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Deadline Dates: No. 146: 2 November 1970
No. 147: 7 December 1970

All Newsletter correspondence, etc., should be addressed to:

Bernard L. Shapiro
Department of Chemistry
Texas A&M University
College Station, Texas 77843
Subject: NMR spectrum of diiodotetrafluorocyclobutene

Dear Professor Shapiro,

during the sabbatical leave spent this Spring at East Anglia University, where I worked with Dr. R.K. Harris, I tackled a few problems of NMR analysis. I like to report here the results obtained in the analysis of the diiodotetrafluorocyclobutene.

The normal NMR spectrum of such a molecule consists of a single line resonance at $\delta = 113.1$, since all the fluorine nuclei are equivalent. In order to obtain information about the coupling constants we have observed the $^{13}$C satellite spectrum of the molecule containing one $^{13}$C atom on the CF$_2$ group. The spectrum can be treated as an approximate AA'XX' system, where the two geminal coupling constants are equal and large ($J_{FF} = \text{ca. } 200 \text{ c/s}$).

The pattern expected must be a simple five-line pattern with intensities 1:2:2:2:1 if $|L| > |N|$ or 2:1:2:1:2 if $|N| > |L|$. The spectrum of the diiodotetrafluorocyclobutene is of the type $|L| > |N|$, and it is therefore immediately clear that $J_{\text{vic}}$ and $J'_{\text{vic}}$ (cis and trans coupling constants) are opposite in sign. The low-field $^{13}$CF$_2$ spectrum at 94.07 Mc/sec is reported in Figure and is consistent with $K$ and $N$ having the same sign, which

/...
must be positive because of the known sign of $J_{FF}^{PF}$. The results are collected in table with those already known for two related compounds \textsuperscript{2}). The assignment of $J_{trans}$ and $J_{cis}$ has been done on the basis of results obtained by Newmark on unsymmetrically substituted cyclobutenes \textsuperscript{3}).

<table>
<thead>
<tr>
<th>$X$</th>
<th>$\varphi^*(CF_2)$</th>
<th>$J_{trans}$</th>
<th>$J_{cis}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>113.10</td>
<td>24.47</td>
<td>-15.35</td>
</tr>
<tr>
<td>Cl</td>
<td>118.47</td>
<td>25.13</td>
<td>-12.77</td>
</tr>
<tr>
<td>F</td>
<td>120.75</td>
<td>26.50</td>
<td>-12.27</td>
</tr>
</tbody>
</table>

With best regards,

Yours sincerely,

L. Cavalli

---

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

Si\textsuperscript{29} NMR; Iron in the Probe

Dear Barry:

Recently Roger Scholl of our department has applied the synthesizer-based, C\textsuperscript{13}-centerband-sweep, F\textsuperscript{19} lock system of our modified HA-100 (Bartuska, Nakashima and Maciel, Rev. Sci. Instr., in press) to Si\textsuperscript{29} magnetic resonance. The attached figure gives an idea of the types of signals he's obtaining.

In the process of probe modification he ran into the difficulty that electronics technicians sometimes forget about the fact that probe components must be non-ferromagnetic. Indeed, some components that "look" as if they shouldn't be ferromagnetic turn out to have this undesirable property. In a tongue-in-cheek attempt to dramatize this fact one of our other students, Mark Bacon, wrote a parody on this experience. It was meant only for local exposure, but I include excerpts here.

Best regards,

Gary E. Maciel
Professor of Chemistry

Centerband-sweep Si\textsuperscript{29} spectrum of TMS, using internal F\textsuperscript{19} lock and proton decoupling, natural abundance, eighteen scans, about one Hz line-width.
An Iron Probe for Doing Ultra-Wide-Line NMR(?) Under High Resolution Conditions*
by Roger L. Scholl

ABSTRACT

Herein is described an NMR probe quite unlike any ever before thrown together. Only the probe body is non-magnetic; all internal components were meticulously screened for their ferromagnetic properties. A good initial test of the completed unit is the suck-in test: is the operator yanked off his feet and strained through the magnet polefaces by the field, while trying to slide the probe into the magnet? The author is presently recuperating in a local hospital from the effects of this test.

Impedances were matched to within ±0.01 ohm of the desired value with the aid of a Boonton RX meter, to insure highest sensitivity consistent with ultrawide lines. This probe gives barely perceptible base line bumps when ordinary high-resolution probes give 0.5 Hz lines. The probe promises to unlock a whole new realm of ultrawide-line NMR under high resolution conditions. This area of NMR has hitherto been scoffed at by even the most naive of NMR practitioners.

ACKNOWLEDGEMENT

The author expresses his profound appreciation to ----- ------, Electronics Designer par excellence, for his invaluable suggestions for choosing only the most strongly ferromagnetic of components. All other persons connected with the project asked that their names not be associated in print with the present work.

*Supported by the Chemistry Committee for Unorthodox Research.
Dear Barry,

1. Fourier Difference Spectroscopy

Many people may have gained the impression that Fourier spectroscopy is rather pretentious with regard to instrumental sophistication. The contrary is true. Except for the indispensable computer system, Fourier spectroscopy is less demanding than conventional spectroscopy. At first, it is possible to dispose of the linear field or frequency sweep because Fourier spectroscopy is a stationary method. In this letter, I would like to demonstrate a new method which further allows to eliminate the field-frequency lock, the field modulation units and even the flux stabilizer.

This method, it may be called "Fourier difference spectroscopy", is based on the use of a linear or quadratic detector to record only difference frequencies between a strong reference line and the weak resonances of the sample to be investigated. These difference frequencies are to a very good approximation independent of variations of the magnetic field strength.

Usually, we put a 1 mm capillary filled with a suitable reference substance (TMS, \( \text{H}_2\text{O} \) or \( \text{H}_2\text{SO}_4 \) for proton resonance) into the sample to be investigated. The radio frequency pulses for the excitation of the free induction decays are selected strong enough to cover the total frequency range through which the resonance lines could drift as caused by the variations of the magnetic field. The composite signal of reference and sample is passed through a diode detector (as it is already contained in the Varian rf unit V4311) to generate the difference frequencies. A low-pass filter eliminates the rf frequencies and passes the desired difference frequencies only, as shown in Fig. 1.
The signal consists of an approximately exponential decay caused by the envelope of the reference signal decay and superimposed are the weak difference frequencies caused by the sample resonances. The reference signal is suppressed as shown in Fig. 2 (we use a Legendre polynomial approximation to the original signal, Fig. 1, to extract the reference response which is then subtracted). The remaining signal, Fig. 2, is equivalent to a free induction decay of the sample signal alone with its zero frequency at the position of the reference line. Its Fourier transform gives a spectrum with enhanced sensitivity equivalent to that of conventional Fourier spectroscopy. Figure 3 shows the Fourier transform of Fig. 2 and may be compared with a single scan recorded in the same total time on the same instrument as shown in Fig. 4.

The operation of this system is extremely simple. The only critical adjustment concerns field homogeneity. But this operation could easily be automated (Rev. Sci. Instr. 39, 998, 1968). The free induction decay stays for days invariably on the scope. It is quite insensitive to spurious field modulation, like power line frequency modulation. Because of the large dynamic range of the composite signal, some attention must be paid to the digitization error of the A/D converter (compare IIT-NMR Newsletter 112, p.53). We used a 9 bit + sign converter which may be at the lower limit, but it did not affect the results. The spectra are sensitive to spinning side bands of the reference line (Fig.3) and also to possible $^{13}C$ sidebands which may appear to be quite strong.

Fourier difference spectroscopy provides an intriguing possibility to solve the notorious field-frequency lock problems in NMR. It also can easily be adapted to more sophisticated refocussing schemes. A more complete account of this work will be published soon.

2. Postdoctoral Fellowship Available

I would like to mention that there is a postdoctoral fellowship available for doing research in our NMR group which is concerned with new NMR techniques including pulse experiments, solid state resonance and multiple resonance. The fellowship is granted for one year and the salary amounts to 24'000.- Swiss Francs/year.

Best regards,

Richard R. Ernst
Fig. 1: Sum of 128 free induction decays of 0.2% ethyl ether and of a reference capillary filled with H₂O/D₂O 1:3 as appearing at the output of the diode detector (60 MHz, pulse spacing 2 sec)

Fig. 2: Free induction decay of Fig. 1 with reference response eliminated by means of a polynomial approximation.
Fig. 3: Fourier transform of Fig. 2

\[ S/N = 2.5 \cdot \frac{60}{6} = 25.0 \]

Residual reference line

Spinning sideband of reference line

Impurity

Fig. 4: Single scan in 250 sec of the same sample as in Figs. 1-3

(Filter bandwidth: 1 Hz)

\[ S/N = 2.5 \cdot \frac{10}{17} = 2.8 \]
Professor B. L. Shapiro,
Department of Chemistry,
Texas A & M University,
College Station, Texas 77843,
U.S.A.

September 10, 1970.

Titles: 1) NMR of thiocarbamate herbicides
        2) Video-taped Spectroscopy Programs Available

Dear Dr. Shapiro:

1) On the premise that (research) money is only to be found in pollution problems we recently ran NMR spectra (at variable temperature) of eight commercially used thiocarbamate herbicides. For all of these we determined the coalescence temperature $t_c$ for the $S\cdot C\cdot NR_1R_2$ alkyl protons, finding a range from $t_c = +35^\circ C$ (for molinate) to $t_c = -1^\circ C$ (for pebulate). Reasoning that higher $t_c$ values are equivalent to higher polarity in the amide group, we sought to correlate the $t_c$ values with other physical, chemical and biological properties. We found no correlation between $t_c$ and general herbicidal activity and rate of chemical breakdown. There are crude correlations between $t_c$ and solubility, rate of leaching and rate of microbial breakdown. Within a group of chemically similar thiocarbamates (change in alkyl groups) $t_c$ correlates with toxicity. Finally, $t_c$ correlates inversely with adsorptivity (on clay), the inversion probably being due to the negative heat of solution of thiocarbamates in water. A paper (with full details) will be published shortly in J. Agr. Food Chemistry.

2) In the past year or so I have made a number of videotapes (mix of film, graphs, stills and "live" studio presentation) on the proper operation of spectrometric equipment. They are intended as do-it-yourself instruction. We use them for all our 3rd and 4th year students taking spectroscopy, for newly arrived graduate students and so on via a monitor room where they can dial the required program.

We have considered that we could sell copies of these. We have facilities to dub onto 2" Quad., 1" Ampex or 1/2" Sony. We are not certain about prices, but it might be about $5.00 per minute of program plus tape costs. (altogether less than 10% of the production costs!). We can also loan tapes for anyone who considers himself a serious potential buyer.
At the moment we have the following programs:
1) Introduction to NMR (40 min)
2) The Varian A-60A; recording a spectrum (36 min)
3) The Varian A-60A; Tuning Procedures (41 min)
4) Atomic Absorption Spectroscopy; the Techtron AA-100 (22 min)
5) Infrared Spectroscopy (42 min)
   a) Recording Spectra with the Beckman IR-8 (19 min)
   b) Sampling Procedures (23 min)

The programs are of professional technical quality (thanks to our excellent AV-TV Centre) while on my side I am preaching my usual gospel "do not touch any knob, until you know what is behind it and what effects it can have on your data".

Anyone interested should write directly to the undersigned.

Sincerely yours,

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

Spin Echoes with a CAT, a BAT, and a Time Shared Computer  

Dear Barry:

We have been measuring the fluorine relaxation times of some p-fluoropolystyrene solutions recently. We are primarily interested in the molecular weight dependence of the relaxation times. Keizo Matsuo has prepared samples over a wide range of molecular weights. It is too early to say anything about the results, but I thought some of the readers of the newsletter might be interested in the instrumental setup we are using to measure $T_2$ by the Carr-Purcell-Meiboom-Gill method. The basic idea is to use the Varian C-1024 not only to record the data, but to control the experiment and to transmit the digital data directly to the computer.

The data transmission problem was solved for us by a local moonlight engineering firm (I.D.M. Inc., Hanover, N.H. 03755). The interface lives in a 4x4x6 inch box, including power supply and controls, plugs with a single cable into a very slightly modified 33 ASR teletype, and can dump the contents of the CAT into the Dartmouth Time-Sharing System in about five minutes. The time limitation is the teletype data transmission rate. Briefly, the thing works by coding the 17 bit word in each channel of the CAT into two six bit words and one five bit word in a shift register. The necessary control bits are loaded and then sent serially to the teletype. The coding of the data is such that each word is a printable character (including blank), and the output is divided into 64 lines 16 channels long that look like this:

```
+T(/) O+X+T1"+T2"+T3"+T4"+T5"+T6"+T7"+T8"+T9"+T10"+T11"+T12"+T13"+T14"+T15"+T16"
```

One could learn to read this if he were willing to learn a 32 digit number system ( =0,!=1,etc.). However, a simple basic program turns this apparent nonsense into numbers, integrates the echoes, and does a weighted least squares fit to find $T_2$ in a little over one second of central processor time. The 10 minutes required to get from an acceptable record in the CAT to a $T_2$ value is peanuts compared to the time required to work up any type of analogue record. We have been getting $T_2$ reproducible to about 1 percent on solutions with 24 mg of polymer per ml of solution (.2M in F).

The technique for using the CAT to control the experiment is based on the binary output jack on the back. After spending an evening with the CAT manual and the oscilloscope I figured out what all those pins were doing. Nine of them present a parallel binary channel number.
In our case the interface between the CAT and the Tektronix type 161 pulse generators controlling our modified V-4311 rf unit is a Tektronix 547 dual time-base oscilloscope. A line from one bit of the channel number (which bit depends on how many echoes you want) is connected to the external trigger input of the scope. Suppose the fifth bit is so connected. When the CAT is triggered and address advance pulses begin, nothing happens to bit 5 until 16 pulses have been applied, then it goes on. The CAT has now gathered 16 samples of the baseline. The rising edge of bit 5 going on triggers one time base of the scope which in turn triggers the 90° pulse. This time base is set for a time long compared to the full CAT sweep, and so fires only once. The next 16 samples the CAT gathers are of the tail following the 90° pulse. At the 32nd address advance pulse bit 5 goes off, triggering the other time base with the negative going signal. This time base triggers a 180° pulse and is set for a time short enough that it is ready to fire when bit 5 again goes off 32 address advance pulses later. Thus we get 32 samples of each of 31 echoes. Successive experiments are in perfect registration and the limitation on the number we can accumulate is presently set by field instability. We are using a high resolution magnet with flux stabilizer control.

I have not yet been able to think of a correspondingly simple way to control T₁ measurements.

Please credit this to Dick Shafer's account as usual.

Sincerely,

Karl F. Kuhlmann
Assistant Professor of Chemistry

KFK/blw
Following Stengle and Baldeschwieler's work with Cl\(^{-}\) [J.A.C.S. 89, 3045, (1967)] we have recently been investigating the use of Br\(^{79}\) and Br\(^{81}\) as probes for determining the properties of mercury binding sites in proteins by signal averaging the Br free induction decay at 15 Mhz. Our conclusions on equine haemoglobin are:

1) There are approximately two active - SH groups capable of binding mercury in the haemoglobin tetramer, although variations in this number (1.5 - 2.6) are noticeable between different samples from the manufacturer (Pentex Inc.). This is in agreement with the results of Stengle and Baldeschwieler and with most other workers using standard analytical techniques.

2) The appropriate transverse relaxation rate expression for halogen X (I = 3/2) probe experiments is:

\[ R_2 - R_2,0 \equiv \left( \frac{\tau_{ex}}{1/\tau_{ex} + 1/\tau_c} \right)^{-1} [\text{Hg}]/[X^-] = \alpha [\text{Hg}] \]  

for a suitably homogeneous magnet, where \( R_2,0 \) and \( R_2 \) are the relaxation rates before and after the addition of HgX\(_2\) to the protein - halide solution; \( \tau_{ex} = [k_1[X^-]]^{-1} \) is the mean lifetime for bound halogen, and \( \tau_c \) is the correlation time for reorientation of the Hg-Br bond at the bound site. Three limiting regions for the exchange follow from this equation:
1) \( \tau_{ex} \gg T_2, \text{bound} \), slow exchange limit, \( \tau_{ex} \) only obtainable

ii) \( \tau_c \ll \tau_{ex} \ll T_2, \text{bound} \), fast exchange limit, \( \tau_c \) only obtainable

iii) \( \tau_{ex} \ll \tau_c \), extreme exchange limit, \( \tau_{ex} \) only obtainable

Region ii) has been assumed by all workers concerned with probe techniques to date. We find that this assumption may not always be valid with chloride probes. For bromide, the marked decrease in \( T_2, \text{bound} \) due to larger \((e^gqQ)^2\) places the two Br isotopes in the intermediate region between i) and ii). Here it is possible in principle to extract both \( \tau_c \) and \( \tau_{ex} \) from the \([X^-]\) dependence of \( \alpha \), with a check from comparison of the two isotopes.

The region between i) and ii) has been discussed by O'Reilly et al. [J. Chem. Phys. 39, 1756, (1963)] and that between ii) and iii) by Marshall [J. Chem. Phys. 52, 2527 (1970)].

3) The \([Br^-]\) dependence of \( \alpha^{-1} \) is not linear in the i)-ii) region as predicted by Eq. (1). We interpret this salt effect on haemoglobin as being due to a decrease of \( \tau_c \) with NaBr concentration at constant pH. This conclusion is at variance with that of Stengle and Baldeschwieler on Cl\(^-\), caused we think by their neglect of the (small) effects of the exchange rate.

4) Both \( \tau_c \) and \( \tau_{ex} \) are influenced by pH. \( k_1 \) decreases slightly from pH 7 to pH 10.5.

5) Not enough is known about \( e^gqQ \) in the Protein-S-Hg-Br environment to be certain about the true average value of \( \tau_c \). Using \( e^gqQ = 320 \text{ Mhz} \) estimated for solid HgBr\(_2\) complexes [O'Reilly et al.], we estimate \( \tau_c \) for haemoglobin in 1M NaBr at pH 7 to have the remarkably small value \( 10^{-10} \text{ sec} \). This is about an order of magnitude smaller than that measured by Stengle and Baldeschwieler with Cl\(^-\) and may indicate a differential salt effect between Cl\(^-\) and Br\(^-\) on the overall conformation of the protein.

A more detailed report is being prepared.

With best wishes,

Z. Starcuk

R. Collins

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

Dear Barry:

During the past several months we have been working intensively with high-resolution C-13 spectra. These have been obtained on our Bruker HFX-90, using a Fabri-Tek 1074 for time averaging. During the course of this work we had occasion to evaluate our resolution and sensitivity under appropriate operating conditions.

The inclosed figure illustrates the performance we are able to obtain under the conditions detailed in the caption. This is the spectrum of the lower-field of the two central resonances of the large (methyl) quartet in acetone. This small quartet shows a long-range coupling, $J_{CH}$, of 1.48 Hz. The line width at half height is within 0.5 Hz, which is typical of the results we have been obtaining by time-averaging on natural abundance samples.

No especial or unusual steps were taken in preparing the sample. The acetone used was the Matheson-Coleman-Bell product transferred from the bottle to the sample tube without out-gassing or sealing.

We would like to learn what resolution has been obtained in other laboratories on natural abundance C-13 spectra with time averaging.

Sincerely,

A. R. Tarpley  
J. H. Goldstein

JHG:lt
Figure 1. The natural abundance carbon-13 spectrum of the small quartet in neat acetone. The spectrum was time averaged for 32 scans at a sweep width of 0.2 Hz/cm and a sweep time of 3.3 sec/Hz in a 13 mm sample tube. Proton stabilization on the methyl resonance of acetone was employed.
Prof. B.L. Shapiro  
Department of Chemistry  
Texas A. & M. University  
College Station, Texas 77843  
USA

"Homonuclear INDO for Structure Elucidation"

Dear Barry:

INDOR experiments have been performed in hetero- and homonuclear systems. Applications however are rather scarce and according to a recent review article on the subject [1] have been focussed either on the determination of chemical shifts of nuclei other than protons or on the determination of relative signs of coupling constants and energy level diagrams. We do not know about an application of $^1H,^1H$-INDOR to solve a complex structural problem. 

Recently we modified our HA-100 spectrometer according to the instructions of Varian AG Switzerland [2] and we have started to investigate the potential of this double resonance method for structural studies.

As a first example we wish to present the complete structure elucidation of a dimer of 11,13-dioxo-12-methyl-12-aza[4.4.3]propellane 1.

\[ \text{O} \quad \text{CH}_3 \quad \Delta \]

[Diagram of molecules 1 and 2]
The 100 MHz and 220 MHz spectra of the dimer (fig. 1) are very complex and do not permit an analysis by conventional double resonance techniques. In the 100 MHz spectrum only four protons exhibit resonances which are clearly resolved whereas the signals of twelve protons show extensive overlap in the vinylic region and in the two aliphatic regions. Two N-methyl signals indicate that the dimer has an unsymmetrical structure.

An expanded spectrum (fig. 2) of the 8 vinylic protons illustrates how the hidden resonance lines of H-5' can be located precisely by INDOR using lines of H-4' as monitor transitions. Similarly, using H-8' as a monitor proton, hidden lines of the vinylic neighbour H-9' and of the two aliphatic protons H-7' and H-10' could be determined (fig 3a).

An important extension of the technique is illustrated in fig. 3b. A hidden line of H-9' which has been determined by INDOR can be used as a monitor line for consecutive INDOR experiments. The importance of consecutive INDOR for structure elucidations is demonstrated in fig. 4 which shows that it was possible, starting from only three directly observed protons, to determine the chemical shifts and coupling constants of eleven of the twelve skeletal protons of the dimer. The vicinal coupling constants obtained are in good agreement with torsional angles estimated from a model of the dimer 2.

The technique of consecutive INDOR has also been successfully applied to determine the parameters of the four diene protons H-2, H-3, H-4 and H-5. The signals of three of these protons are hidden. Starting from only six primary monitor lines, we have been able to obtain 32 INDOR lines which were used to analyse the four-spin system.

A detailed account of this work is in press [3] and we are engaged in further studies on carbohydrates and peptides.

With best wishes,

Yours sincerely,

W.von Philipsborn O.Sciacovelli

Fig. 1

Fig. 2

Fig. 3
fig.4 Sequence of protons as derived from INDO
* indicates directly observed protons

H-C(3') 2.55 ppm \( J(3'2') \) 5.5 Hz; \( J(3'5') \) 0.9 Hz
H-C(4') 6.32 \( J(4'5') \) 8.9 \( J(4'3') \) 7.8
H-C(5') 5.95
H-C(7') 2.77 \( J(7'8') \) 6.5 \( J(7'9') \) 1.2
H-C(8') 6.53 \( J(8'9') \) 6.1 \( J(8'10') \) 1.3
H-C(9') 5.97 \( J(9'10') \) 6.2
H-C(10') 2.85 \( J(10'9') \) 2.8
H-C(8) 1.91 \( J(8'9) \) 10.5
H-C(9) 1.60 \( J(9'10) \) 2.0
H-C(2') 2.95 \( J(2'10) \) 6.1 \( J(2'9) \) 2.0
H-C(10) 2.71
H-C(2) 5.63 \( J(2'3) \) 9.5 \( J(2'4) \) 0.8
H-C(3) 6.10 \( J(3'4) \) 5.6 \( J(3'5) \) 1.0
H-C(4) 5.99 \( J(4'5) \) 9.5
H-C(5) 5.90 \( J(5'2) \) 1.1
BAT SHEVA SUMMER SCHOOL ON MOLECULAR DYNAMICS IN LIQUIDS

A Summer School on Molecular Dynamics in Liquids sponsored by the Bat-Sheva de Rottschild Foundation will be held at the Tecinlion, Haifa, Israel between September 1-17, 1971.

Lectures and discussions will be held on the theoretical and experimental aspects of the study of molecular motions in the liquid phase. Special emphasis will be given to modern approaches to the study of relaxation phenomena in liquids through such techniques as light scattering, IR lineshapes, nmr and esr dielectric dispersion, etc.

Amongst those who have agreed to attend are:

A. Ben Reuven (Rehovot) - Orientational Motion in Liquids
M. Bixon (Tel-Aviv), Polymer Dynamics in Solutions
P.G. de Gennes (Orsay) - Dynamical Properties of Liquid Crystals
D. Kivelson (UCLA) - Spin Relaxation
T.A. Litowitz (Washington, D.C.) - Light Scattering and Sound Absorption
I. Oppenheim (MIT) - Generalized Hydrodynamics
R. Zwanzig (Maryland) - The Linear Response Theory

The School is open to Research Scientists and Graduate Students interested in the field. For application and further information please write to:

A. Loewenstein
Department of Chemistry
Technion, Haifa, Israel


Registration fee is I.L.140 ($40) and includes communal lunch. Accommodation and other meals are not included but will be available at moderate rates in the Students' Residence. A very limited number of grants may be available upon request.
Dr. B. L. Shapiro
Department of Chemistry
Texas A and M University
College Station, Texas  77843

Dear Doctor Shapiro:

In this laboratory the aromatic proton spectra of a variety of naphthalene sulfonic acid derivatives and their salts have been measured using a Varian A-60 spectrometer. The usual solvents for this work were H$_2$O or dimethylsulfoxide-d$_6$ but occasionally, because of low solubility in DMSO-d$_6$ or interference from the strong H$_2$O signals, D$_2$O was used. Except for minor shifts due to differences in sample concentration the aromatic proton spectra in D$_2$O and H$_2$O were usually identical for a given compound. In DMSO-d$_6$ the chemical shifts can differ markedly from those in the aqueous solvents but the overall patterns of the signals are similar.

Recently the spectra of 2-aminonaphthalene-6,8-disulfonic acid (Amino G-Acid), were prepared in all three solvents. In both H$_2$O and DMSO-d$_6$ this compound gave similar patterns for the five aromatic protons consisting of overlapping ABX (for protons 1, 3 and 4) and AB (for protons 5 and 7) subspectra. The disodium salt of this compound also gave the expected patterns for the five aromatic protons in H$_2$O. The observed shifts are given in the attached table.

In D$_2$O the spectra were anomalous; signals were observed for only four protons, forming two separate AB subspectra. The signal for proton 1 was absent in the spectra of both the free acid and the salt (see table). When the D$_2$O solutions were evaporated to dryness and redissolved in H$_2$O the signal for proton 1 reappeared, giving the familiar ABX subspectrum.

September 23, 1970
This facile exchange of an aromatic proton with D₂O had not been observed with any of the naphthalene sulfonic acids previously examined. However, other examples of this phenomenon may have been overlooked since D₂O was not usually used as the solvent. Compounds with related structures, such as the isomeric Amino J-Acid (2-naphthylamine-5,7-disulfonic acid), the sodium salt of the monosulfonate (2-naphthylamine-8-sulfonic acid) and the di-potassium salt of the naphthol analog (2-naphthol-6,8-disulfonic acid), do not exhibit this exchange with D₂O.

Very recently preliminary measurements were made on the sodium salt of Gamma Acid (8-hydroxy-2-naphthylamine-6-sulfonic acid) but signal assignments have not been completed. One of the aromatic protons of this compound exchanges with D₂O and it appears probable that either proton 1 or proton 7 is affected.

The exchange of an aromatic proton with D₂O does not seem to be a common phenomenon and too few examples have been observed to permit prediction of the occurrence of a labile proton in this class of compounds. It is known that position 1 in β-naphthols and β-naphthylamines is generally the most active site for substitution reactions. This experience indicates that compound identification or structural assignments of naphthalene sulfonic acid derivatives should not be based solely upon spectra prepared using D₂O as the solvent.

Please credit this communication to the subscription of American Cyanamid Company (Dr. J. Lancaster).

Sincerely yours,

Jessie L. Gove
NMR Laboratory

Suggested Title: Aromatic Proton Exchange in Naphthalene Sulfonic Acids
Table I: Chemical Shifts of Naphthalene Sulfonic Acid Derivatives

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<th>T (6)</th>
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<td>D₂O</td>
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<td>2.43</td>
<td>1.82</td>
<td>1.71</td>
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<td>-</td>
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<td>D₂O</td>
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<td>1.95</td>
<td>-</td>
<td>1.58</td>
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<td>D₂O</td>
<td>1.02</td>
<td>2.43</td>
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<td>1.71</td>
<td>-</td>
<td>1.53</td>
<td>-</td>
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<td>1.50</td>
<td>-</td>
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<tr>
<td>H₂O</td>
<td>D₂O</td>
<td>1.92</td>
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<td>2.70</td>
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Dear Barry:

We would like to propose a system of nomenclature for the important situation where ligands are found in different chemical and/or magnetic environments through an exchange of position without alteration of the chemical species involved. A typical example is the exchange of the equatorial and axial fluorine atoms in 1,1-difluorocyclohexane, in this case by ring inversion. Names have been coined for the process of exchange, notably "degenerate isomerization", "isodynamic change" (1) and "automerization" (2); and the species which undergo the exchange have been called "automers" (2). We feel that all these terms leave something to be desired, the first because the process is obviously not an isomerization (the structures involved are the same, not isomeric) and the second because it relates to energy rather than to structure. "Automerization" is more apt, but, in our opinion, focusses attention on the uninteresting part of the phenomenon (the sameness of the structures involved) rather than on the interesting aspect, and the one which deserves description, namely the fact that the process of interchange puts structurally identical ligands in different environments (using the word structure in its most general sense of constitution plus configuration plus conformation).

Recently, a nomenclature has been coined (3), and is becoming accepted and extended (4, 5), designating ligands in stereochemically different environments as "enantiotopic" or "diastereotopic" (3), the overall term for the two cases being "heterotopic" (4) or stereoheterotopic (5); in contrast, ligands in identical surroundings are called "homotopic" (4, 5). We therefore propose that the process leading to exchange of ligands of the same structure, which differ in "topicity" (derived from Greek topos = place) be called "topomerization" and that the indistinguishable species being involved in this exchange be called "topomers". Common examples from the current literature are shown below; many additional examples have recently been discussed by one of us (8). It is to be noted that the new terms can be used regardless of whether the interchange in question comes about by rotation, inversion, bond shifting or by some other process; this is particularly advantageous in cases where the actual mechanism of exchange is not known (8).

* For prochiral enantiotopic and diastereotopic ligands (3) we use the designations L_R and L_S defined elsewhere (4, 6). For heterotopic ligands in an olefin (cis or trans to a given group at the other end of the double bond) we use the symbols L_Z and L_E (cf. 7) according as to whether the ligand is cis (Z) or trans (E) to the group of higher Cahn-Ingold-Prelog sequence.
I

\[
\begin{array}{c}
\text{X} \quad \text{Y} \\
\text{C} \quad \text{C} \\
\text{A}_Z \quad \text{A}_E
\end{array}
\]

\[
\begin{array}{c}
\text{X} \quad \text{Y} \\
\text{C} \quad \text{C} \\
\text{A}_Z \quad \text{A}_E
\end{array}
\]
e.g.

\[
\begin{array}{c}
\text{Me}_2\text{N} \quad \text{NMe}_2 \\
\text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5
\end{array}
\]

(9, 10)

II

\[
\begin{array}{c}
\text{F} \\
\text{R}
\end{array}
\]

\[
\begin{array}{c}
\text{F} \\
\text{R}
\end{array}
\]

(11)

III

\[
\begin{array}{c}
\text{C}_6\text{H}_{12}
\end{array}
\]

\[
\begin{array}{c}
\text{C}_6\text{H}_{12}
\end{array}
\]

(12)

IV

\[
\begin{array}{c}
\text{N} \quad \text{R} \\
\text{A}_R \quad \text{A}_S
\end{array}
\]

\[
\begin{array}{c}
\text{N} \quad \text{R} \\
\text{A}_S \quad \text{A}_R
\end{array}
\]

(13)

V

\[
\begin{array}{c}
\text{Cl} \quad \text{Br} \\
\text{I}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \quad \text{Br} \\
\text{I}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \quad \text{Br} \\
\text{I}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \quad \text{Br} \\
\text{I}
\end{array}
\]

(13)
Topomers can be classified just as isomers into constitutional topomers (e.g., valence bond topomers, III) and stereotopomers. The latter may be diastereotopomers (I, II) or enantiotopomers (IV). Case I represents cis-trans topomerization or diastereotopomerization, since \( A_E \) and \( A_E' \) are diastereotropic groups; similarly case II represents diastereotopomers by virtue of exchange of equatorial and axial fluorine. Case III (bullvalene) represents valence bond topomerization; the topomers are constitutional since one and the same ligand (carbon, hydrogen) is placed in chemically different positions (allylic, two kinds of vinylic and cyclopropanoid). Case IV is one of enantiotopomerism; the enantiotopic groups \( A_R \) and \( A_S \) might, in principle, be distinguishable in a chiral solvent when inversion is slow. Case V as case II may be described as one of conformational diastereotopomerism since the three conformations differ in the location of designated hydrogen ligands.

The phenomenon of topomerization is, obviously, of particular importance in NMR spectroscopy, since, depending on its time scale, the ligands interchanged in the process may be isochronous or anisochronous (3) and/or magnetically equivalent or nonequivalent and the rate of topomerization is frequently ascertained by NMR line-shape studies.

So far, the nomenclature has dealt with ligands which are, in principle, structurally non-equivalent. However, for completeness and maximum usefulness, it should be able to deal also with cases of nuclei which are structurally equivalent but, in principle, magnetically non-equivalent. The most general case of such ligands is shown in example VI. Here the three hydrogens (and also the three fluorines) are, of course, structurally equivalent, not only in the case

\[
\text{VI}
\]

\[
\text{VII}
\]

* Topomerization by rotation about the carbon-carbon bond of V is confined to cyclic permutations \((123 \rightarrow 231 \rightarrow 312)\); the remaining permutational possibilities \((213 \rightarrow 132 \rightarrow 321)\) are inaccessible by rotation. The situation could be characterized by an extension of the Cahn-Ingold-Prelog rules, where the labeling determines the priority sequence and the "configurational" symbol is enclosed in square brackets. In the topomers of V the methyl group then belongs to the \([R]\) family.
when rotation about the C-C bond is fast, but also when it is slow on the time scale of the experiment. However, the magnetic equivalence which exists in the limit of fast rotation (system $A_A''X_3$) is lost in the limit of slow rotation (system $AA'A''XX'X''$), since a distinction now exists between the gauche H/F coupling and the anti H/F coupling. Thus, although the nuclei hydrogen (or fluorine) cannot be distinguished even in the case of slow rotation (since they are equivalent), their magnetic non-equivalence can be recognized in the spectral pattern. We propose to label the case represented by example VI one of "homotopomerization" and call the three interconverting structures "homotopomers". It should be noted that, whereas the exchanging ligands in ordinary topomers (which, for the sake of distinction, may be called "heterotopomers" if necessary) are heterotopic, either constitutionally or stereochemically, the exchanging ligands in homotopomers are constitutionally and stereochemically equivalent, their only non-equivalence being of the magnetic kind.

Another interesting case of (constitutional) homotopomerization is represented by the bond shift process in cyclooctatetraene (VII). Here (at least in the average planar model) all nuclei are equivalent but $^{13}$C coupling reveals the difference of adjacent carbon atoms being linked by a single or a double bond (14).

Case VIII, though similar to case VI, differs in that protons $H_R$ and $H_S$ are enantiotopic rather than homotopic. Thus this is a case of enantiotopomerization, but, in distinction to case IV, in this instance in the limit of slow exchange $H_R$ and $H_S$ can be distinguished by their magnetic nonequivalence through unequal coupling with the adjacent methylene protons (15).

---

* It should be noted that this case is not dependent on the simultaneous presence of $^{12}$C and $^{13}$C in the cyclooctatetraene. Rather, the presence of two magnetic nuclei ($^1$H and $^{13}$C) makes it possible to see the coupling of vicinal protons; the same phenomenon (albeit complicated by additional $^{13}$C coupling) would be seen in cyclooctatetraene-per-$^{13}$C; cf. R.M. Lynden-Bell and N. Sheppard, Proc. Roy. Soc., Ser. A, 262, 385 (1962). Thus this is truly a case of homotopomerization.
We realize that the introduction of new jargon in chemistry is usually not greeted with universal joy. We therefore solicit comments (both sweet and sour) regarding the usefulness and propriety of the terms here proposed from TAMUNMRN readers.

Sincerely yours,

Gerhard Binsch
Ernest L. Eliel
Horst Kessler

Chemisches Institut der Universität Tübingen, Wilhelmsstr. 33, 74 Tübingen, Germany.

References

(3) K. Mislow and M. Raban, Topics in Stereochemistry, 1, I (1967).
(5) K. R. Hanson and H. Hirschmann, personal communication.
(13) For cases of this type, see W. E. Heyd and C. A. Cupas, J. Amer. Chem. Soc., 91, 1559 (1969) and Fig. 6 in ref. 9.

P. S. Please credit this contribution to the Notre Dame subscription, (Binsch/Pasto).
28 September, 1970

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

Dear Barry,

**LAOCOON versus HYDRA**

Some time ago we decided to compare the n.m.r. parameters of some of our pet compounds with those of dibenzothiophene. At that time only an approximate analysis existed so we undertook a more thorough study. Our normal analytical method is LAOCOON III but out of interest we also performed a direct analysis based on the ABMX approximation, with the AB part close to the deceptively simple limit. (The sample was a 5% solution in CCl₄.) Although a small difference in these two results was expected, the disagreement was a bit disturbing. Specifically, LAOCOON III had the magnitude of $J_{12}$ and $J_{34}$ (and of $J_{13}$ and $J_{24}$) in the reverse order to the direct solution, and that expected on empirical grounds. ($J_{12}$ is usually larger than $J_{34}$.)

Further investigation showed that LAOCOON III was extremely sensitive to the input parameter and the experimental data. Unless trial parameters were carefully chosen, the iteration diverged or converged to a false solution due to the extensive line label changes in the region where $\delta_{23} \approx 0$. Secondly, the final parameters were very sensitive to the separation of lines which were unresolved (marked * in the spectrum). The experimental separations had been estimated from line widths. When the estimates were increased from an average of 0.08 Hz to 0.16 Hz the coupling constants changed from those in column 2 to those in column 3 of the table below. More reliable values are probably those in column 4 where all unresolved lines have been omitted from the input data. Surprisingly the direct ABMX calculation is fairly insensitive to these line positions. During the course of this work, Clín and Lemanceau published the results of their analysis of dibenzothiophene. They used the Reilly and Swalen iterative method and their results (column 6) were substantially different. Their value for $(J_{24} + J_{34})$ was also significantly different, whereas all our solutions give the same value of 9.22.

The results indicate that iterative methods of analysis should be used with caution in cases where shifts and/or coupling constants become similar in magnitude. The program should be checked for sensitivity to the experimental line positions and if possible, another analytical method used as a double check. A similar warning has been given by MacDonald and Schaefer who found the same sensitivity in the spectrum of epichlorohydrin. It seems this effect is more widespread than is commonly supposed.
<table>
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<tr>
<th></th>
<th>LAOCOON III</th>
<th>LAOCOON III</th>
<th>LAOCOON III</th>
<th>LAOCOON III/C₆D₆</th>
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<td>W(1)</td>
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<td>225.24</td>
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<td>W(2)</td>
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<td>J₁₂</td>
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<td>J₁₃</td>
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<td>1.08</td>
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<tr>
<td>J₂₃</td>
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<td>7.20</td>
<td>7.21</td>
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<tr>
<td>J₂₄</td>
<td>1.65</td>
<td>1.08</td>
<td>1.23</td>
<td>1.35</td>
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<td>J₃₄</td>
<td>7.57</td>
<td>8.14</td>
<td>7.99</td>
<td>7.87</td>
<td>7.96</td>
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J₂₄ + J₃₄ = 9.23 9.22 9.22 9.22 8.8

RMSE=0.022  RMSE=0.021  RMSE=0.012  RMSE=0.023

* In Hz measured upfield from the origin of the τ-scale.

To confirm that the parameters in column 4 are approximately correct the spectra in C₆D₆ (column 5), acetone and CDCl₃ were also analyzed. In C₆D₆ solution δ₂₃ = 4.1 Hz and the results are less sensitive to the measured frequency. As a further check, studies of C¹₃ satellite spectra are under way. If this fails, we will have to resort to something truly Heraclean; fire... brands perhaps?

Best wishes,

[Signature]
M. L. Heffernan  F. Balkau

Georgia AML University
Attn: Prof. B. L. Shapiro
College Station, TX 77843

Dear Prof. Shapiro:

The magnetic non-equivalence of syn and anti protons in oximes has been known for a long time. Several NMR studies have established and exploited the fact that a proton attached to an alpha carbon syn to the hydroxyl group in the oxime resonates at lower field than an anti proton on an alpha carbon. However, stereochemical assignments based on this generality can only be made if the NMR spectra of both stereoisomers can be obtained.

We have found (serendipity again) that the addition of small amounts of concentrated hydrochloric acid vapor to a benzene solution of a ketoxime caused the alpha proton syn to the hydroxyl group to shift to higher field, while the anti-alpha protons were shifted to lower field. Using dialkyl, cycloalkyl and alkylphenyl ketoximes of known stereochemistry, we found that in every case, the addition of ten ml of the reagent to approximately 1 ml of oxime solution produced shifts large enough to be unambiguously recognized and measured.

The technique involves recording the spectrum of a benzene solution of the ketoxime and measuring the chemical shift of the alpha protons. Hydrochloric acid vapor is then withdrawn from the atmosphere in a concentrated HCl reagent bottle by means of an eyedropper long enough to reach to the bottom of the NMR sample tube. The gas is then slowly bubbled through the sample. The spectrum is recorded and the chemical shifts measured after each addition of HCl.

The method is not only simple and inexpensive, but it also obviates the need for comparing one's own experimental data with previously compiled values.

Roger E. Rondeau
Exploratory Studies Branch
Materials Physics Division
September 30, 1970

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

Dear Professor Shapiro:


Proton Relaxation Enhancement with Protein-Bound Flavin Radicals

by Graham Palmer, Biophysics Research Division, University of Michigan and Albert S. Mildvan Institute for Cancer Research, Fox Chase.

Previous work has shown that enzyme-bound nitroxide radicals and paramagnetic ions, in which the unpaired electrons are well localized, are effective in enhancing the nuclear relaxation rates of the protons of water and substrates. To determine the effects of radicals with highly delocalized spins, such as flavin semiquinones, the proton relaxation rates of water solutions of a free flavin radical, 5-ethyl-10-methyl-lumiflavin semiquinone (LSQ) and a protein-bound flavin radical, flavodoxin semiquinone (FSQ) were studied. At 24.3 MHz, the longitudinal ($1/T_1$) and transverse ($1/T_2$) molar relaxivities of LSQ are equal (133 M$^{-1}$ sec$^{-1}$) but are less than those of Cu$^{2+}$ (875 M$^{-1}$ sec$^{-1}$). The immobilization of the flavin semiquinone in flavodoxin causes a 3.6-fold enhancement of $1/T_1$ and a 7.1-fold enhancement of $1/T_2$. Both relaxation rates decrease with increasing temperature ($E_a$ = 1.1 KCal/mole), indicating that water protons exchange at a rate $>10^5$ sec$^{-1}$ into a site which is in contact with the bound flavin. Hyperfine coupling of the order of 0.04 gauss consistent with hydrogen bonding is detected. The average distance between water protons and the unpaired electron of FSQ is $2.5(q)^{1/6}$ where $q$ is the "coordination number" for exchangeable protons on or near the FSQ. Reasonable distances ($3.2 \pm 1.0 \text{ Å}$) are obtained if $q = 4 \pm 2$, consistent with the results of ENDOR and optical spectroscopy. Hence the accessibility of water protons to enzyme-bound flavin radicals may be studied by relaxation enhancement.

Sincerely yours,

Albert S. Mildvan

ASM/deh
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