

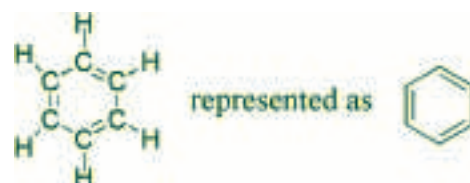
## Serendipity: How a Failed Experiment Opened the Door to Studies of Antiaromaticity

I want to thank you for the honor of being named a CUR Fellow and for the opportunity to speak briefly about my research. I remember sitting in the audience during the talks by the first two CUR fellows, Mary Allen of Wellesley and Julio Ramirez of Davidson, and being so impressed with the quality of their science. I thought at that time that this award is very appropriate for CUR because it showcases the quality of the science that can be done at predominantly undergraduate institutions, with undergraduates. Raising the consciousness of the “outside world” about the quality of the research done at PUI’s was one of the original intents of CUR and it has done this very successfully although, as always, there is still much to be done.

I am also honored to have been recognized by CUR. My time as a counselor in the Chemistry Division, from 1990-2001, was one of the most rewarding periods of my career. At the time that I became active in CUR, it was moving from a grassroots organization in which Mike Doyle produced the CUR Newsletter out of his office to one with a National Office and staff in Washington, DC. In 1990, it was an organization in which a person with a good idea could run with that idea and feel that he or she had the opportunity to make significant changes in the undergraduate research enterprise. I have never been involved in an organization before or since that offered these kinds of opportunities. It was heady stuff and great fun. So, to be standing before you at a CUR meeting is indeed a rare pleasure.

I am going to talk with you briefly about our adventures with one of the important concepts in organic chemistry, aromaticity, and how we stumbled into a research area that has allowed us to make useful contributions to its understanding. I will try to do so in such a way that the non-chemists in the audience remain reasonably engaged while still showing the chemists why we think this area is nifty.

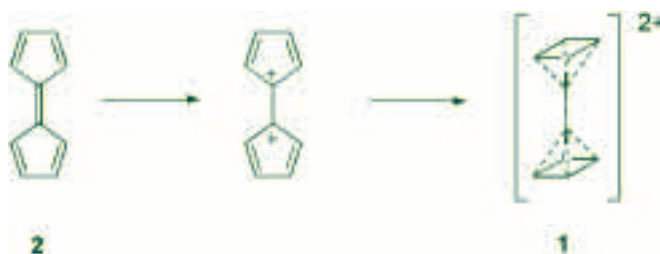
Aromaticity is one of the guiding principles of organic chemistry. It was originally used to define the characteristics of a benzene ring, a structural unit that was found in many naturally occurring compounds, including the essential oils of cloves, cinnamon, and vanilla, hence its name. Because the benzene ring was found in so many different compounds, people began to be curious about its properties. That is, since it was ubiquitous, was there something special about it?

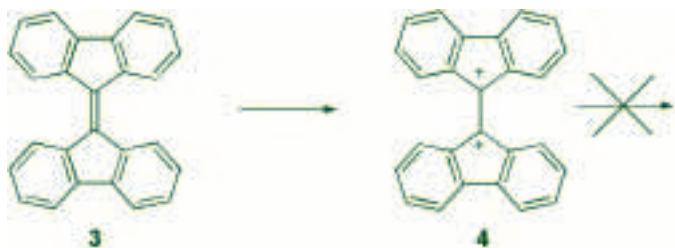


The chemistry of benzene is very different from other compounds with double bonds, resulting in reactions that preserve the structure of benzene, shown above. This suggests that benzene is particularly stable, and understanding stability allows one to predict the products of reactions. Since the goal of chemistry is often to make compounds, understanding what makes something stable is very valuable.

The explanation for benzene’s great stability lies in the number of electrons contained in the double bonds, in what is known as the  $\pi$ -system. Compounds with  $4n + 2$   $\pi$ -electrons, where  $n$  is an integer, should be particularly stable, aromatic, while those with  $4n$   $\pi$ -electrons should be very unstable, or antiaromatic. This “rule” was known as Hückel’s rule.

Chemists then began to ask whether other compounds that fit this rule were also aromatic and they set out to make those compounds. This then required that they identify the physical properties that typify an aromatic compound, and they looked at the properties possessed by benzene that could serve to characterize other aromatic compounds. Those properties included the stability of the compound, whether the bonds were of equal lengths, and whether the molecule possessed a ring current, when placed in a magnetic field. Unfortunately, these different properties can give differing answers to the question of whether a molecule is aromatic. If we are going to be able to use aromaticity to predict stability in reactions, we need to know what properties are most consistently associated with aromaticity.



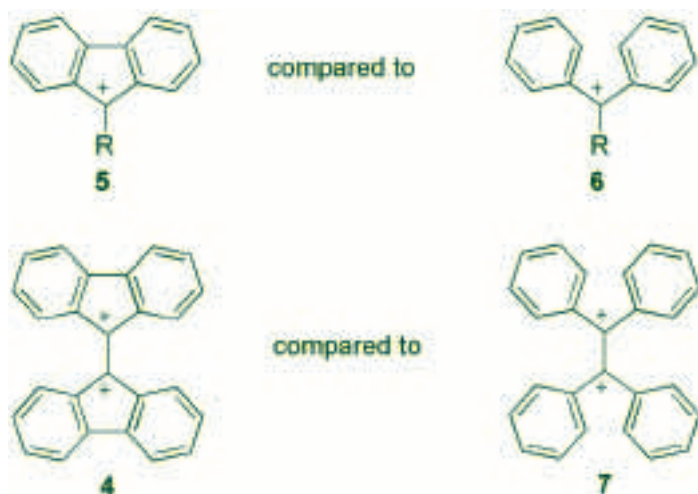
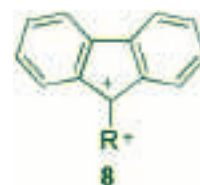


At the time that our research began, we were interested in unusual forms of aromaticity, such as three-dimensional aromaticity, in molecules that weren't flat. We were interested in making the dication (**1**) shown below in which 6  $\pi$ -electrons hold a carbon to the four-membered ring. We thought that it might be accessible by removing two electrons from the [5.5]fulvalene, **2**, because doing so would initially give two antiaromatic rings held together by a single bond, which should be very unstable. Because **2** is very unstable, we decided to start with compound **3**, tetrabenz[5.5]fulvalene, which is much easier to work with, but when we removed two electrons from it, we didn't get a species like **1**, but rather formed the intermediate dication that should have been antiaromatic, **4**. But was it? From this "failed" experiment, we started looking at antiaromatic species, ultimately deciding that if we could determine the characteristics of an antiaromatic species, we would also know the characteristics that define an aromatic species.

Dication **4** has all of the magnetic properties expected of an antiaromatic species. The hydrogens on the rings resonate between 4.97-5.77 ppm in the NMR spectrum, instead of around 7 ppm where the hydrogens of benzene resonate. They are shifted upfield rather than down-

field. If we put a probe atom in the center of the ring and measure/calculate its shift, the resonance of that atom, its nucleus independent chemical shift or NICS, is shifted downfield. The magnetism of the compound is greater than would be expected because of the presence of the ring current. Finally, when we calculate its stability, it is significantly less stable than other dications, with an (anti)aromatic (de)stabilization energy of 32.7 kcal/mole, a large number.<sup>1</sup>

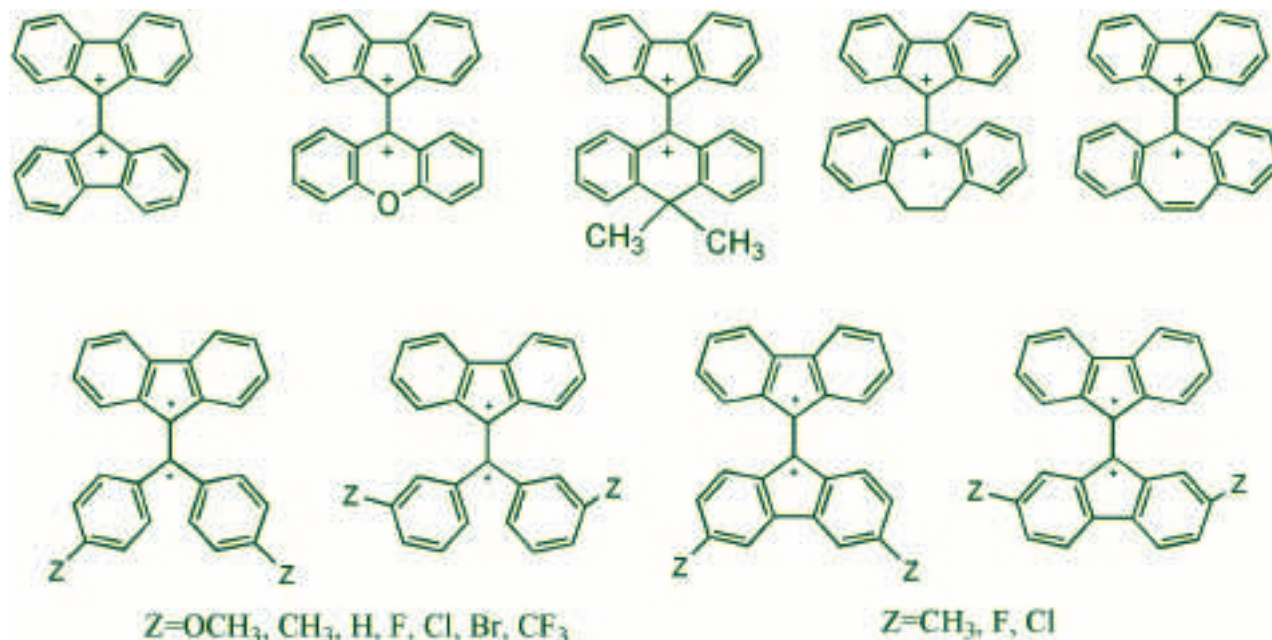
The two ring systems of **4** are called fluorenyl rings and we, and others, were interested in whether a single fluorenyl cation, **5**, was antiaromatic. When the NMR spectrum of **5** is compared to the spectrum of a reference system, **6**, the hydrogens of **5** are shifted upfield, as would be expected for an antiaromatic system, but by only about 0.5 ppm while the hydrogens of **4** are shifted upfield by 3.34 ppm in comparison to its reference system, **7**.<sup>2</sup> Thus **4** is much more antiaromatic than **5** and the question is why?



change in chemical shift

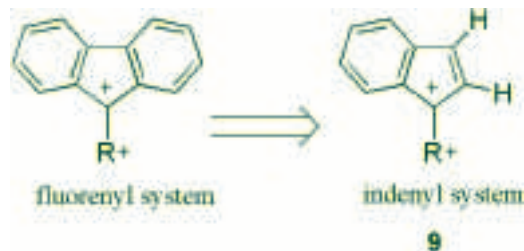
0.50 ppm when R=Cl

3.34 ppm



Scheme 1

ility of dications that were both antiaromatic and stable enough to study. So, we then set out to try to make as many compounds related to **8** as we could, and to examine them by the criteria associated with aromaticity. If these compounds proved to be consistently antiaromatic, then we could look for relationships in the criteria that would show whether all criteria equally effectively measured the aromaticity/antiaromaticity of compounds. Some of the compounds that we have examined are shown below in Scheme 1.<sup>1,3-8</sup>

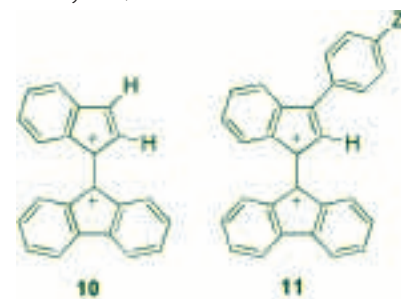


We have learned that we can indeed alter the antiaromaticity fluorenyl cations by changing the  $R^+$  substituent on the fluorenyl cation of **8**, that electron-withdrawing substituents increase the antiaromaticity of the fluorenyl cation, and that magnetic and energetic properties appear to be linearly related. Properties that are related to the structure of the molecule, like bond length alternation, are not very sensi-

tive to changes in the substituent  $R^+$ , making these properties less effective measures of aromaticity/antiaromaticity.

But there is still a lot that we don't understand about antiaromaticity. By focusing our efforts on the fluorenyl cation, we are unable to really examine the effect of structural changes on antiaromaticity because the 6-membered rings won't deform because they are benzene rings, and the 5-membered central ring can't deform because it is trapped by the benzene rings. In addition, NICS calculations suggest that the 5-membered ring is more antiaromatic than the 6-membered ring, but there are no hydrogens on that ring whose NMR chemical shifts might be examined. We can solve these problems by looking at dications that contain indenyl systems, **9**. In addition, because the indenyl cation has been shown to be less stable than the fluorenyl cation, we should see greater antiaromaticity in it, and have an even more sensitive system with which to look at aromaticity/antiaromaticity.

Because we had developed some expertise with fluorenyl systems, we decided to prepare



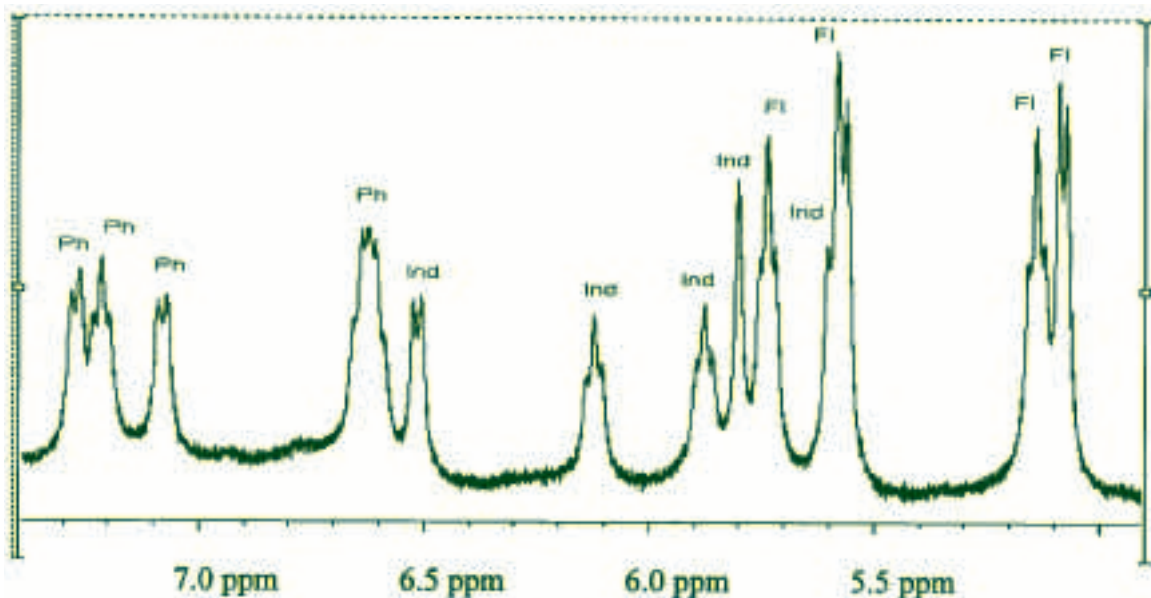


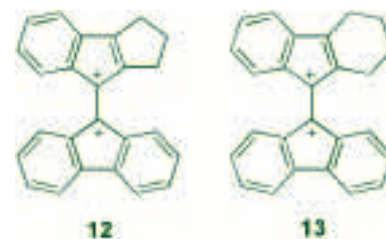
Figure 1.  $^1\text{H}$  NMR spectrum of **11**, Z=H, in  $\text{SO}_2\text{ClF}$ , referenced to external TMS

dications of **9** in which the R' substituent was a fluorenyl cation, as in **10**. Furthermore, because we were concerned about the instability of the indenyl cation, we decided to put a stabilizing substituent on the five-membered ring of the indenyl system that could diminish the positive charge through resonance. If that substituent were a benzene ring, we could also vary the substituent Z, species **11**, and examine their effect on the antiaromaticity of the indenyl system.<sup>9</sup>

The  $^1\text{H}$  NMR spectrum of **11**, Z=H, is shown in Figure 1. The peaks from the indenyl system are marked with Ind, those from the fluorenyl system with Fl, and those from the benzene ring substituent, Ph. We were anticipating that the indenyl protons would be further upfield than the fluorenyl ones, further to the right, and that is obviously not correct. This would suggest that the fluorenyl system is more antiaromatic than the indenyl system. Perhaps the problem was that we stabilized the indenyl system too much, that the phenyl substituent made the indenyl ring so stable that it was no longer antiaromatic. If we just

removed the phenyl substituent, would the indenyl ring become more antiaromatic than the fluorenyl substituent?

We have yet to make that dication, **10**, but we have calculated some of its properties. The nucleus independent chemical shift values for **10** and **11**, Z=H, are shown in Table 1. First of all, both the indenyl and fluorenyl ring systems are antiaromatic, as indicated by the positive value for NICS for each ring. Dication **10** is more antiaromatic than **11** because the NICS values are more positive for all rings than for the same rings in **11**. However, our real question asked if a phenyl substituent was absent from **11**, would the antiaromaticity of the indenyl substituent be greater than that of the fluorenyl substituent as predicted? It is apparent that this is not the case because the NICS values are still larger and more positive for the fluorenyl system than for the indenyl system. There




are a number of possible explanations, including the possibility that deformation in the five-membered ring of the indenyl system allows it to reduce its antiaromaticity. We are examining these possibilities by preparing compounds like **12** or **13** in which the five-membered ring has less flexibility because we have tied it up in a ring.

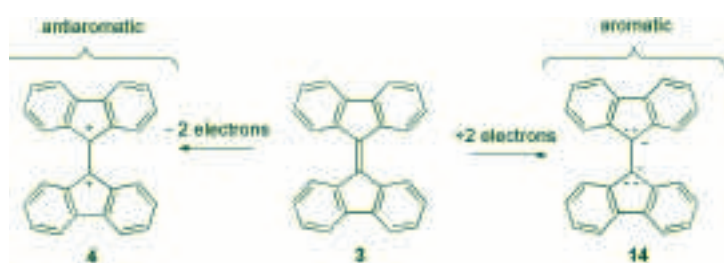
Table 1.

NICS	Indenyl ring		Fluorenyl ring	
	5	6	5	6
Ring size	5	6	5	6
<b>11</b> , Z=H	10.8	-0.4	20.0	6.5
<b>10</b>	27.8	14.0	28.6	18.3

I have reported on our experiences in making antiaromatic dications and the methods that we have used to describe their antiaromaticity, but we still have a problem. In the analysis of antiaromaticity, we generate a lot of numbers, NICS values, aromatic stabilization energies, etc., and we have used those numbers to indicate relative antiaromaticity, but what do those numbers really mean? That is, if a ring has a NICS value of 27, is this a big number, is the ring very antiaromatic, or is it actually not very antiaromatic at all? We need a context and the easiest way to get that context is to make aromatic species that are closely related to the antiaromatic species under study. Because aromatic species have been studied much more than antiaromatic

the aromaticity of **14**. But, interestingly, **4** is more antiaromatic than **14** is aromatic. The dogma in organic chemistry has said that species will do whatever they can to reduce antiaromaticity. For example, cyclobutadiene deforms from the square shape that would allow maximum electron delocalization (organic compounds normally exist in a format that would allow the maximum electron delocalization) to a rectangular shape that should have less electron delocalization,  but which would also have less antiaromaticity. However, in this case, we actually have greater antiaromaticity than aromaticity in species that have the same carbon framework but differing numbers of electrons.

#### Antiaromaticity/aromaticity continuum

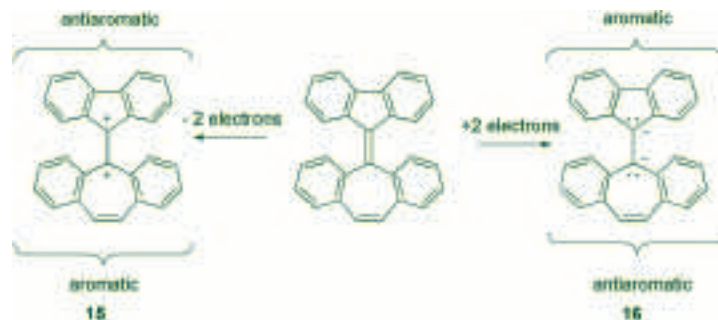


species, there is a greater comfort level with their properties, which means easier acceptance of properties that reflect their aromaticity.

Luckily, our systems lend themselves to a study of aromaticity as easily as to a study of antiaromaticity. For example, while removal of two electrons from **3** gives the doubly antiaromatic dication **4**, adding two electrons gives the doubly aromatic dianion **14**. We call this relationship the antiaromaticity/aromaticity continuum. We have compared the properties of **4** to **14**, Table 2, and as would be expected, **14** is aromatic, while **4** is antiaromatic, as shown by the different signs of the values (Mills & Benish, 2006). The aromaticity of **14** has already been confirmed. Our interest was in the magnitude of the values and it is apparent that the antiaromaticity of **4** is comparable to

That suggested to us that we might be able to make other examples of the aromaticity/antiaromaticity continuum that might shed additional light on aromaticity. We decided to look at dications and dianions of tetrabenzo[5.7]fulvalene, as shown below.

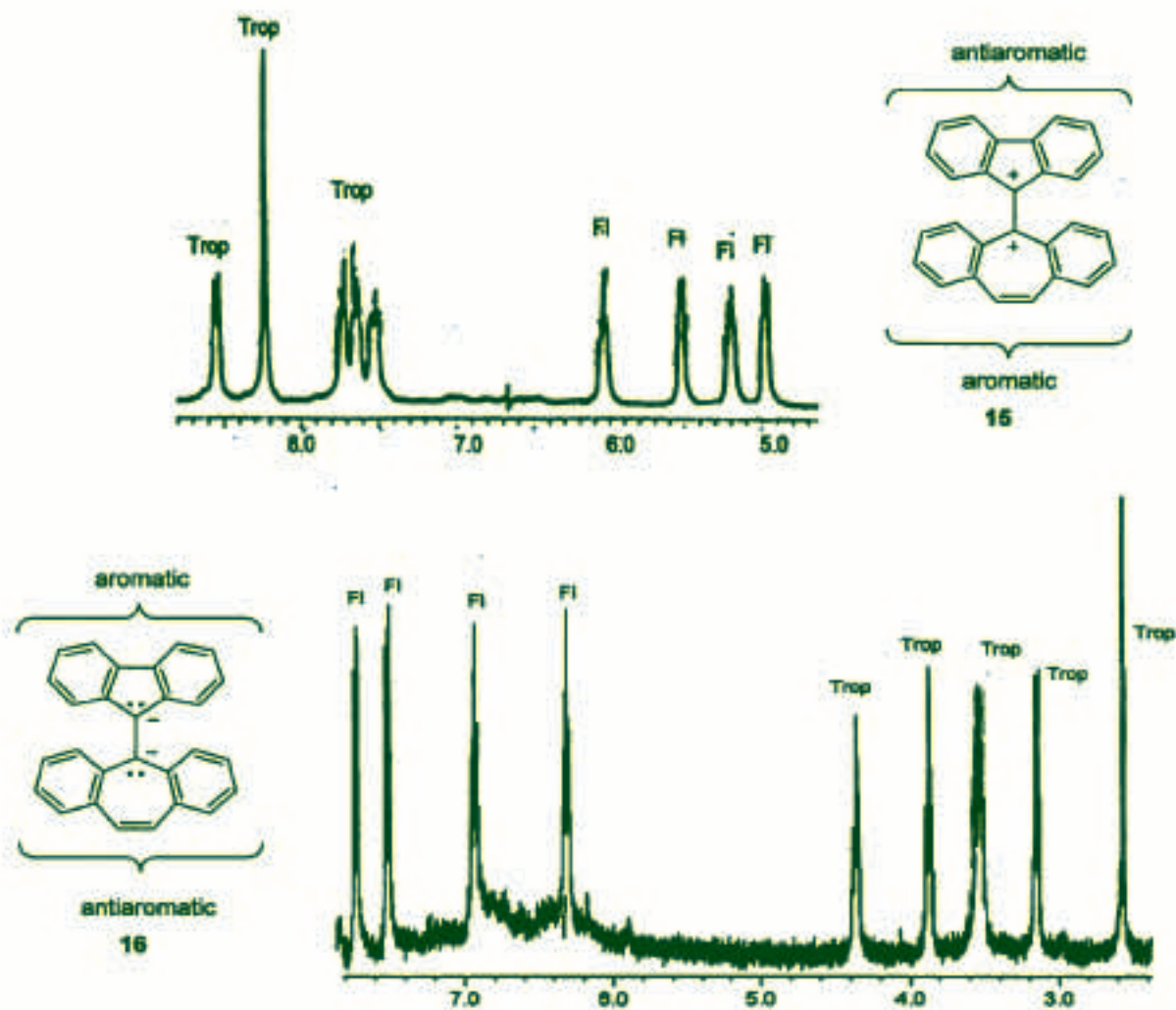
This system is interesting because each di-ion is composed of an aromatic and an antiaromatic half, thus allowing us the opportunity to examine aromaticity and antiaromaticity in two different ring systems at the same time. But the first question is, can we make dianions of a system in which one of the ring systems is antiaromatic?



The spectra of the dication **15** and the dianion **16** are shown below. Comparison of the two spectra shows that the fluorenyl system of **15**, which is antiaromatic, is further upfield than the seven-membered ring system, the aromatic tropylium system. Analogously, the antiaromatic tropylium system of **16** is further upfield than the aromatic fluorenyl system. Antiaromatic anions are certainly accessible in systems like this. We are in the process of characterizing these systems in which the differences in aromaticity and antiaromaticity are almost entirely due to the number of electrons and not differences in the geometry of the systems.

**Table 2.**

	Dication <b>4</b>	Dianion <b>14</b>
Sum of NICS	38.2	-35.2
Magnetic susceptibility exaltation	95.8	-81.8
Aromatic stabilization energy	32.7	-24.7



So, what have we learned? First and foremost, we can make relatively stable antiaromatic systems that have both an excess of electron density, dianions, and a deficiency of electron density, dications. Prior to our work in the field, no one would have believed that antiaromatic dications/dianions were accessible. Very few people looked at antiaromaticity because no one thought that the species were stable enough to be studied. Because we stumbled into the area, we inadvertently discovered that the species were much more easily prepared and studied than anyone would have imagined.

This may be of value because antiaromatic species are predicted to have small differences in energy between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Most organic compounds are insulators because the gap

between the HOMO and LUMO is large, so electrons are effectively immobilized. In contrast, the HOMO/LUMO gap in metals is very small, allowing a sea of mobile electrons, and conduction of electricity. If an organic compound could be made with a small HOMO/LUMO gap, it could be a kind of organic metal. And, since we are able to change the properties of organic molecules by thoughtful modification of their structure, we might be able to create organic metals with precisely the properties, melting point, color, shape, that meet particular needs.

I would like to acknowledge the generous financial support of the Welch Foundation, the National Science Foundation, the Petroleum Research Fund of the American Chemical Society, and the Research Corporation. The credit for the success that we have had goes direct-

ly to the more than 170 Trinity University students with whom I have had the pleasure to work. They are smart, hard working, and thoughtful. And they are a ton of fun. I firmly believe that the best education in chemistry comes in the context of a well-designed research program. This was the philosophy of the founders of the Council on Undergraduate Research and I am honored to be named a CUR Fellow on the basis of the work of my students.

**References, undergraduates indicated by an asterisk**

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**Nancy Mills**

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The focus of the 2007 Dialogues is the "Art of Grantsmanship." Attendees will have the opportunity to meet with funding agency officers and policy makers from agencies such as NSF, NIH, USDA, to name a few, in a number of dialogue sessions, to discuss a host of funding issues.

For more information on the CUR Dialogues, please contact the National Office at 202-783-4810 or by e-mail at [cur@cur.org](mailto:cur@cur.org). A complete program and meeting registration materials are available on our web site at [www.cur.org/conferences.html](http://www.cur.org/conferences.html). As a CUR Member, please remember that you will receive a discount on your registration fees. We encourage you to review the program as it provides program highlights, a detailed schedule of the Dialogue Sessions, as well as travel and lodging information.

Several members have contributed to developing this year's program, allowing CUR to offer a conference that we are confident you will find exciting and informative. We look forward to seeing you at the 2007 CUR Dialogues!



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