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My First Publication

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In honor of Barry Carpenter

Abstract: An undergraduate lab course in the physics department was what led me to a 50+-year career in physical organic chemistry, solving a wide range of puzzles regarding chemical reactivity.

My first publication developed through a roundabout series of happenings. Physics 12 at Harvard was a requirement for undergraduate chemistry majors, but it had a reputation of being a terrible course, with poor lecturers. I petitioned to skip that course, and the Chemistry Department approved, subject to my passing the final exam. Over the summer of 1957 I read the textbook, did the exercises, and then took the exam with the enrolled students. I passed with a C-, of which I was proud, because my roommate, who was taking the course for credit, got a D.

The Chemistry Department was not impressed with a C-, and they encouraged me to take one or two more advanced courses for which Physics 12 was prerequisite. So in my junior year I took Edward M. Purcell's upper-

division Electricity & Magnetism. It was an excellent course, making clear the utility of the mathematical quantities such as gradient, divergence, and curl that I had learned about in the abstract in the course on Advanced Calculus. Purcell was a gifted teacher, and his final lecture was on the behavior of nuclear magnets in a magnetic field, a topic for which he had won the 1952 Nobel Prize for the discovery of nuclear magnetic resonance.

That semester I was also taking P. D. Bartlett's Advanced Organic Chemistry course on reaction mechanisms. Bartlett was my adviser and with a distinct lack of tact I complained to him that his lectures were not as clear as Purcell's. Bartlett patiently explained that that was because electricity and magnetism are completely understood. In contrast there was still more to learn about reaction mechanisms, which was why he was continuing to carry out research in that area. That was some of the best and most inspiring advice that I have ever received.

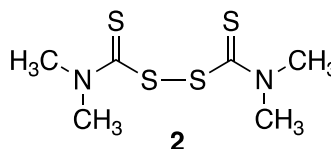
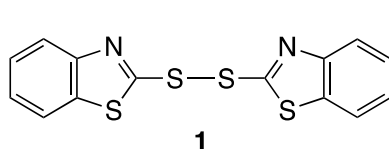
Purcell's course was so stimulating that for the next semester I chose to take a subsequent course on physical optics. This was a lab course where half the time was devoted to a set of prescribed experiments, followed by an individual project in the second half. Physical optics focuses on the wave nature of light, in contrast to geometrical optics, which views light as rays. A prerequisite for this lab course was the third semester of introductory physics, which I never took. However, the only overlap between the two courses was how to use lenses to collimate light beams, so I was not at a disadvantage.

Among the experiments we did was to build an interferometer to demonstrate the double-slit experiment. Another experiment, perhaps in the other physics lab, was to measure the speed of light as the ratio of SI and cgs units. I got a value of 4×10^{-2} cm/sec, and concluded that I had made a mistake somewhere, which I then carefully corrected. Another experiment was to assemble a polarimeter, which I used to measure the rate of mutarotation of glucose.

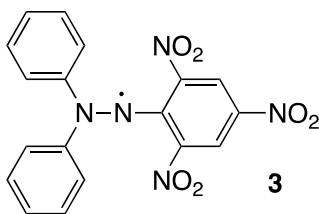
But the fun part was the individual project. I got permission from the physics instructor to carry out a research project on a chemistry topic that used the wave nature of light. I asked Professor Bartlett if he could propose one, and he turned me over to one of his postdocs, Robert Earl Davis. Bob had received his PhD at Indiana University and would leave Bartlett to take a faculty position at Purdue. There he continued his research into sulfur chemistry as well as into the hydrolysis of borohydride. He also wrote a book on how to use computers to guide investments.^[1] He used that technique to speculate in the stock market, and succeeded until the bear market of 1973-1974. He had retired from Purdue as an Associate Professor and he died in April 1974 at age 40.^[2]

Bob proposed to me a spectrophotometric project involving two disulfides, 2,2'-dibenzothiazolyl disulfide (**1**) and tetramethylthiuram disulfide (**2**). They are thermochromic,^[3] meaning that they reversibly turn color (yellow) on heating. Both **1** and **2** are accelerators used in vulcanizing rubber, which is a process involving crosslinking of polyisoprene chains,

promoted by allylic C-H abstraction by radicals generated from **1** or **2**. The question then was whether the color was due to reversible homolytic dissociation of the weak sulfur-sulfur bond, to form thiyl radicals (eq 1). Those are considered likely to be colored, owing to delocalization of the unpaired electron over an extended pi system.

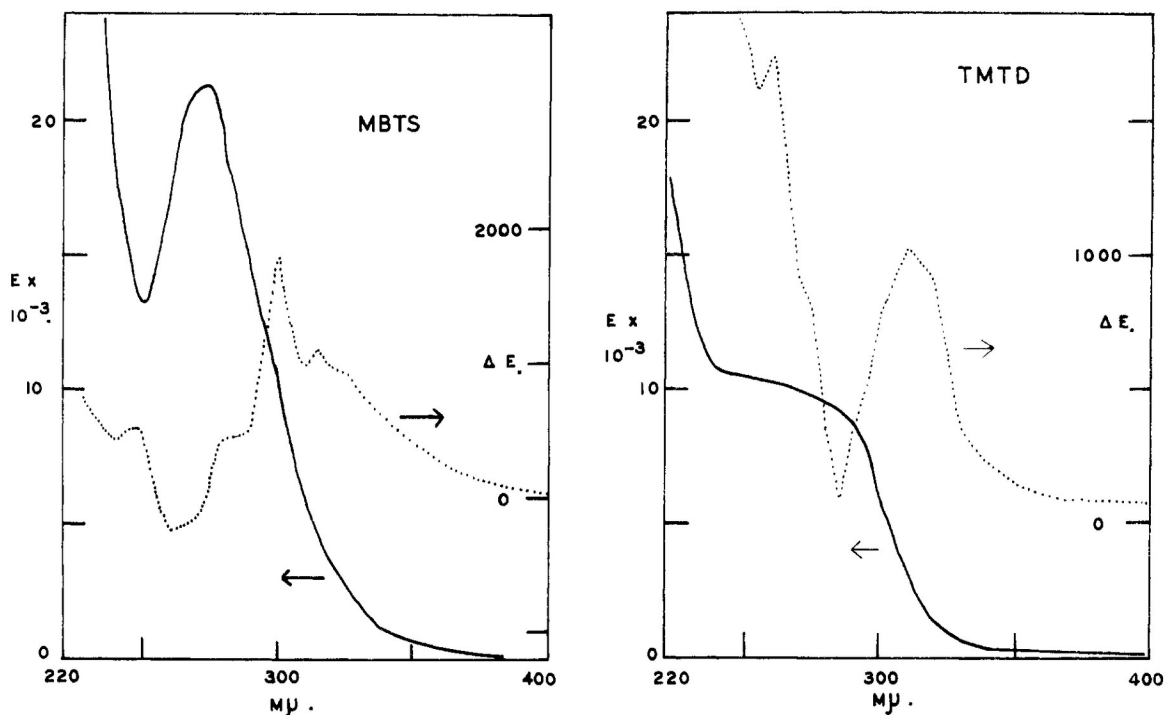


Bob could verify the production of radicals from both **1** and **2** by trapping them with diphenylpicrylhydrazyl (**3**), a stable free radical. It is intensely purple (like KMnO_4), so that its rate of disappearance could be monitored spectrophotometrically. That rate then provides the rate of homolytic dissociation in eq 1, and thereby the maximum concentration of $\text{RS}\cdot$ that could be produced.



My project was to measure the UV-VIS spectra of **1** and **2**. Samples were prepared at concentrations near 10^{-4} M in decalin as solvent. The spectrophotometer available in Bartlett's lab was a Beckman DU, with a 12-volt automobile battery as its power source, and with a thermostatted cell that could heat the sample in quartz cells to elevated temperatures. It was necessary to switch between a deuterium lamp for UV and a tungsten lamp for visible. To take a spectrum, the monochromator dial was set to the desired wavelength and the potentiometer was zeroed with pure solvent in the light path. Then the sample was moved into the light path and the transmittance T was read from the potentiometer needle and converted to absorbance ($= \log_{10}T$). If necessary, the concentration of disulfide was adjusted so that the transmittance would be near the optimum of 37%. Measurements at successive wavelengths then allowed each spectrum to be transcribed onto graph paper. Figure 1 shows the spectra for both **1** and **2**, along with the difference between extinction coefficients at 100°C and 25°C.

Figure 1. UV-vis spectra of dibenzothiazolyl disulfide (MBTS, **1**) and



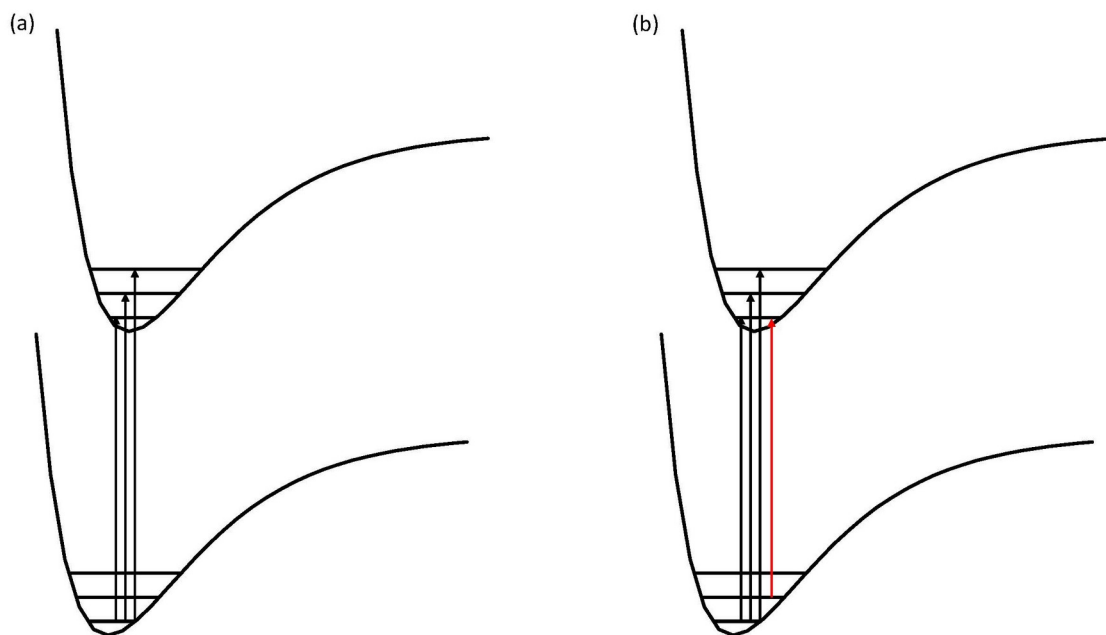
tetramethylthiuram disulfide (TMTD, **2**): solid curve = $\epsilon_{25^{\circ}\text{C}}$ vs. left ordinate, dotted curve = $\epsilon_{100^{\circ}\text{C}} - \epsilon_{25^{\circ}\text{C}}$ vs. right ordinate. Reproduced by permission from

Ref. 4.

That difference represents the absorption spectrum to be attributed to radicals produced on heating. According to the rates of homolytic dissociation of RS-SR, the maximum concentration of RS· that could have been produced was 6×10^{-7} M for **1** and 1.4×10^{-7} M for **2**. If those radicals were responsible for the spectral changes, their extinction coefficients would need to be 3×10^9 or 10^{10} (acknowledged simply as $> 3 \times 10^5$). Although line spectra of atoms can show enormous extinction coefficients, molecules, whose absorption spectra are spread over a range of wavelengths, are limited to extinction coefficients $< 10^5$. Moreover, the spectra at 100 °C are

time-independent, even though the concentration of $RS\cdot$ would increase. Therefore we concluded that the thermochromism of these two disulfides cannot be due to dissociation but must be due to the disulfides themselves.

Bob and I thus endorsed an alternative interpretation, that the thermochromism is due to thermal broadening of the absorption band. This phenomenon is illustrated in Figure 2. At higher temperatures the Boltzmann distribution permits excited vibrational states of the ground electronic state to be populated, and transitions to lower vibrational states of the excited electronic state, sometimes called "hot bands", can be seen. Because vibrational frequency is inversely proportional to the square root of reduced mass, thermally populated low-frequency vibrations are particularly likely with sulfur compounds. Those transitions are at lower energy and longer wavelength, so that the overall absorption spectrum broadens and



extends into the visible.

Figure 2. Transitions from vibrational states on the ground electronic state to vibrational states on an excited electronic state (a) at 25°C, when only the ground vibrational state is populated. (b) at 100°C, when an excited vibrational state is populated. For clarity the vibrational spacing is exaggerated.

This study was submitted to JACS in April 1959 but not published until April 1960.^[4] I never knew the reason for the delay. Also I presented this orally at the 135th National Meeting of the American Chemical Society, held in Boston April 5-10, 1959, which was a bit daunting for an undergraduate.

That project was a wonderful introduction to research. I have long enjoyed solving puzzles, and this was a chance to solve a puzzle that Nature proposed. It is thrilling to be the first to answer a question and to be able to explain how we know what we know. Throughout my career of over 60 years I have chosen projects that were designed to add to fundamental knowledge, without any concern for applications. That is part of the reason why I chose to pursue an academic career, even while most of my contemporaries in graduate school took positions in the chemical industry.

That goal of pursuing basic research was what led me to do my PhD thesis with Frank Westheimer. In my senior year I took his graduate course in Physical Organic Chemistry. One of the topics he covered was the solvent effect on ionic reactions. The electrostatic contribution to the molar free

energy of activation is given in eq 2, where $Z_A e$ and $Z_B e$ are the ionic charges, separated in the transition state by a distance r , and where ϵ is the dielectric constant of the solvent. It then follows that the electrostatic contribution to the entropy of activation is given by eq 3, and the electrostatic contribution to the enthalpy of activation is given by eq 4. For reactions between ions of opposite charge, ΔG_{el}^\ddagger is negative, so the reaction is accelerated by electrostatic attraction. For water, $\partial \ln \epsilon / \partial T = -0.005$, so that at 300K the factor $(1 + T \partial \ln \epsilon / \partial T)$ is negative. Then ΔH_{el}^\ddagger is positive, and the electrostatic interaction increases the activation enthalpy (while the rate acceleration resides in the activation entropy). This is a characteristic of $\partial \ln \epsilon / \partial T$ for most normal solvents, because higher temperature increases the solvent disorder and interferes with the ability to solvate ions. Exceptions are solvents like acetic acid, where higher temperature dissociates the dimers and makes the solvent effectively more polar, so that $\partial \ln \epsilon / \partial T$ is > 0 . Then ΔH_{el}^\ddagger would be negative, meaning that the electrostatic interaction might lead to a negative activation enthalpy, or a reaction that is faster at lower temperature.

$$\Delta G_{el}^\ddagger = \frac{Z_A Z_B e^2}{\epsilon r} \quad (2)$$

$$\Delta S_{el}^\ddagger = - \frac{\partial \Delta G_{el}^\ddagger}{\partial T} = \frac{Z_A Z_B e^2}{\epsilon r} \frac{1}{\epsilon} \frac{\partial \epsilon}{\partial T} = \frac{Z_A Z_B e^2}{\epsilon r} \frac{\partial \ln \epsilon}{\partial T} \quad (3)$$

$$\Delta H_{el}^\ddagger = \Delta G_{el}^\ddagger + T \Delta S_{el}^\ddagger = \frac{Z_A Z_B e^2}{\epsilon r} + T \frac{Z_A Z_B e^2}{\epsilon r} \frac{\partial \ln \epsilon}{\partial T} = \frac{Z_A Z_B e^2}{\epsilon r} \left(1 + T \frac{\partial \ln \epsilon}{\partial T} \right) \quad (4)$$

In class Westheimer told us that he had always wanted a student to search for a reaction that is faster at lower temperature, owing to this feature of solvent dielectric constants. That was just the kind of puzzle that intrigued me. So I went up to him and asked if I could work on that project if I stayed at Harvard for graduate school. He advised that it was advantageous to go elsewhere for graduate school, but he would be willing to take me. So I declined admittance to PhD programs at UC Berkeley and CalTech and continued at Harvard.

Within a few months it became obvious that the project was futile. Although $\partial \ln \epsilon / \partial T$ is > 0 in acetic acid, that solvent is so nonpolar that there are no free ions and therefore no reactions between ions of opposite charge. And in more polar solvents, such as formic acid, $\partial \ln \epsilon / \partial T$ is < 0 , a normal behavior, because the molecules are polymeric, not dimeric. In desperation I suggested trying some solvent mixtures, but he was not at all optimistic, and we abandoned the project.

To Westheimer's credit, he devised another project for me. Fifteen years earlier he had studied the mercuriation of benzene, an electrophilic aromatic substitution with Hg^{++} as electrophile. The reaction is accelerated by acid, but there is no obvious role for acid catalysis. That was an intriguing puzzle that I was happy to work on and provide a solution to,^[5] and it guided me to further insight into acidity functions in general.^[6]

That study with Westheimer led me to a career involving many other projects across a range of physical organic chemistry. Among the topics

studied were the synthesis and decomposition of malonic anhydrides,^[7] where we needed to take into account an inversion of configuration as elaborated by Barry Carpenter,^[8] and the cycloaromatization of enediynes and the nucleophilic capture of the resulting *p*-benzyne diradical,^[9] with similarities to Barry Carpenter's cycloaromatization of enyneallenes.^[10] Other topics included the symmetry of hydrogen bonds, relative acidities as measured by a highly accurate NMR titration method that we developed, isotope effects, stereoelectronic control, the so-called reverse anomeric effect, 2D-EXSY for site-to-site rate constants by NMR, vibronic borrowing, ipso reactivity, proton exchange in amides and amidinium ions, and the idea of solvatomers, but those are additional stories, as summarized in two previous publications.^[11] It is remarkable that all those studies developed in consequence of a spectroscopic investigation of two disulfides.

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