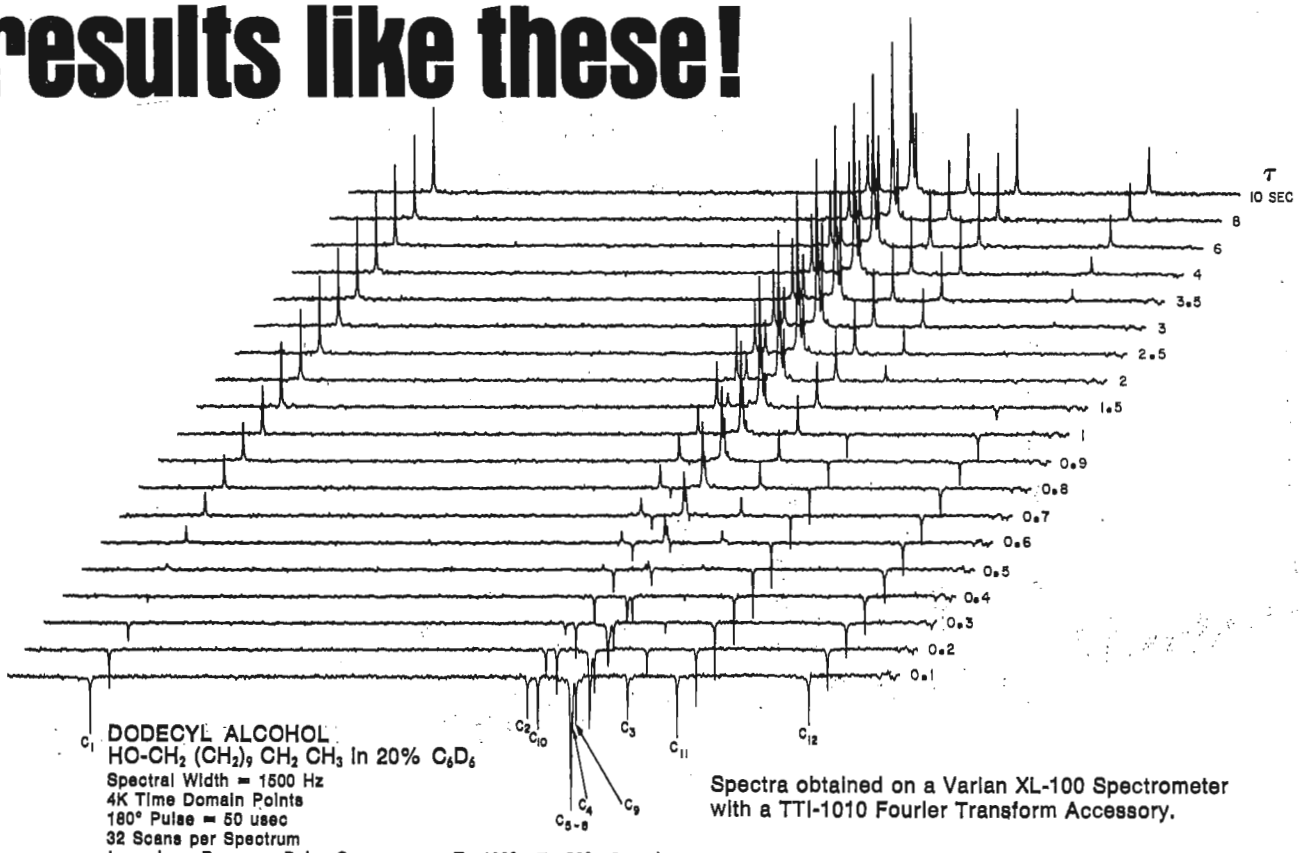
0.15 M CQDP : 0.01 M MES : 0.06 M ($PO_4^{\equiv}$) DNA

pH = 6.5



Hz from HMDS

Your Ft nmr system can provide results like these!



DODECYL ALCOHOL
$HO\text{-}CH_2\ (CH_2)_9\ CH_2\ CH_3$ in 20% C_6D_6
Spectral Width = 1500 Hz
4K Time Domain Points
180° Pulse = 50 usec
32 Scans per Spectrum
Inversion—Recovery Pulse Sequence . . . T - 180° - τ - 90° - Sample . .

Spectra obtained on a Varian XL-100 Spectrometer with a TTI-1010 Fourier Transform Accessory.

It's easy using the Nicolet 1080 Data System. The 1080 incorporates unique concepts designed specifically for the scientific laboratory. It has two processing units—a wired one for acquiring data and a programmable one for processing data. Thus each unit performs the functions it does best. Signals are digitized and added to memory by the wired processor while it is displaying the entire averaged signal in a continuous, flicker-free display. This unique signal averager approach to data acquisition allows the display to continue regardless of the data acquisition rate (up to 100 kHz) so that the user can examine the input signal or the averaged signal, at any vertical or horizontal expansion, **without interrupting the data acquisition process.** This allows instantaneous inspection of the signal to noise as well as examination of the data for pulse feedthrough, decoupling power, and frequency offset.

The unique 20-bit word 1080 data processor not only allows more single-precision dynamic range than any other, but it also has a much more powerful instruction set. This permits faster and more efficient data reduction and programming simplicity.

The above spectra of dodecyl alcohol were obtained using the Nicolet automatic T_1 program, which utilizes the $[180° - \tau - 90° - (\text{sample}) - T]_n$ inversion recovery[1] or PRFT[2] pulse sequence. In this experiment, the value of the inter-pulse interval τ is varied from a time much less than the shortest T_1 to a time about 5 times longer than the longest T_1 in the sample. Data are signal averaged at each value of τ and stored on the Nicolet 600,000 word cartridge disk memory.

For $\tau \ll T_1$, nuclear magnetization will still be inverted when the 90° pulse is applied, leading to inverted peaks in the transformed spectrum. For $\tau \approx T_1 \ln 2$, a null will be observed, since at this time the magnetization is just passing through zero when the 90° pulse is applied. Finally, when $\tau \gg T_1$, the nuclei will have returned to their usual precession about the +z axis before the 90° pulse is applied, and the experiment reduces to the usual single pulse Ft nmr experiment.

After all spectra are obtained, they are processed all at once and displayed or plotted as shown. The spin-lattice relaxation times of each line can be estimated from the plots or calculated using a least squares treatment, from the equation $A = A_0\ [1 - 2 \exp(-\tau/T_1)]$. This calculation is performed directly by the program upon command.

This quality of data and ease of operation can be yours with the Nicolet 1080 Data System, including the 600,000, 20-bit word NIC-294 cartridge disk system and the NIC-293 Pulse Controller. This latter unit allows the production of up to eight computer-selectable times corresponding to rf pulses and pulse intervals. This unit is already in use measuring T_1's, T_2's, performing gated decoupling and homonuclear pulsed decoupling and providing the versatility for use in almost any definable experiment.

The Nicolet 1080 Data System has been successfully used with all major spectrometers and is also available with a complete Fourier pulse accessory package for the Varian XL-100 through Nicolet's affiliate, Transform Technology, Incorporated.

Why not investigate the features of the 1080 Data System and find out how it can make your nmr spectrometer perform more efficiently.

1. R. L. Void, J. S. Waugh, M. P. Klein, and D. E. Phelps, **J. Chem. Phys. 48,** 3831 (1968).
2. A. Allerhand, D. Doddrell, V. Glushko, D. W. Cochran, E. Wenkert, P. J. Lawson and F. Gurd, **J. Am. Chem. Soc. 93,** 544 (1971).

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4 Mai, 1973.

Prof. B. L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843
U.S.A.

Additivity rule for the estimation of ^{13}C-chemical shifts in aliphatic compounds

Dear Prof. Shapiro,

There are many useful additivity rules for estimating ^{13}C-chemical shifts in various classes of compounds. For aliphatic compounds, they are mostly extensions of the rule for aliphatic hydrocarbons originally published by Grant and Paul [1]. We have collected and extended these rules, amalgamating them into a single formula giving acceptable results for a wide variety of aliphatic compounds [2].

In the past year, the ^{13}C-chemical shifts thus predicted were compared to those actually measured for a large and motley collection of compounds. The deviations found are generally smaller than $\pm$ 3 ppm; for shifts above 100 ppm or so, large errors have to be taken into account. This rule is completely unsuited for applications to polyhalogenated compounds.

The rule and the increments are given in Tab. 1 and 2.

Yours sincerely

J. T. Clerc E. Pretsch

[1]. D.M. Grant and E.G. Paul, J.Am.Chem.Soc. 86, 2984 (1964).
[2]. J.T. Clerc, E. Pretsch and S. Sternhell, ^{13}C-Kernresonanzspektroskopie, to be published at Akademische Verlagsgesellschaft, Frankfurt a.M. 1973.

Tab. 1. Additivity increments for the estimation of ^{13}C- chemical shifts in ppm rel. to TMS.

$$\delta = -2.3 + \sum_i Z_i + S$$

	Substituent	Increments for substituents in position α	β	γ	δ
	-H	0.0	0.0	0.0	0.0
*	$-C\lesssim$	9.1	9.4	-2.5	0.3
*	-C=C-	21.5	6.9	-2.1	0.4
	-C≡C-	4.4	5.6	-3.4	-0.6
	$-C_6H_5$	22.1	9.3	-2.6	0.3
	-F	70.1	7.8	-6.8	0.0
	-Cl	31.0	10.0	-5.1	-0.5
	-Br	18.9	11.0	-3.8	-0.7
	-I	-7.2	10.9	-1.5	-0.9
*	-O-	49.0	10.1	-6.2	0.0
	-O-CO-	54.5	6.5	-6.0	0.0
	-O-CO-(on quat.C)	62.5	6.5	-6.0	0.0
*	$-N\lesssim$	28.3	11.3	-5.1	0.0
*	$-N\lesssim^{+}$	30.7	5.4	-7.2	-1.4
	$-NH_3^+$	26.0	7.5	-4.6	0.0
	-CN	3.1	2.4	-3.3	-0.5
	$-NO_2$	61.6	3.1	-4.6	-0.9
	-C=N-OH syn	11.7	0.6	-1.8	0.0
	-C=N-OH anti	16.1	4.3	-1.5	0.0
	-SCN	23.0	9.7		
*	-S-	10.6	11.4	-3.6	-0.4
	-SO-	31.1	9.0	-3.5	0.0
	-CHO	29.9	-0.6	-2.7	0.0
	-CO-	22.5	3.0	-3.0	0.0
	-COOH	20.1	2.0	-2.8	0.0
	-COO-	22.6	2.0	-2.8	0.0
	$-COO^-$	24.5	3.5	-2.5	0.0
	-CON	22.0	2.6	-3.2	-0.4
	-COCl	33.1	2.3	-3.6	0.0

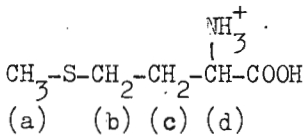
If a γ-substituent is in a fixed conformation, add the following additional increments:

cis: -4.0 , trans: +2.5

Tab. 2. Steric corrections S

^{13}C-Atom observed	Number of non-H substituents on most branched α-substituent (to be applied only to those substituents marked with an asterisk * in Table 1).			
	1	2	3	4
primary	0.0	0.0	-1.1	-3.4
secondary	0.0	0.0	-2.5	-7.5
tertiary	0.0	-3.7	-9.5	-15
quaternary	-1.5	-8.4	-15	

Example



(a)	base value	-2.3
	α S	10.6
	β C	9.4
	γ C	-2.5
	δ C	0.3
	S (p,2)	0.0
	calc.	15.5
	found	15.2

(b)	base value	-2.3
	α S	10.6
	α C	9.1
	2 β C	18.8
	γ NH_3^+	-4.6
	γ COOH	-2.8
	S (s,2)	0.0
	calc.	28.8
	found	30.1

(c)	base value	-2.3
	2 α C	18.2
	β S	11.4
	β NH_3^+	7.5
	β COOH	2.0
	γ C	-2.5
	S (s,3)	-2.5
	calc.	31.8
	found	31.0

(d)	base value	-2.3
	α C	9.1
	α NH_3^+	26.0
	α COOH	20.1
	β C	9.4
	γ S	-3.6
	δ C	0.3
	S (t,2)	-3.7
	calc.	55.3
	found	55.3

Boston College, Chestnut Hill, Massachusetts 02167 Telephone (617) 969-0100

Department of Chemistry

May 16, 1973

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

Dear Barry:

Before temporarily deserting NMR for a sabbatical year of ESR and enzymology, I thought I would bring your readers up-to-date on the progress of a semiempirical theory of substituent effects on ^{13}C chemical shifts.

In my last letter (TAMUN MRN No. 170, p. 14) I indicated that, if one assumes the substituent-induced change in a ^{13}C shift to reflect the change in electron density at carbon then the SCS of C_i in a substituted π-system is given by first-order perturbational molecular orbital theory as

$$\Delta\delta_i = \sum_j K \Delta\alpha_j \pi_{ij} \qquad (1)$$

where $\Delta\alpha_j$ is the substituent-induced change is the Coulomb integral of C_j, π_{ij} is the atom-atom polarizibility and K is an empirically-determined constant. Thus, for a given substituent ($\Delta\alpha_j$ fixed), the SCS can be calculated for any molecular π-system simply by evaluating (or looking up in the Streitwieser-Coulson tables) π_{ij} from a simple Huckel MO calculation. This basic idea will appear shortly in JACS.

It is worth mentioning parenthetically that the above equation provides a rationale for the additivity schemes for ^{13}C shifts which abound in the literature. However, its virtue is that it requires but one parameter per substituent and is transferable between molecular systems, whereas additivity schemes require several parameters per substituent and are confined to one π-system per parameter set.

Having applied my method to most of the systematic data in the literature, I find it to predict successfully (i.e., ± 3 ppm in most cases) methyl- and methoxyl-induced shifts in benzenes, butadienes, styrenes, anisoles, acetophenones, ortho- and para-quinones and (less well) thiophenes. A paper describing this is somewhere between the gleam-in-the-eye and first draft stage.

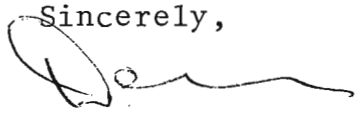
A similar approach has allowed calculation of ^{13}C shifts (not SCS's) of alternant hydrocarbons (i.e., styrene, naphthalene, phenanthrene, biphenyl, pyrene and biphenylene) to within ±2.5ppm. excluding cases where ring current effects are dominant, and a manuscript has just been completed and sent off.

The next-to-last item in this excessively-long letter concerns the parameters $K\Delta\alpha$. Having evaluated them for nine substituents, I did the time-honored organic exercise of plotting them versus Hammett σ-values and found no correlation. The same is true for the Swain-Lupton field (F) and resonance (R) parameters. If, however, one selects only the four halogens, for which the F-values are all about the same, a plot of $K\Delta\alpha$ versus the Taft steric parameter, E_s, gives an excellent (correlation coefficient=0.994) linear correlation, prompting question of whether sterically-induced shielding or deshielding may not be more widespread than one might have suspected.

Finally, since the electronic effects of H and D should be virtually identical, the above results lead to a tentative explanation of isotope effects on ^{13}C shifts as the result of sterically-induced charge reorganization. Since I have neither ^{13}C facilities nor access to the data needed to test the idea, I'd very much like to hear from any of your readers who may have shift data for deuterated, unsubstituted alternant hydrocarbons, with a view toward collaboration.

Please send future issues of the Newsletter to me at the Biophysics Research Laboratory, Peter Bent Brigham Hospital, Harvard Medical School, Boston, Mass.

Sincerely,



Dennis J. Sardella
Associate Professor

Short Title: Running it up the flagpole: predicting ^{13}C chemical shifts; sterically-induced shifts; isotope shifts.

TEXAS CHRISTIAN UNIVERSITY
Fort Worth, Texas 76129

Department of Chemistry

May 10, 1973

Dr. Bernard L. Shapiro
Department of Chemistry
Texas A. & M. University
College Station, Texas 77843

Dear Barry:

We have recently been entertaining ourselves by attempting to systematically apply the affect of lanthanide shift reagents to the assignment of resonances in the C-13 spectra of some steroids. For this purpose we have used our own version of the Willcott, Lenkinski, Davis program (J. A. C. S., 94, 1742 (1972)).

The coordinates of the ring carbons of the appropriate steroids were determined from Dreiding models via photographs taken against a grid from long range to avoid paralax.

Noise decoupled and off-resonance decoupled spectra were taken as described by us in J. Mag. Res., 6, 256 (1972). The shift reagent was incremented in and the decoupled spectra redetermined. By using small changes in reagent concentration the movement of the lines in the original spectra could be followed. The shift reagent effect and off-resonance decoupling data were used to assign 5-7 lines as being "sure." Then one ascertains a "best" position of the lanthanide *à la* Willcott, et al.

Given a position for the lanthanide one may then generate a calculated set of lines of the reagent perturbed spectra which are matched against the experimental values. Quality of fit is measured by Hamilton's agreement factor. In cases where it is not apparent which of two possible lines may be assigned to a given carbon one can appeal to the off-resonance spectrum or other consideration to complete the assignment.

We found $Eu(DPM)_3$ to be considerably less satisfactory for our purposes than $Yb(DPM)_3$, particularly for those carbons at and immediately adjacent to the coordination site. Clearly contact term or off-axis symmetry effects are operative here.

Secondly, using cholesterol as a trial balloon worked fine except that the assignments by Roberts, et al (J. A. C. S., 91, 7445 (1969)) for carbons 12 and 16 consistently had to be reversed.

The assignments for cholesterol, i-cholesterol, and epi-i-cholesterol are appended.

Yours sincerely,

Bill

W. B. Smith
Chairman
Department of Chemistry

End of Table

	Cholesterol			i-Cholesterol			epi i-Cholesterol		
C	δ	$Yb^{b,e}$	Eu^b	δ	$Yb^{b,e}$	Eu^b	δ	$Yb^{b,e}$	Eu^b
24	40.3	0.000	0.005	40.1	0.005	0.007	40.4	0.007	0.000
25	28.6	0.001	d	28.5	0.010	d	28.6	0.000	d
26	23.0	0.002	0.005	22.8	0.015	0.000	23.1	0.003	0.000
27	23.2	0.004	0.000	22.9	0.000	0.000	23.2	0.003	0.000

(a) Chemical shifts in ppm for TMS. (b) Relative shifts for maximum reagent concentration of $Yb(DPM)_3$ and $Eu(DPM)_3$. The maximum reagent effects at the hydroxyl carbons for $Yb(DPM)_3$ were 23.0, 20.6, and 26.8 ppm respectively. (c) The assignments for the side chain carbons came from Roberts ~~ref 4~~ and these carbons were not included in the calculations. (d) These resonances were hidden under those due to the reagent. (e) The Hamilton agreement factors were 0.026, 0.048, and 0.033 respectively. The length of the O-Yb bonds were 2.4, 2.3, and 2.3 Å respectively. The C-O-Yb angles were 131.9°, 152.7°, and 157.3° respectively.

Table I. Carbon-13 Chemical Shifts and Relative Shifts for $Yb(DPM)_3$ and $Eu(DPM)_3$[a]

	Cholesterol			i-Cholesterol			epi i-Cholesterol		
C	δ	Yb[b,e]	Eu[b]	δ	Yb[b,e]	Eu[b]	δ	Yb[b,e]	Eu[b]
1	38.1	0.189	0.115	33.9	0.136	0.103	33.5	0.097	0.090
2	32.4	0.451	0.280	25.6	0.141	0.089	25.7	0.158	0.132
3	72.1	1.000	1.000	20.4	0.223	0.213	19.2	0.338	0.257
4	43.0	0.457	0.286	12.1	0.262	0.207	7.2	0.325	0.257
5	141.4	0.194	0.099	39.3	0.485	0.151	40.4	0.464	0.240
6	122.2	0.093	0.060	73.6	1.000	1.000	67.5	1.000	1.000
7	32.6	0.047	0.027	38.0	0.476	0.370	40.8	0.478	0.413
8	32.6	0.047	0.027	30.4	0.320	0.279	35.5	0.200	0.144
9	51.0	0.076	0.049	48.4	0.233	0.192	48.5	0.163	0.162
10	37.2	0.149	0.115	43.2	0.242	0.243	45.4	0.202	0.150
11	21.9	0.030	0.033	23.2	0.121	0.099	23.8	0.080	0.060
12	40.6	0.027	0.022	40.9	0.083	0.063	40.9	0.059	0.036
13	43.0	0.021	0.016	43.4	0.078	0.049	43.3	0.055	0.036
14	57.5	0.028	0.027	56.9	0.136	0.086	56.9	0.089	0.096
15	24.8	0.021	0.011	24.6	0.068	0.055	24.8	0.046	0.036
16	28.6	0.019	d	28.7	0.019	d	28.8	0.018	d
17	57.1	0.015	0.011	56.9	0.044	0.007	57.1	0.025	0.036
18	12.5	0.014	0.016	12.6	0.058	0.043	12.6	0.027	0.018
19	19.9	0.131	0.088	24.4	0.204	0.151	18.3	0.117	0.096
20	36.5	0.010	0.005	36.4	0.015	0.013	36.4	0.018	0.006
21[c]	19.4	0.003	0.005	19.2	0.019	0.020	19.3	0.013	0.012
22	37.0	0.004	0.000	36.9	0.000	0.000	36.9	0.006	0.000
23	24.5	0.006	0.000	24.5	0.000	0.007	24.6	0.003	0.000

UNIVERSITÉ D'OTTAWA UNIVERSITY OF OTTAWA
OTTAWA 2 CANADA
DÉPARTEMENT DE CHIMIE DEPARTMENT OF CHEMISTRY

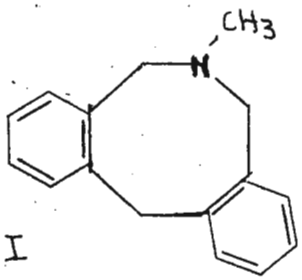
April 26, 1973

Prof. B.L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

Use of $J_{H-\overset{+}{N}-C-H}$ —
A 1,4-Cyclooctadiene Model; N-Methyl-5,6-dihydro-7H, 12H-dibenz[c,f]azocine

Dear Barry:

I'd like to describe some of the results of a joint project with Roger Renaud and Bob Layton of N.R.C. here in Ottawa. We have been studying the proton spectra of the title azocine(I).



I

II

Its conformational properties are of more than casual interest as it should serve as a good model for 1,4-cyclooctadiene II, whose spectral complexity has likely discouraged its investigation. Dreiding models of I or II suggest two stable conformations, the crown (a) and the flexible (b) forms.

a)

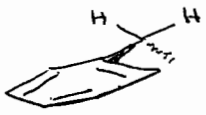
b)

PROF. B.L. SHAPIRO April 26, 1973

The pmr spectrum of I in $CDCl_3$ shows two N-methyl absorptions in a ratio of 92:8. The major isomer is assigned the crown conformation on the following evidence.

(1) The spectrum of the major isomer in TFA (seen to decrease linearly to 66% as TFA is added to $CDCl_3$) shows no vicinal coupling constant for the lowest field protons alpha to nitrogen ($J_{H-\overset{+}{N}-C-H} < 1$ Hz) as can be seen in Figure 1A. Such a lack of vicinal coupling is indicative of a dihedral angle, θ of about 90°≠, an arrangement present only in the crown conformation.

(2) The geminal coupling constant for the isolated CH_2 group of the major isomer is 13.5 Hz, and of the minor isomer 19.0 Hz (measured from the spectrum of I-d_4 in TFA-d shown in Figure 1b). The much larger (negative) ^2J for the minor isomer indicates a greater hyperconjugative withdrawal of electrons from the antisymmetric MO of the CH_2 group in this conformer. Again, an examination of models shows this withdrawal is allowable in the flexible form (Ø = 30° for one benzene ring, 90° for the other), but not in the crown form (Ø = 90° for both rings). Thus, the minor isomer, J = 19, has the flexible conformation.



$\phi = 90°$

(3) The entropy difference between the major and minor isomers is 7 eu with the latter having the larger entropy (obtained from K_{eq} = 11 at 27° and = 124 at -62°C). Such an entropy difference is consistent only with assignment of the flexible form to the minor isomer.

We have also determined the barrier for the conversion of flexible to crown forms to be 15.3 kcal (at -62°C) and are currently studying effects of other substituents at the nitrogen on the conformational properties of I.

Best regards,

Bob

RRF:cmg R.R. Fraser

≠ a paper on the dihedral angular dependence of $J_{H-\overset{+}{N}-C-H}$ is due to appear in Can. J. Chem. in about three months.

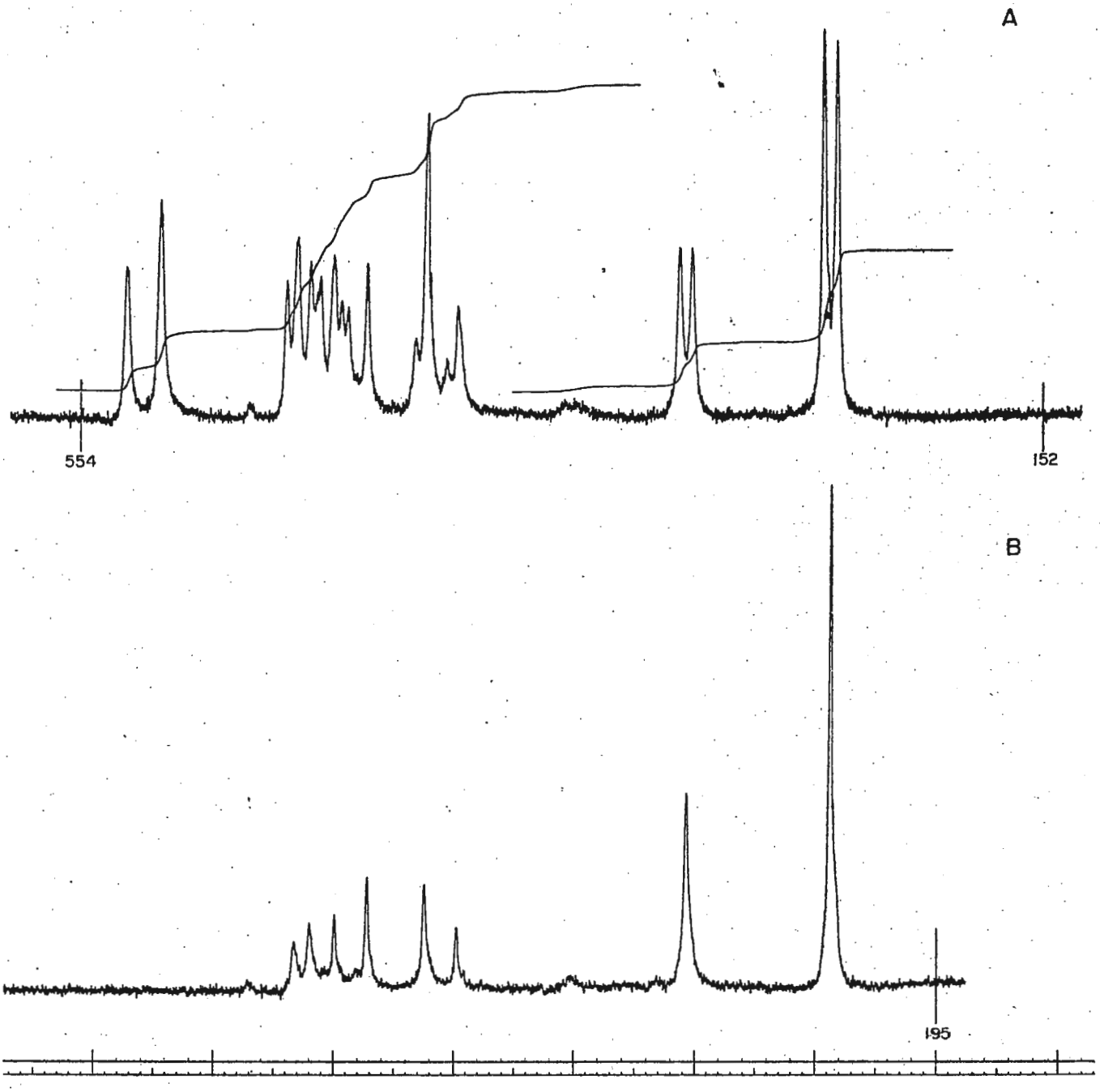


Fig. 1 (A) The ^1H n.m.r. spectrum of $\underset{\sim}{3}H^+$ in TFA.
(B) The ^1H n.m.r. spectrum of $\underset{\sim}{3}D^+$ (d_4) in deuterated TFA.

PHYSICAL CHEMISTRY 2, LUND INSTITUTE OF TECHNOLOGY, LUND, SWEDEN

A COMPARISON OF THE NMR METHODS FOR DETERMINING EXCHANGE RATES

April 12, 1973

Prof. B.L. Shapiro
Texas A & M University
College of Science
College Station
Texas 77843
U S A

Dear Prof. Shapiro,

Recently we have been doing some measurements in the continuing series[1,2] of comparisons of the various methods for determining chemical exchange rates by NMR. The methods we have been comparing are the complete line shape analysis[3], double resonance[4], and spin echo[5] techniques. The complete line shape and double resonance measurements were performed on Varian XL-100 and A-60 A spectrometers and the spin-echo measurements on a Bruker 322s spectrometer with a home-made, single coil probe, which was designed to minimize rf field inhomogeneities.

The first system studied was the internal rotation of methyl nitrite (CH_3ONO) dissolved in deuterated chloroform. A single sample was used for all three types of measurements, and the agreement between methods was excellent. The complete line shape and spin-echo methods produced activation enthalpies (ΔH) of 11.53±0.10 kcal/mole and 11.40±0.13 kcal/mole, respectively. (These are in agreement with Inglefield, et.al.[2] who obtained 11.4±0.3 kcal/mole by complete line shape analysis.) Our double resonance measurements corroborated the other data.

The second system was partially deuterated methyl diazoacetate ($N_2CHCO_2CD_3$) in deuterated chloroform. In this case, the mixture was prepared in common; however, part of it was transferred to a tube containing an internal methanol capillary for temperature determination, a small amount of TMS (final concentration: 0.1 M), and was not degassed.(This sample was used for the high resolution and double resonance measurements.) Another part of the mixture was transferred to an empty tube and partially degassed. (This was used in the spin-echo work.)

The results of the various measurements are shown in Figure 1. The complete line shape analysis corresponds to an activation enthalpy of 12.93±0.12 kcal/mole, while the spin-echo measurements yield 11.8±0.2 kcal/mole. (Kaplan and Melog's[6] value is about 12.0±0.9 kcal/mole, using

a line shape analysis; however the scatter of their points is quite large.) Our activation entropies were determined to be +0.87 e.u. and -3.38 e.u. for the line shape and spin-echo methods, respectively.

The activation enthalpy from the line shape data was determined while excluding many of the points at the extreme ends of the temperature range; however, inclusion of these points increases the discrepancy (by as much as 0.9 kcal/mole). Repeating the measurements did not change the results; and the possibility of a systematic error in the temperature determination was investigated and rejected.

Our attempts to force the two determinations to agree by changing parameters resulted in ridiculous values for the parameters. And no chemical deterioration of the sample could be detected in the high resolution spectrum.

In short, we would be tempted to conclude that the two samples are quite different if it were not for the double resonance data. These data were obtained from the sample used for the line shape measurements, but the value agrees with the spin-echo data.

This tends to indicate that either a) there is something wrong with the complete line shape analysis under certain corcumstances or b) one should normally expect an error of 1-2 kcal/mole in the activation enthalpy, regardless of the standard deviation of the fit. We are reluctant to believe either conclusion without further evidence. Consequently, we would greatly appreciate knowing if any of your readers have ever observed a discrepancy between their complete line shape and double resonance data.

Best wishes

Tom Bull — T.E. Bull

R.E. Carter[7]

Torbjörn Drakenberg

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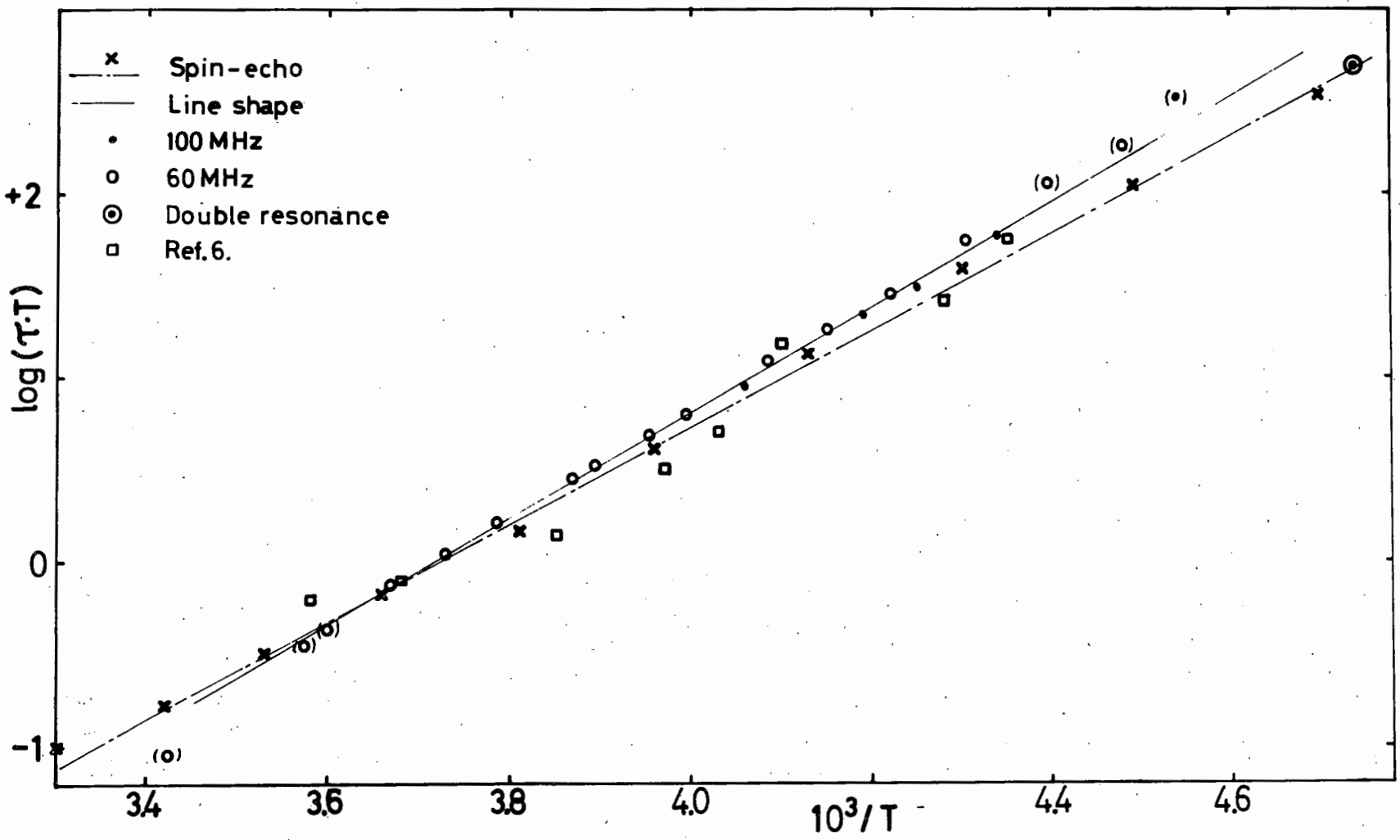
7. Currently on leave of absence at Ohio State Univ., Columbus, Ohio.


Spin-echo
Line shape
100 MHz
60 MHz
Double resonance
Ref. 6.
log (τ·T)
+2
0
-1
3.4
3.6
3.8
4.0
4.4
4.6
10³/T

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

May 11, 1973

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

TITLE: NMR STUDY OF CYTOCHROME C IN FRAGMENTED MITOCHONDRIAL MEMBRANES

Dear Professor Shapiro:

We have recently been interested in using NMR to investigate the interaction of cytochrome c with the mitochondrial membrane. Since cytochrome c is uniquely characterized by the hyperfine-shifted resonance absorptions in its NMR spectrum, it should be possible, in principle, to monitor its in vivo state in the mitochondria, without interference from other proteins present, by NMR technique. Unfortunately, however, the concentration of cytochrome c in intact mitochondria is too low (much less than 100 micromolar) to be detectable by the presently available NMR instruments. We have attempted to use NMR to examine the state of cytochrome c in cytochrome c enriched submitochondrial particles (1) derived from beef heart mitochondria by sonic disruption in the presence of EDTA. The endogenous cytochrome c of the mitochondria was removed by the method of Jacobs and Sanadi (2). The cytochrome c depleted mitochondria thus obtained were then converted into cytochrome c enriched particles by sonic disruption followed by treatment with excess cytochrome c. The level of the reincorporated cytochrome c was about thirty times higher than the normal level occurring in mitochondria (3). A pulsed Fourier transform NMR spectrometer operating at 100 MHz was used for our measurements (4). The experiments were performed in 0.25 molar sucrose solution buffered at pH 7.5 with 0.01 molar tris-acetate. The concentration of cytochrome c was measured optically in the reduced state and found to be approximately 0.4 milimolar for the enriched preparations.

Figure 1 shows the experimental results. In the region of the spectrum shown, free cytochrome c is known to exhibit two hyperfine shifted heme ring methyl resonances around -27 and -30 ppm (from H_2O resonance) (5). Figure 1a shows the result of time-averaging 10,000 pulses of NMR signal from the cytochrome c enriched particle preparation. No detectable NMR absorption can be seen. The methyl resonances in a 0.4 milimolar free cytochrome c solution

are easily observed with 1,000 pulses under the same conditions. Further, on adding 0.5 molar KCl to the submitochondrial preparation, the resonances appeared at the expected frequencies, as shown in figure 1b. A search for the shifted absorptions from membrane fragments covering a wider region (-30 to -5 and +5 to +30 ppm from H_2O resonance) also gave negative results; whereas, for KCl treated preparations, all cytochrome c resonances were observed at the expected frequencies (5). No noticeable change in the NMR signal was observed on adding detergent (Lubrol) to the KCl treated membrane solution, the effect of the detergent being to solubilize the membranes. Similar results were obtained with reduced cytochrome c.

The experimental results above suggest that all cytochrome c incorporated into the membrane is in some way immobilized, perhaps by binding to the membrane, resulting in NMR resonances broadened beyond detection. The observed line-width of a heme-ring methyl is a sum of proton-proton dipolar, and electron-proton dipolar and scalar contributions. The contribution of electron-proton interactions to the line-width is expected to be independent of the tumbling motion of protein molecules, since for cytochrome c, such motion is slow compared to electronic relaxations. The proton-proton dipolar contribution to line-widths is, on the other hand, averaged by the fast rotation of the methyl group around the carbon-carbon bond axis and the slower isotropic tumbling motion of the whole protein. Since the methyl rotational motion is anisotropic, the effect of the much slower tumbling motion becomes observable. The fast anisotropic rotation thus partially averages the proton-proton dipolar interactions, which are then averaged by the tumbling motion of the protein molecule as a whole, resulting in observed line-widths proportional to the tumbling correlation time of the protein molecule. When the protein is bound to membrane, the tumbling correlation time is increased considerably (it is in fact equal to the tumbling correlation time of the membrane fragment if the binding is tight) giving rise to large line-widths due to residual proton-proton dipolar interactions. Our experiments further indicate that the binding of cytochrome c to the membrane is sensitive to the ionic strength of the solution, the bound cytochrome c being released free into solution on addition of 0.5 molar KCl. These conclusions are in agreement with those arrived at by EPR studies on spin-labeled cytochrome c (6). In contrast to our work, the spin label studies are, however, subject to the general criticism that the incorporated spin-label and not the protein may be involved in binding to the membrane. Further, the possibility of a conformational change in cytochrome c upon binding of a spin label can not be ruled out and thus one may not be studying the properties of the native conformation of the protein in these situations.

Yours sincerely,

R. K. Gupta

Raj K. Gupta

P.S. This work was done in collaboration with Dr. C. P. Lee of Johnson Research Foundation, University of Pennsylvania, Philadelphia. Please credit it to the account of Dr. James A. Ferretti.

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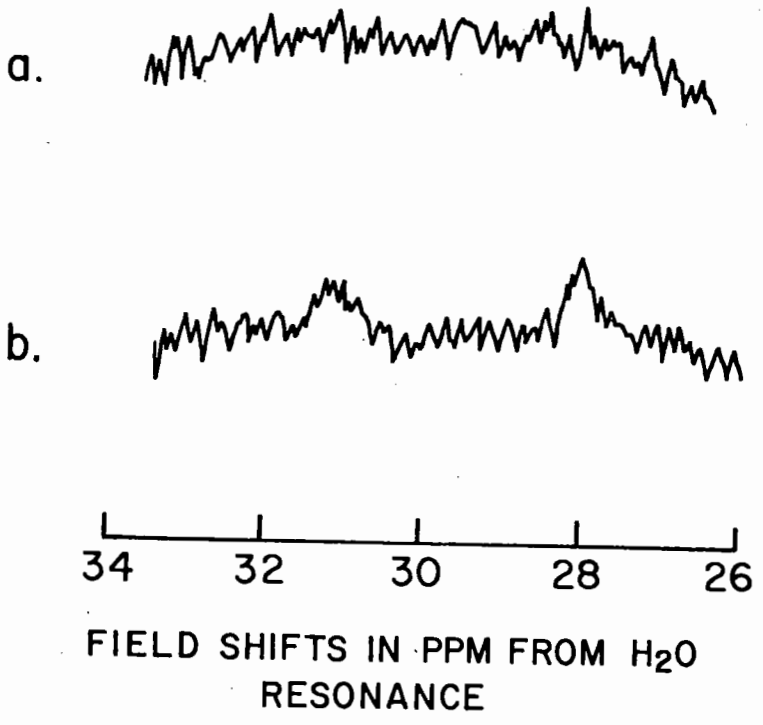


Figure 1. NMR absorption from fragmented mitochondrial membranes enriched with cytochrome c (a) in the absence of any salt obtained after time-averaging 10,000 pulses of NMR signal (b) in the presence of 0.5 molar KCl obtained after time-averaging 1,000 pulses of NMR signal.

177-30

DEPARTMENT OF ORGANIC CHEMISTRY
THE ROBERT ROBINSON LABORATORIES P.O. BOX 147 LIVERPOOL L69 3BX TEL: 051 – 709 - 6022

The University of Liverpool

Professor Bernard L. Shapiro,
Department of Chemistry,
Texas A and M University,
College Station,
Texas 77843,
U.S.A.

14th May, 1973.

Dear Barry,

^{19}F N.M.R. Reference Shifts.

Some time ago when we were investigating ^{19}F shifts in fluoroaromatics, we discovered to our amazement that no survey of the shifts of ^{19}F reference compounds in different solvents existed in the literature. (Or, perhaps more correctly, if it did exist we didn't find it). I am therefore enclosing the results of our own measurements of a variety of ^{19}F compounds, including most of the usual reference compounds in the common solvents. These were measured from an external reference, corrected for the solvent bulk susceptibility and then referred to $CFCl_3$ in $CFCl_3$ as 0.00 ppm. This means that the bulk susceptibility correction is invoked on going across the table, but going down the table (i.e. in any one solvent) the values are internal chemical shifts and may be used for reference purposes. The number in parenthesis after the solute is to be added to the number in the table. e.g. C_6F_6 in $CFCl_3$ is 163.06 ppm to high field of $CFCl_3$ in this solvent etc.

These shifts were then used by us to consider the various theories of the solvent dependence of ^{19}F shifts. We came to the conclusion that although the Van-der-Waals mechanism provides a basis for the explanation of the shifts in non-polar solvents, none of the present theories could begin to account for the observed shifts in polar solvents.

This work has been submitted for publication[1,2] if anyone wishes to have further details.

Yours sincerely,

Ray

Dr. R.J. Abraham.

1. R.J. Abraham, D.F. Wileman and G.R. Bedford, J. Chem. Soc. Perkin II
2. R.J. Abraham and D.F. Wileman, J. Chem. Soc. Perkin II.

TABLE 2. ^{19}F Chemical Shifts (p.p.m. upfield[a]) of some fluorocompounds in Anisotropic and Polar solvents, corrected for bulk susceptibility.

SOLUTE		SOLVENT: Anisotropic		Polar					
		CS_2	C_6H_6	$CDCl_3$	CH_2ClCH_2Cl	$(CH_3)_2CO$	CH_3CN	$(CH_3)_2SO$	GAS
(1) CF_2Br_2	(-8.00)	0.53	1.93	0.81	1.67	4.01	3.77	4.98	5.73
(2) $CFCl_3$	(0.00)	-0.75	0.06	-0.63	-0.15	0.89	1.04	-0.03	5.12
(3) CF_2ClBr	(0.00)	-1.05	0.23	-0.74	-0.08	1.76	1.57	1.79	4.64
(4) CF_2Cl_2	(5.00)	0.84	1.93	1.19	1.61	2.82	2.80	1.55	7.17
(5) $CFCl_2CFCl_2$	(66.00)	0.56	1.63	1.18	1.49	2.46	2.44	1.75	5.65
(6) CF_3CCl_3	(81.00)	-0.35	0.79	0.47	0.58	1.39	1.26	-0.22	6.04
(7) $CF_3CHClBr$	(75.00)	-	-	0.90	0.98	1.82	1.69	-0.32	7.38
(8) $C_6H_5CF_3$	(62.00)	-	0.86	0.85	0.72	1.39	1.25	-1.02	7.68
(9) $SymC_6F_3Cl_3$	(111.00)	-0.54	2.82	1.36	2.00	3.90	3.95	2.59	8.12
(10) C_6F_6	(161.00)	-1.03	2.18	0.96	1.56	3.85	3.60	1.63	9.73
(11) α	(80.00)	0.55	1.40	0.80	0.89	1.78	1.52	c	6.33
(12) β nC_6F_{14}	(126.00)	-0.55	0.53	-0.06	0.05	0.80	0.44	c	4.37
(13) γ	(122.00)	0.36	1.34	0.71	0.88	1.55	1.27	c	4.73
(14) C_4F_8	(133.00)	0.32	1.63	1.00	1.02	2.11	1.68	-0.20	7.85
(15) CF_4	(61.00)	-0.05[b]	1.09	0.30	0.51	1.61	1.34	-0.88	7.76[b]

a) Relative to $CFCl_3$ in $CFCl_3$ as 0.00 p.p.m.

b) Taken from W.T. Raynes and M.A. Raza, Mol. Phys., 1971, 20, 555.

c) Insoluble.

Table 3 ^{19}F Chemical Shifts[a] (p.p.m.) of Reference Compounds in Common Solvents; corrected for bulk susceptibility.

Solute		Solvent								
		CCl_4	$CFCl_3$	C_7H_{16}	C_6H_{12}	C_6H_{14}	C_5H_{12}	C_6F_{14}	C_4F_8	Gas
CF_2Br_2	(-8.00)	0.33	1.20	1.06	1.16	1.26	1.49	3.36	3.59	5.73
$CFCl_3$	(0.00)	-0.98	0.00	-0.08	0.01	0.14	0.38	2.50	2.75	5.12
CF_2ClBr	(0.00)	-1.12	-0.18	-0.27	-0.16	-0.05	0.19	2.17	2.41	4.64
$CFCl_2CFCl_2$	(66.00)	0.91	1.69	1.65	1.67	1.81	2.01	3.65	3.75	5.65[c]
sym$C_6F_3Cl_3$	(111.00)	0.75	1.92	1.77	1.87	2.03	2.35	4.94	5.14	8.12[c]
CF_2Cl_2	(5.00)	0.90	1.91	1.89	1.98	2.13	2.37	4.42	4.65	7.17
cisCFCl:CFCl	(103.00)	0.81	2.25	2.12	2.17	2.47	2.79	5.62	5.87	8.91
trsCFCl:CFCl	(118.00)	0.55	1.76	1.63	1.68	1.92	2.21	4.63	4.81	7.46
C_6F_6	(161.00)	0.52	2.06	2.01	2.11	2.35	2.83	5.86	6.01	9.73
CF_3CCl_3	(81.00)	0.34	1.27	1.34	1.37	1.35	1.81	3.58	3.71	6.04
$CF_2:CCl_2$	(87.00)	0.27	1.79	1.84	1.91	2.14	2.49	5.31	5.51	8.67
$C_6H_5.CF_3$	(62.00)	0.77	1.90	2.02	2.17	2.30	2.60	4.93	5.05	7.68[c]
$CF_3CHClBr$	(75.00)	0.70	1.89	2.00	2.06	2.26	2.55	4.70	4.86	7.38[c]
$CF_3C{:}CCF_3$	(52.00)	0.78	1.98	2.01	2.11	2.29	2.56	4.57	4.79	7.29
α	(80.00)	0.75	1.67	1.85	1.89	2.05	2.27	3.80	4.01	6.33
β } nC_6F_{14}	(126.00)	0.04	0.71	0.84	0.86	1.00	1.18	2.37	2.48	4.37
δ	(122.00)	0.79	1.41	1.42	1.49	1.65	1.76	2.82	2.88	4.73[c]
C_4F_8	(133.00)	0.91	2.06	2.23	2.36	2.51	2.89	4.77	4.98	7.85
CF_4	(61.00)	0.16	1.64	1.68	1.82	1.99	2.32	4.42	4.72	7.76[b]

a) Relative to $CFCl_3$ in $CFCl_3$ (0.00) b) Taken from Ref. 4 c) Calculated see text.

Dr. A. Boicelli

Laboratorio dei composti del carbonio contenenti etero-atomi e loro applicazioni
Consiglio Nazionale delle Ricerche
40064 OZZANO EMILIA (Bologna) ITALIA - Via Tolara di Sotto, 81/a - Tel. 799425

16th April 1973

Prof. Bernard L. Shapiro
Texas A & M University
College of Science - Department of Chemistry
College Station, TEXAS, 77843 (U.S.A.)

Dear Professor Shapiro,

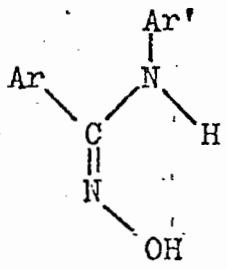
I was very surprised to receive your "Final Notice". Infact I sent my contribution at the end of February. I suppose my letter have been lost along the way or still travelling. It is likely: normally the TAMU NMR NEWSLETTER reaches my laboratory after three months or more (last issue received: n. 171 - Dec. 1972) Aniway I send you again my February contribution plus another one hoping a succesful arrival.

We have studied a set of N-arylbenzamidoximes (Ar-C=NOH.NHAr') to establish their stereochemistry (see table). The 1H-NMR spectra of (1-4) show the presence of only one compound, whereas for the ortho substituted derivatives (5-8), two species are present. This fact suggests either the presence of a syn-anti isomerism at the oximino group or a conformational isomerism due to the hindered rotation around the bond in the C-NHAr' group.

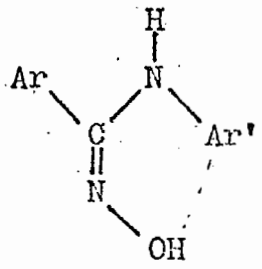
The first hypotesis seems less likely since the syn and anti isomers should have been observed for all the compounds and the Ar pattern shows no indication of syn-anti isomerism.

Hence hindered rotation gives a consistent explanation of the observed spectra.

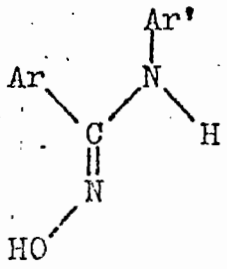
For each configuration of the oximinic group two limiting spatial arrangements of the NHAr' are possible:



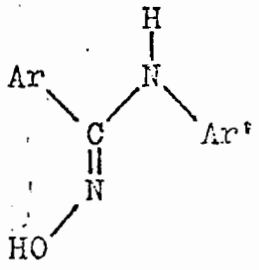
(I)



(II)



(III)



(IV)

The highly simmetric spectral shape in the aromatic region and the equivalence of the ortho methyl groups in (5) and (6) suggest that the averaged positions of Ar and Ar' are those lying in plans perpendicular to that containing the C= NH group.

In this case a shielding effect is expected on the hydroxilic proton in each of the possible configurational isomer. However, for each conformation arising from the hindered rotation around the C-NH bond the higher difference of the shielding condition on the oximinic proton is expected to be observed in the case of syn isomers (I,II). The most aboundant conformer for (5-8) as well the one obseved for (1-4) is more likely (I) than (II). Hence, if (I) is the only stable conformer in (1-4), (II) may become important when ortho substitution generates strong steric repulsion between Ar and Ar' and free rotation is no more possible (in (6) the coalesence of the ortho methyl signals accours at 120°C).

The role of the steric effects appears also from the similar percentages of the two isomers in (5) and (8) where the electronic effects of the substituents are opposite while their steric hindrances are almost the same.

Yours Sincerely

Andrea Boicelli Andrea Boicelli

TITLE: Stereochemistry of N-arylbenzemidoximes

Dear Dr. Boicelli:

Your original contribution sent "the end of February" arrived here on April 10th, one week after our dread pink notice. The second version and the follow-up arrived today (May 24th), despite the fact that you used Air Mail-Special Delivery. We do not have comparable problems with other foreign countries, perhaps in part because most people send things *REGISTERED Air Mail* . I believe that registration helps a great deal. An alternative suggestion is that you send me some Alitalia tickets and I will come to Bologna to pick up your contribution in person. For economic reasons, you may wish to try the registered mail idea first.

By the way, thank you for the lovely Italian stamps which came on your letter.

B. L. Shapiro

TABLE

^{1}H-NMR data[a] for Ar-C(=NOH)-NHAr'

Comp.	Ar	Ar'	NOH	NH	Ar	Ar'	4-Me	2-Me	Is[c] (%)
(1)	C_6H_5	C_6H_5	10.57	8.28	7.35	7.20 - 6.50			
(2)	C_6H_5	4-MeC_6H_4	10.50	8.15	7.35	6.90 - 6.50	2.13		
(3)	C_6H_5	4-ClC_4H_4	10.67	8.50	7.35	7.20 - 6.70			
(4)	4-ClC_6H_4	C_6H_5	10.65	8.35	7.40	7.20 - 6.70			
(5)	2,4,6-$Me_3C_6H_2$	C_6H_5	10.10	8.33	7.35	7.70 - 6.50	2.23	2.11	67
			9.10	8.08			2.28	2.17	33
(6)	3,5-Cl_2-2,4,6-Me_3C_6	C_5H_5	10.35	8.60		7.70 - 6.50		2.18	54.5
			9.40	8.30				2.25	45.5
(7)	2-MeC_6H_4	C_6H_5	10.35	8.35	7.45-	7.80 - 6.60		2.10	83.5
			9.23	8.18	-7.20			2.25	16.5
(8)	2,6-$Cl_2C_6H_3$	C_6H_5	10.45	8.64	7.65 -	7.30 - 6.70			62
			9.50	8.51	-7.35				38

[a] Chemical shifts are in δ units with a standard error of 0.01 ppm. Spectra were recorded in solution of DMSO-d_6 at ca. 7%. [b] Overlapped with CD_2H-SO-CD_3 (1%) in the solvent. [c] Percentages of isomers (I) and (II).

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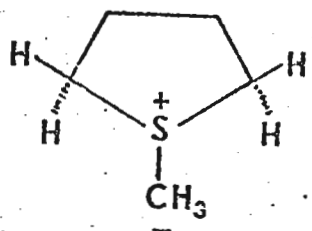
40064 OZZANO EMILIA (Bologna) ITALIA - Via Tolara di Sotto, 81/a - Tel. 799425

li, ...

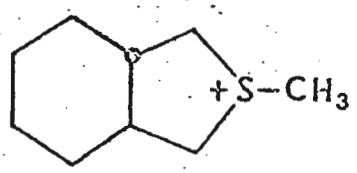
Title: ^{1}H-NMR study on a conformationally rigid thiolanonium cation

Dear Professor Shapiro,

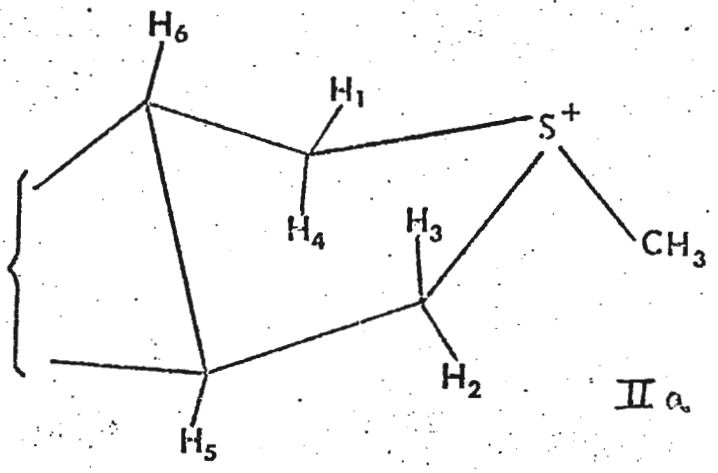
we have studied the compound II, where the trans ring fusion constrains



I



II



IIa

the thiolane rigidly in the half-chair conformation (IIa). This conformational rigidity ensures for each of the α-ring protons a fixed torsional angle with respect to the "direction" of the lone pair on the sulfur atom making this system a very useful model for testing the Wolfe-Czimandia thoery.

Under conditions of base catalysis sulfonium cations are know to undergo ready H-D exchange at α positions. The $\overset{\oplus}{S}-CH_3$ group exchanges much faster than $\overset{\oplus}{S}-CH_2-$, however, of the four α ring protons, one of them, H_2, exchange relatively rapidly with specific rates 9×10^{-5} and 5×10^{-4} l. m^{-1} $sec.^{-1}$ at 59° and 75° respectively (D_2O/NaOD 1.7 or 1.2 N). Of the remaining protons, two, H_3 and H_4 appears to have the same reactivity; the second order specific rates are, aproximately, 7×10^{-6} at 75° and 85° re-

spectively. Thus, the ratio between H_2 and H_3 (or H_4) is about 75 . The fourth proton, H_1, is less reactive still: its apparent exchange rate is about 2 ~ 3 times slower than that of H_3 or H_4, hence some 200 times slower than H_2. It appears, however, that the observed ratio is an upper limit, as pyramidal inversion (which interchanges H_1 with H_2) becomes competitive. It is remarkable that exchange of H_2 and, respectively, H_4 is accompanied by a gradual change of the signal for H_3 and H_1, which eventually become doublets, indicating that H_1, H_4 and H_2, H_3 are geminal pairs.

The irradiation of $\overset{+}{S}-CH_3$ in a derivative of (II) with deuterium replacing H_1, H_3 and H_4 gave a n.O.e. of $15\pm1\%$ for H_2. In the parent ring cation (I), the n.O.e. were 12-1% for the cis protons and $2\pm1\%$ for the trans protons (1). As the conformation of five-numbered ring appears to be the same in (I) and (II), the 15% n.O.e. indicates that in (II) also, H_2 and $\overset{+}{S}-CH_3$ are cis with respect to each other.

1) A. Garbesi, G. Barbarella, A. Fava - Chem. Comm. (in press.)

Best regards

Andrea Boicelli

Andrea Boicelli

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

May 21, 1973

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

Dear Barry:

A New Look at Correlation Spectroscopy

During the past several months we have been engaged in the development of NMR FT-correlation spectroscopy originally suggested by Dadok (1-3). We were successful in obtaining what appeared to be a true slow passage NMR spectrum (free from fast passage ringing effects) of a standard sample by cross correlating its fast passage NMR response with that of TMS reference (known to yield a single sharp line under slow passage conditions) scanned under similar conditions (Fig. 1). Rapid cross correlation is made possible by the use of fast Fourier transform computer programs (the mathematical operation of cross correlation in time-domain is equivalent to complex conjugate multiplication in frequency domain, the operation of complex conjugation in frequency domain being equivalent to time-reversal of a real function in time-domain.)

Following Kisslinger and Cooper (4), we also tried cross correlating the fast passage spectrum with a theoretical function $\exp(-\Delta\omega/bT_2)\sin(\Delta\omega)^2/2b$ which represents only an approximate solution to the Bloch equations for a single spin 1/2 case. However, in disagreement with Ref. (4), our results in this case were not good, the final spectrum showing a distorted baseline. This led us to investigate the theoretical basis of correlation spectroscopy.

The rapid passage response of a spin system in its linear range is given by (5)

$$\int_{-\infty}^{\infty} h(\tau)\, \exp[i(\tau^2 - 2t\tau)b/2]\, d\tau$$

where h(t) is the response to a δ-function in time (the expression is simply the phase-detected convolution integral of h(t) with $\exp(ibt^2/2)$ which represents an r.f. field sweeping at a rapid rate of b radians/sec^2). For TMS the response is given by a similar expression, with h'(t) as its

response to a δ-function. Using the relationship $\int_{-\infty}^{\infty} \exp(i\omega t)dt = \delta(\omega)$ we obtain the cross correlation to be

$$\int_{-\infty}^{\infty} h'^*(\tau)\, h(\tau)\, \exp(ibt\tau)d\tau = FT\,[h'^*(t)h(t)]$$

which is an approximation to the desired cw spectrum. One can see that the line-widths obtained in this way will be sum of the true line-width and the line-width of the reference line. It is possible to obtain a true slow passage spectrum without introducing any additional broadening. This becomes apparent when one finds that the Fourier transform of the fast passage spectrum is simply $h(t)\exp(ibt^2/2)$. All that one therefore needs to do is to transform the rapid passage response and to complex multiply this with $\exp(-ibt^2/2)$ and inverse transform the result (Fig. 2). (This conclusion has also been independently arrived at by Dadok on the basis of a slightly different mathematical reasoning.)

In practice, however, when complex detection is not used, we can show that the Fourier transform of the fast passage spectrum is $\{h(t)\exp[i(\theta+bt^2/2)] + h^*(-t)\exp[-i(\theta+bt^2/2)]\}$ where the phase detector is aligned to detect a component of the signal at an angle θ from the transmitter r.f. phase. Since $h(t) \equiv 0$ for $t<0$, we set the negative half of the transformed result to zero to obtain $h(t)\exp[i(\theta+bt^2/2)]$ which on multiplication with $\exp(-ibt^2/2)$ and inverse Fourier transformation yields real and imaginary parts which are linear combinations of the slow passage absorption and dispersion signals. A rotation of the complex result by an angle θ in the complex plane then yields pure absorption and dispersion.

Our experience with the experimental aspects of the technique is summarized below.

1. The optimum filter bandwidth for the spectrometer filter is $\sim bT^*_{2m}$. T^*_{2m} is the longest T^*_2 of interest.

2. Since in all variations of the technique the data just before the final inverse transformation is like a simple free induction decay (response of spins to a δ-function), it is possible to apply digital filtering (sensitivity and resolution enhancement) ideas of the pulse-FT method at this point, e.g. for optimum S/N an exponential filter with a time constant T_2^*, as pointed out by Ernst, should be useful.

3. While correlating with TMS the output spectrum gets referenced to TMS. However, if there are resonances appearing at frequencies higher than TMS then one runs into a problem similar to foldover in FT-NMR. In such a situation the resonance instead of appearing at $(\omega_{TMS} - \omega_K)$ appears at $(\omega_K - \omega_{TMS})$ so that one must adjust the field such that the reference line occurs above all resonances of interest.

4. R. F. reference phase setting on the spectrometer does not need to be adjusted. In correlating with TMS the final spectrum is phased correctly as long as the unknown and TMS are recorded under identical phase setting.

5. Truncation of wiggles broadens resonances , so one would need to record the fast passage spectrum for a time T_2^* beyond the last resonance of interest.

Sincerely yours,

R. K. Gupta

J. A. Ferretti

E. D. Becker

REFERENCES

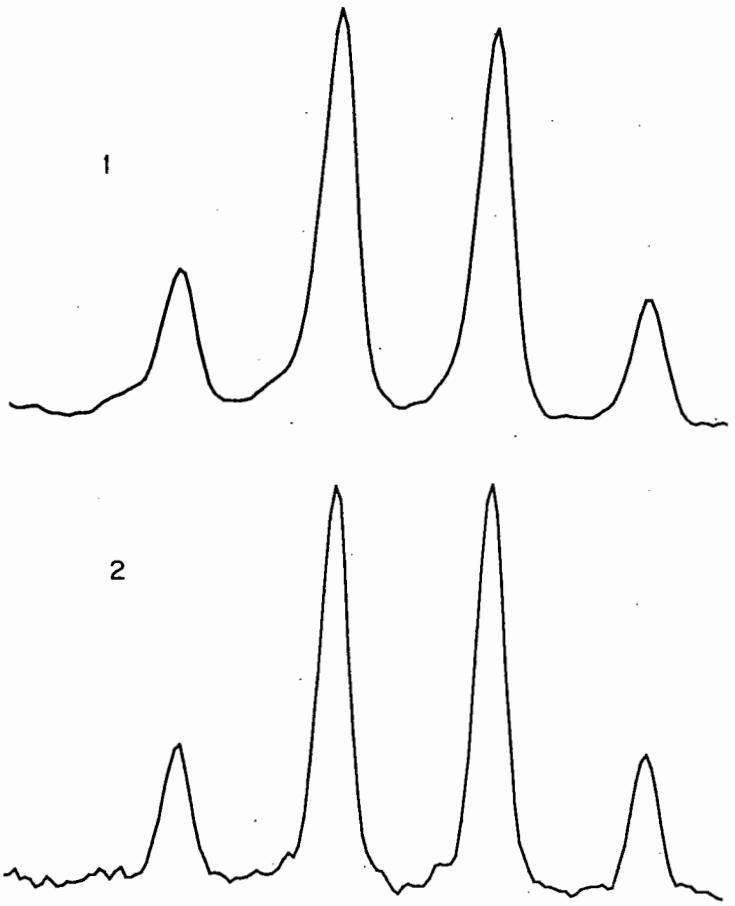
1. J. Dadok, R. F. Sprecher and A. A. Bothner-By, 13th ENC, Asilomar, California.

2. J. Dadok and R. F. Sprecher, 14th ENC, Coulder, Colorado.

3. J. Dadok, Internatl. Symp. Magn. Reson. Biol. Systems, New York City, 1972.

4. J. Kisslinger and J. Cooper, NMR News Letter, p. 168-26.

5. R. R. Ernst, J. Magn. Reson. 1, 7 (1969).



Spectrum of the quartet of Ethyl Benzene obtained from the fast passage response by cross correlation with the TMS reference (fig. 1) and also by multiplying the Fourier transform of the fast passage response with $\exp(-ibt^2/2)$ and inverse Fourier transforming the result (fig. 2).

KEMISK INSTITUT

AARHUS UNIVERSITET
8000 ÅRHUS C, DENMARK

LABORATORIET FOR ORGANISK KEMI
HANS JØRGEN JAKOBSEN

8000 Århus C, den May 24, 1973
Telefon (06) 124633 HJJ/ATL

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
COLLEGE STATION, Texas 77843
USA

Dear Professor Shapiro:

HIGH RESOLUTION ^{13}C FT NMR ON THE XL-100-15: PYRIDINE

Having just had our XL-100-15 spectrometer equipped with the Varian FT accessory (Varian 620L computer, 16K) we would like to add to the steadily increasing number of contributions in your newsletters on ^{13}C NMR. For comparison purposes with corresponding CW spectra and as an illustration of the results we have been able to obtain in the field of proton undecoupled ^{13}C NMR using our FT equipment (not presently equipped for gated decoupling) the accompanying figures show details of the undecoupled natural abundance ^{13}C spectrum of pyridine. Recently we reported on the complete analysis (including ^{13}C isotope effects of the ^{1}H chemical shifts) of the undecoupled ^{13}C spectrum of pyridine [1]. This analysis was based on XL-100 spectra obtained in the CW mode using a Varian C-1024 CAT. The spectra a and b in figures 1 and 2 show part of the observed (CW) and simulated spectra of the C4 and C2 carbons; the obtained spectral parameters (J_{CH}'s) are given in [1]. For comparison of the spectral quality we have recorded the corresponding ^{13}C FT spectra of the same sample of pyridine. These spectra, shown in c of figures 1 and 2, compare even more favorably in quality with the simulated spectra (b).

Several projects in the field of proton undecoupled ^{13}C NMR spectroscopy are presently being undertaken on our XL-100-15 FT system.

Yours sincerely,

Hans J. Jakobsen Marianne Hansen Rigmor S. Hansen

Hans J. Jakobsen Marianne Hansen Rigmor S. Hansen

Reference

[1] M. Hansen and H. J. Jakobsen, J. Magn. Resonance 10, 74 (1973).

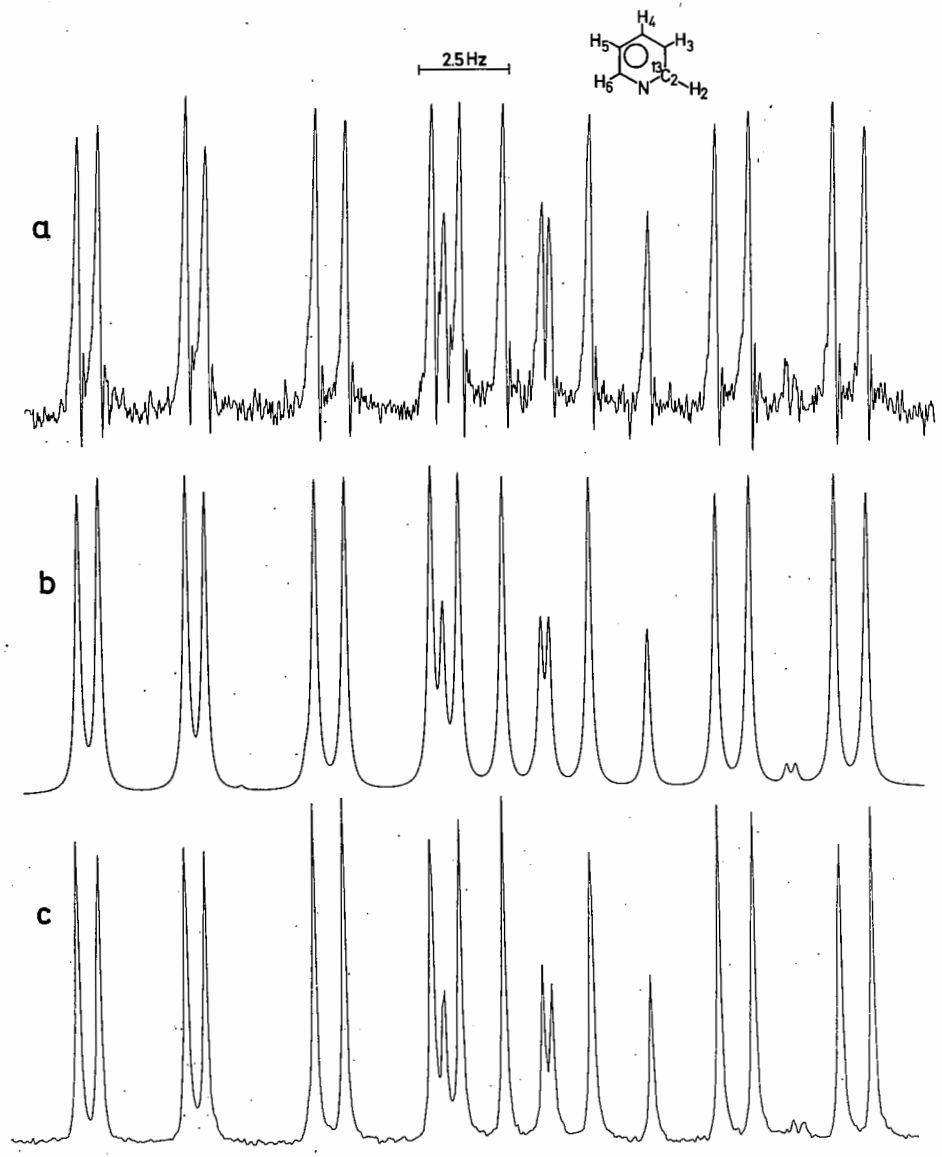


Figure 1. Natural abundance undecoupled ^{13}C NMR spectrum (high-field half) of C-2 in pyridine; (a) CW, (b) simulated [1] and (c) FT spectrum.

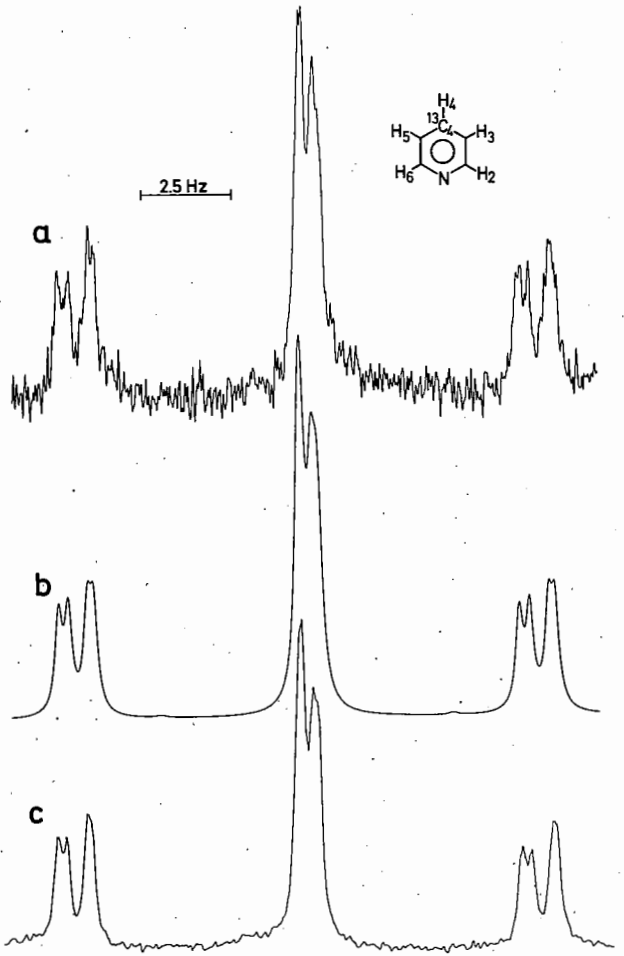


Figure 2. Natural abundance undecoupled ^{13}C NMR spectrum (low-field half) of C-4 in pyridine; (a) CW, (b) simulated [1] and (c) FT spectrum.

177-44

Dr. W. Bremser c/o
Badische Anilin- & Soda-Fabrik AG
Hauptlaboratorium

BASF

Telefon (0621) 601 (Vermittlung)
Telex 464811 basf d (Zentrale)
Telegramme: BASF Ludwigshafenrhein
Bankverbindung: Landeszentralbank
6700 Ludwigshafen, Girokonto 545 07300

Luftpost

BASF · 6700 Ludwigshafen

Prof. Dr. B.L. Shapiro

Department of Chemistry
Texas A & M University

College Station, TX 77843

U S A

Ihre Zeichen	Ihre Nachricht vom	Unsere Zeichen	Telefon-Durchwahl	Telex	Ludwigshafen
		WHE-WBr/Dr	(0621) 60-8401	464-	April 17, 1973

Betreff

Lanthanide Induced Shifts in Mixtures of Isomers

Dear Barry,

Your interesting lecture in Aachen and the recent paper in OMR [1] prompted me to relate some of our experiences with the use of LIS-spectra.

In our practical work we are often faced with the problem of assigning the structures of a pair of two possible isomers A and B. We believed in the beginning that a two to one mixture of the isomeric compounds would guarantee identical conditions for both substances when shift reagent is added. However, this is not the case and is theoretically not be expected because of different complexation tendency of the two compounds. For a one step mechanism

$$L + A \rightleftharpoons LA \qquad K_A$$

$$L + B \rightleftharpoons LB \qquad K_B$$

the equilibrium constants K_A and K_B are seldom identical. On the other hand, for the case $K_A \neq K_B$ we no longer observe a straight line dependence of LIS vs. C_L for the two isomers present as shown in the accompanying example (fig. 1). This case can be called representative because it falls right between the better and the worse examples we encountered.

The aim of this letter is to express a word of warning to all those attempting to apply LIS-data for investigations of mixtures (or even impure solutions) because in most cases we were unable to make unequivocal assignments. On the other hand it seems to me equally dangerous to draw conclusions from the LIS-spectra on the conformational equilibria in non-complexed molecules.

Best regards,
Yours sincerely,

W. Bremser

Badische Anilin- & Soda-Fabrik AG

Empfänger
Prof. Shapiro

Unsere Zeichen
WHE-WBr/Dr

67 Ludwigshafen am Rhein
17.4.1973

Blatt

Betreff

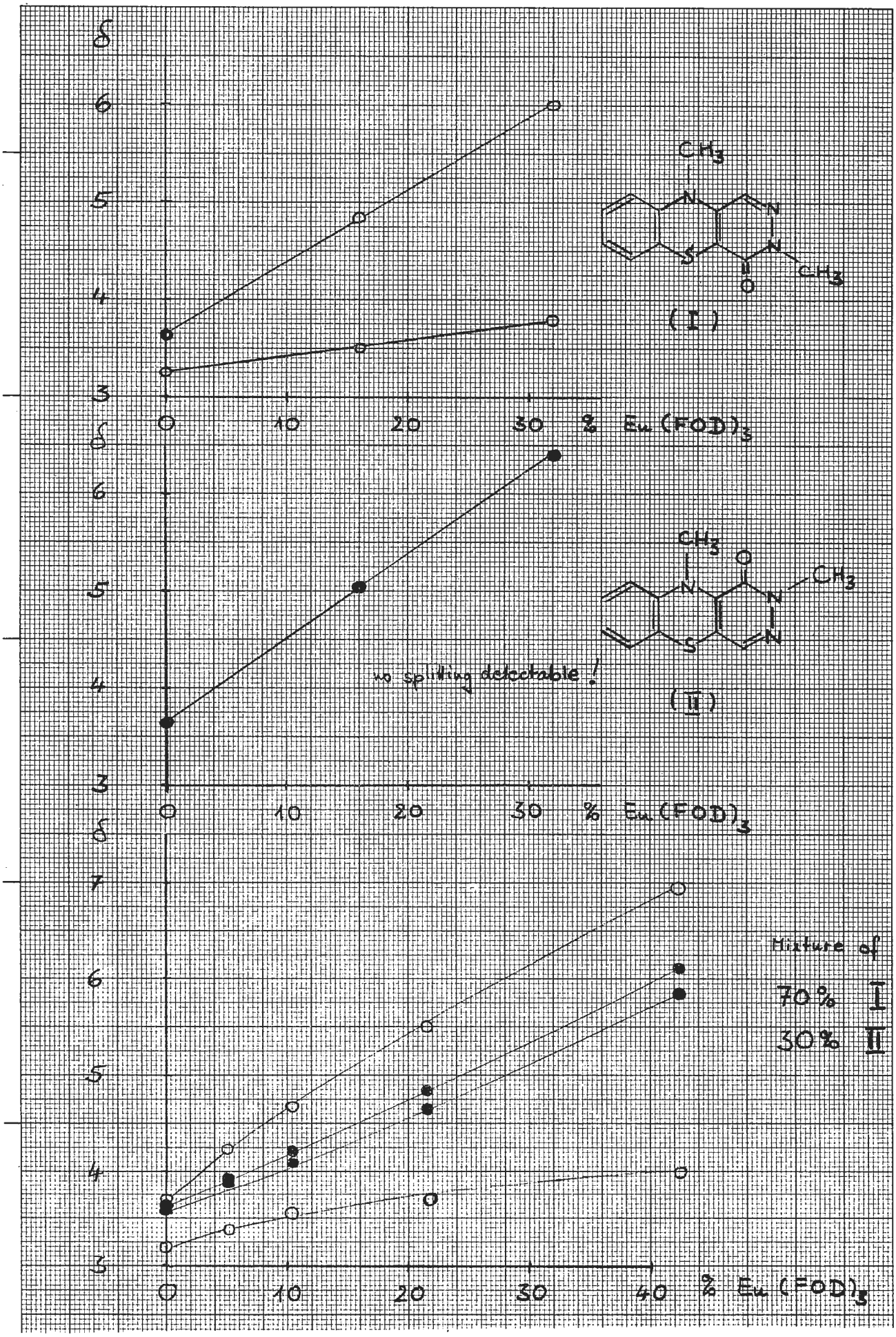
References

[1] B.L. Shapiro, M.D. Johnston jr., and M.J. Shapiro, Org.Mag.Res. 5, 21 (1973)

[2] G. Scapini, F. Duro, and R. Mondelli, Chim.Ind. (Milan) 50, 1328 (1968)
F. Yoneda, T. Ohtaka, and Y. Nitta, J.pharm.Soc.Japan 86, 887 (1966)

Fig. 1

^{1}H-chemical shifts of both methylgroups in the two isomeric diazaphenthiazines [2] as a function of Eu(FOD)$_3$-concentration. The assignment is straightforward because of the varying distance of the methyl proton from the carbonylgroup where the Europium attacs. The difference in behaviour between the solutions of the pure compounds (upper two graphs) and the solution of the 2:1 mixture is obvious, the complexation tendency of isomer I is greater because of less steric inhibition. Relative concentrations of shift reagent in mole %, observation frequency 60 MHz (Varian HA-60).


δ
6
5
4
3
0
10
20
30
% Eu (FOD)3
CH3
N
S
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(I)
δ
6
5
4
3
0
10
20
30
% Eu (FOD)3
CH3
O
N
S
(II)
no splitting detectable !
δ
7
6
5
4
3
0
10
20
30
40
% Eu (FOD)3
Mixture of
70% I
30% II

UNIVERSITY OF WISCONSIN-MADISON

CENTER FOR HEALTH SCIENCES

School of Pharmacy
Pharmacy Building
425 North Charter Street
Madison, Wisconsin 53706
Telephone: 608/262-1415

May 30, 1973

Professor B. L. Shapiro
Department of Chemistry
Texas A and M University
College Station, Texas 77843

Dear Professor Shapiro:

We need a person to operate and maintain our Bruker HX90E NMR spectrometer. The instrument is equipped with a Nicolet 1080 computer, 293 pulse programmer and disc unit so the person we are looking for should be familiar with FT NMR spectroscopy and should have a working knowledge of RF electronics.

Anyone interested in this job can get further particulars by writing or calling:

Phillip A. Hart
School of Pharmacy
University of Wisconsin
Madison, Wisconsin 53706
608-262-3083

Sincerely yours,

Phillip A. Hart

Phillip A. Hart
Associate Professor

PAH:bh

UNIVERSITY OF BRADFORD

Bradford Yorkshire BD7 1DP , England.
Telephone 33466 , Ext. 288, 498 (or 289)
Telex 51309 University Brad

School of Studies in Chemistry

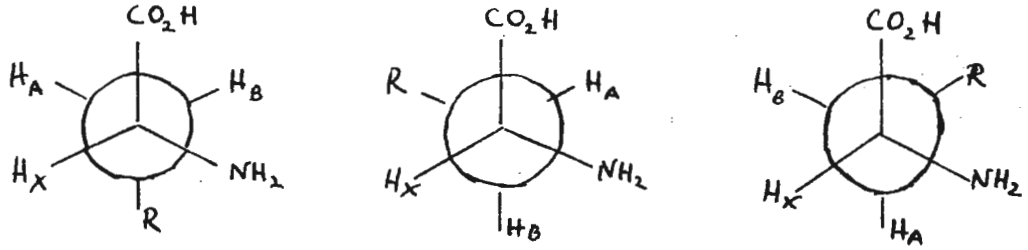
29th May, 1973.

Professor Bernard L. Shapiro,
TAMUNMR Newsletter,
Department of Chemistry,
College of Science,
Texas A and M. University,
College Station,
TEXAS 77843, U.S.A.

Dear Dr. Shapiro,

Rotamer populations of amino acids and peptides.

Following our recent 60 MHz ^1H studies of sulphur-containing amino acids[1] and dipeptides[2], B.J.D. has recorded the 220 MHz ^1H spectra of some amino acids and tripeptides in aqueous solution. Populations of the rotational isomers about the $C^{\alpha} - C^{\beta}$ bond have been calculated by the Pachler procedure[3,4].



Rotamers: I II III

Populations: a b c

If R does not couple to the methylene protons, the spectrum is an ABX weighted average of those of the three rotamers.

Previous analyses of deceptively simple ABX spectra of L-Asp[4,5], L-CySH[6,7], and L-His[6] in acid solution as A_2X made incorrect assumptions about the equality of J_{AX} and J_{BX} and of the derived rotamer populations. With trans and gauche coupling constants of 13.6 Hz and 2.6 Hz, respectively, the average vicinal coupling constant $\frac{1}{3}[(J_t + 2J_g)]$ is 6.3 Hz. Consequently, when rotamer populations are the same, $J_{AX} = J_{BX} = 6.3$ Hz and the quantity $|J_{AX} + J_{BX}|$ (which can be measured from a deceptively simple ABX spectrum) should be 12.6 Hz.

In Table 1, the vicinal coupling constants for L-Asp at both 60 MHz and 220 MHz show that the populations are unequal. Degeneracy in the 60 MHz spectrum enables only population c to be calculated; when the degeneracy is removed at 220 MHz, all three populations may be calculated. Populations a and b were assigned unambiguously by comparison with the spectrum of erythro-3-deuterio-L-Asp.

The side-chain conformations of the Phe and Tyr residues of some tripeptides are very similar (Table 2), despite rather different 220 MHz ABX spectra. While Gly-Phe-Ala, Met-Phe-Gly, and Gly-Tyr-Gly have twelve-line ABX spectra, the spectra of Val-Tyr-Val and Met-Phe-Met have five lines and are deceptively simple.

Yours sincerely,

Brian J Dale B.J. Dale.

D. W. Jones.

T. T. Mokoena.

(Rotamer populations of amino acids and peptides)
(Dale, Jones, and Mokoena)

Table 1. P.m.r. parameters and rotamer populations for aspartic acid

Frequency	pD of solution	T/K	Chemical shifts in Hz downfield of int. t-BuOH ν_B	ν_A	ν_X	Coupling constants J/Hz J_{AB}	J_{BX}	J_{AX}	Fractional rotamer populations a	b	c
220 MHz	0.4	293	428	419	702	-18.3	6.3	4.3	0.34	0.15	0.51
60 MHz	0.4	295	116[I]		191	10.6[‡]			(0.49)		0.51

I $\frac{1}{2}(\nu_A + \nu_B)$ ‡ $|J_{AX} + J_{BX}|$

Table 2. P.m.r. and rotamer population data for tripeptides

Peptide	pD of solution	T/K	Chemical shifts (p.p.m.) from int. t-BuOH δ_B	δ_A	δ_X	Coupling constants J/Hz J_{AB}	J_{BX}	J_{AX}	Fractional rotamer populations a	b	c
Gly-Phe-Ala	1.3	300	1.78	1.93	3.44	-13.9	8.4	6.4	0.53	0.35	0.12
Met-Phe-Met	0.8	293	1.85[I]		3.42	15.2[‡]			(0.91)		0.09
Met-Phe-Gly	0.5	302	1.86	1.92	3.47	-14.1	8.5	7.1	0.54	0.41	0.05
Gly-Tyr-Gly	0.9	296	1.67	1.83	3.39	-13.9	8.4	6.4	0.53	0.35	0.12
Val-Tyr-Val	0.8	297	1.75		3.43	15.5			(0.94)		0.06

I $\frac{1}{2}(\delta_A + \delta_B)$ ‡ $|J_{AX} + J_{BX}|$

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7. R. B. Martin and R. Mathur (1965) J. Amer. Chem. Soc., 87, 1065.

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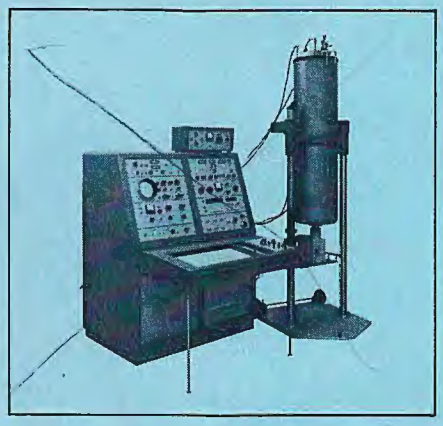

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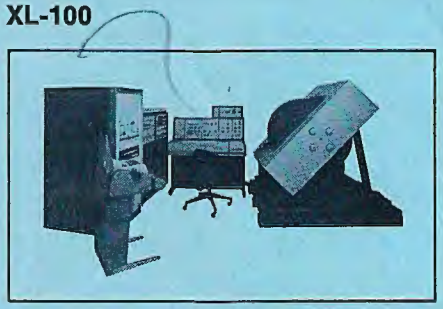

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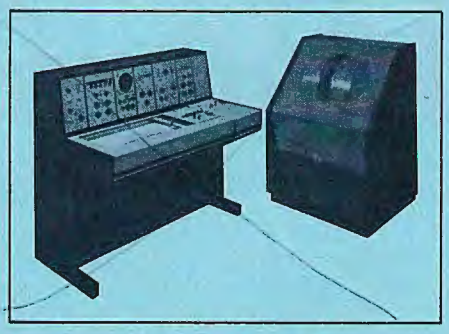

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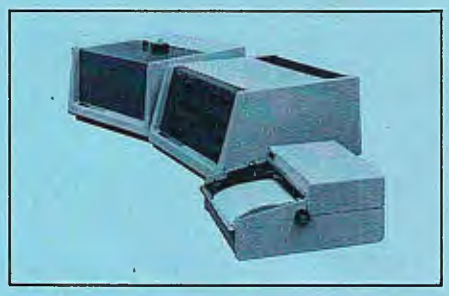

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