

Professor B. S. Thyagarajan*A TRIBUTE**

DROPLETS ON A LOTUS LEAF
NIRVANA IN GENTLE BREEZE
*MANY BECOME ONE**

Professor Budalur S. Thyagarajan was born and raised in the small, historic town of Tiruvarur, India. His values were steeped in the traditions of his homeland and in the tumultuous journey of his countrymen toward independence. Professionally, Thyagarajan's scholarly activities traversed a broad range of the more important organic problems of his time and he conducted these efforts boldly, in an international fashion that characterizes much of modern chemistry.

Thyagarajan's family name derives from ancient legend: The Lord God Thyagaraja ("King of Sacrifices" in Tamil) was gravely injured when he consumed poisons generated during creation in order to save the universe. Thyagarajan and his family embrace the public service values associated with the legend. His father, a Shakespeare and Sanskrit scholar, became a devotee of Gandhi and was jailed for nine months in 1930 for participating in Gandhi's heroic march to the Arabian Sea. Further protesting colonial rule, he assisted the independence movement by establishing weaving and spinning centers in the villages. Thyagarajan's grandmother was another strong influence, admonishing that when you recognize that "the other man is in need of help and go immediately to offer it, only then are you a human being." Such were the influences that shaped the personal development and social commitment of the honoree.

Professor Thyagarajan began his professional life in chemistry as a Masters degree student under the direction of the eminent scientist Dr. T.R. Govindachari at Presidency College. Hardly twenty

* Haiku by Professor Thyagarajan appearing in the *Asahi Shimbun (Tokyo) English Edition*, August 24, 2001 (reprinted with permission).

years old, Thyagarajan wrote a review on the chemistry of quinolizines.¹ The paper, containing 157 references, was published in *Chemical Reviews* with the honoree as the sole author. During his doctoral studies (also with Dr. Govindachari), Thyagarajan established a record as a prolific researcher, this despite having been eclipsed on his first two projects. His doctoral studies included efforts in natural products isolation, characterization, and synthesis. His graduate work in the structural studies of lycorine, chelerythrine, and Feronia lactone with Dr. Govindachari resulted in six publications. Thyagarajan completed his Ph.D. at Presidency College in 1956.

Thyagarajan accepted an appointment to conduct post-doctoral research with Professor Howard Zimmerman, then an Assistant Professor at Northwestern University. During his two years at Northwestern, he examined several issues related to the emerging field of stereoelectronic effects. Considering the limited spectroscopic and analytical capabilities of the day, this project presented considerable technical challenges that required demanding skills and unwavering dedication. Impressively, during this busy period Thyagarajan found time to author two reviews.^{2,3}

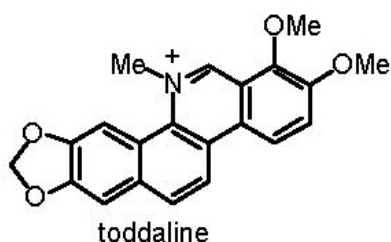
The next ten years of Dr. Thyagarajan's career reflected his adventurous scientific and personal spirit. The honoree accepted a one-year appointment in the laboratory of Professor Morris Kupchan at the University of Wisconsin to examine the alkaloid components of *Cyclea peltata*⁴ and *Stephania hernandifolia*.⁵ Thyagarajan returned to assume an appointment at the University of Madras where he remained until 1968. During this period, he supervised the doctoral research of Balasubramanian, Bimarao, Gopalakrishnan and Rajagopalan. These former students, who were to become leaders in Indian rearrangement and heterocyclic chemistry, published many important papers with Professor Thyagarajan.

Professor Thyagarajan's successes, which occurred despite the well-known, difficult research environment in India, did not go unnoticed in the international scientific community. He accepted Visiting Professorships at the University of Southern California in the spring of 1966 and Hokkaido University in Sapporo, Japan in early 1969. Subsequently, Thyagarajan was invited to join the faculty at the University of Idaho (his reputation was such that his immigration was facilitated by U.S. senators and the president of the U.S. National Academy of Sciences). During this period, Thyagarajan received a prestigious invitation to participate in the US-Japan Joint Lectures in Takarazuka, Japan (1971). After five years in Idaho, he accepted the position of founding Division Director of Earth and Physical Sciences at the newly established University of Texas at San Antonio. At UTSA, he established the departments of chemistry, physics, and geology, and led these units as an administrator and subsequently as a senior faculty member. His leadership resulted in the first polymer science degree program in the U.S. In 1984, Thyagarajan lectured under the auspices of the China-U.S. Exchange of Academic Faculty at the University of Beijing and the Institute of Organic Chemistry in Shanghai. Thyagarajan remained at UTSA, serving it with distinction, until he retired in 2000.

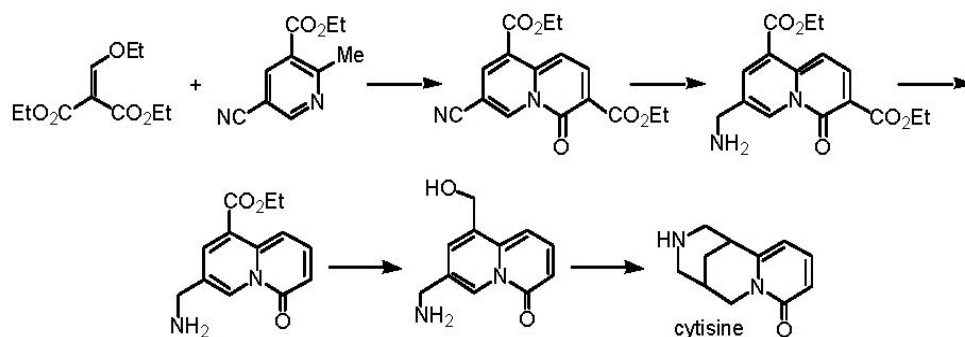
Dr. Thyagarajan's research as an independent investigator centered on important problems of the times. His research spanned natural product isolation and characterization, natural products synthesis, heterocyclic chemistry, organic reaction mechanisms, pericyclic reactions, acetylenic addition reactions, mass spectrometry, high-energy materials, and sulfur chemistry. Below is a brief summary of several of his contributions in these areas.

SUMMARY OF PROFESSOR THYAGARAJAN'S RESEARCH

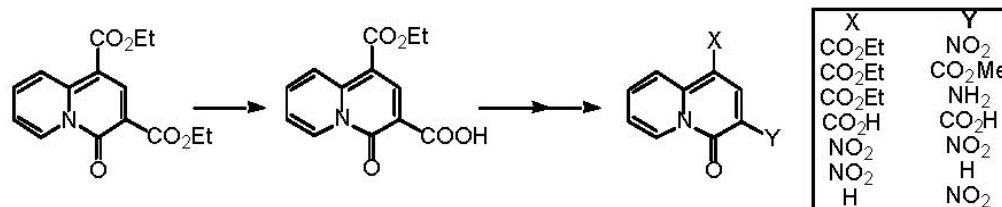
Natural products isolation and characterization. In his doctoral studies, Thyagarajan worked in natural products isolation, synthesis and heterocyclic chemistry. His first research article described the identification and isolation of Toddaline.⁶ This major constituent of the root bark of *Toddalia aculeate* had a similar structure to *Chelerythrine* an alkaloid isolated from *Papaveraceae*. As previously mentioned, Thyagarajan isolated and characterized alkaloids from the *Menispermaceae* species *Cyclea peltata*⁴ and *Stephania hernandifolia*⁵ while on sabbatical at the University of Wisconsin.



Natural products synthesis. Under the direction of Govindachari, Thyagarajan undertook the synthesis of cytosine, an alkaloid isolated from *Laburnum anagyroides* seeds. The molecule was pharmaceutically important, and consequently, several prominent groups were in competition toward the synthesis during this period. Though not the first, Thyagarajan completed the synthesis of cytosine⁷ via a unique heterocyclization route (Scheme 1). In addition, he synthesized quinolizone^{8,9} and multiple analogues^{10,11} according to Scheme 2.

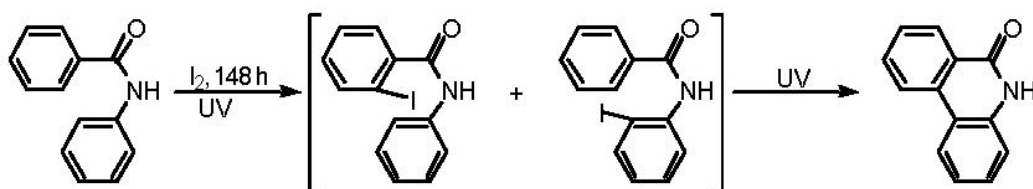


Scheme 1



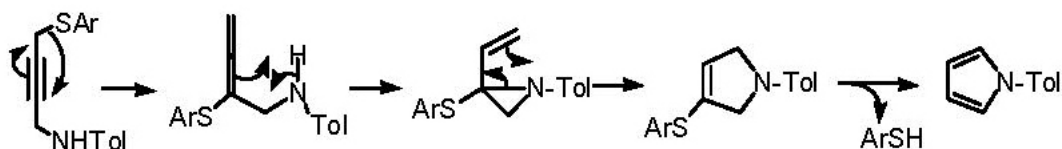
Scheme 2

At USC, Thyagarajan developed a photochemical route to the cyclization of benzanilide, anilide and phenanthridione analogs (Scheme 3).¹² He showed that the iodoaryl intermediate (on either end of the amide) preceded aryl coupling by independently preparing each isomer and demonstrating the conversion of each to the biaryl product. This work was the first demonstration of the photocyclization of benzanilide compounds.



Scheme 3

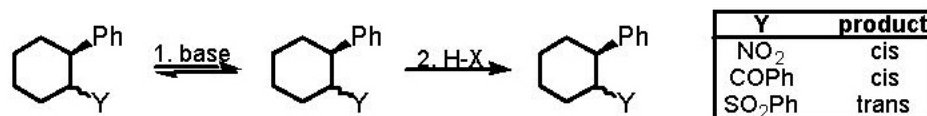
Heterocyclic chemistry. Thyagarajan published multiple mechanistically interesting and novel pathways to heterocycles and contributed an important review on aromatic quinoxilines.¹³ He and Glaspy discovered that acetylenic derivatives with non-geminal propargylic thiophenyl and *N*-alkylamino units undergo rearrangements to *N*-arylpyrroles with concomitant extrusion of thiophenol (scheme 4).¹³ The authors invoked a 1,3-arylthio shift to the allene followed by a rearrangement to generate a vinyl aziridine. The known vinyl aziridine-type cyclization led to ring expansion to the target compound.



Scheme 4

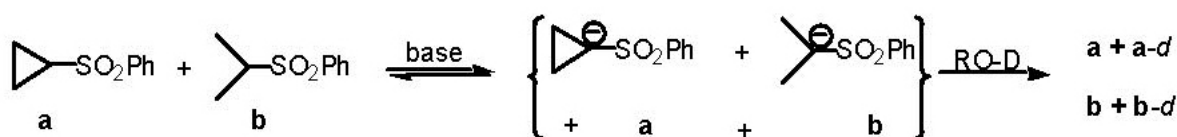
Organic reaction mechanisms. During his collaborations with Zimmerman at Northwestern University, Thyagarajan made significant contributions to understanding the stereoelectronic effects of the proton transfer reactions of sulfonyl anions. Thyagarajan and Zimmerman discovered that the kinetic protonation of the carbanions derived from 1-phenylsulfonyl-2-phenylcyclohexane generated trans products, in sharp contrast to the cis products generated from the nitro and benzoyl analogs (scheme 5).¹⁴ This selectivity was exhibited irrespective of initial stereochemistry, counterion, or solvent. The protonation stereoselectivity, however, was

influenced by proton donor acidity and steric demand. The team advanced the hypothesis that the conjugate base of the sulfone was more strongly influenced by sp^3 hybridized α -carbon resonance form than the nitro or benzoyl analogs. The hybridization difference results in an axial proton-accepting sp^3 orbital leading to a trans product. Conversely, the nitro and benzoyl analogs have increased proportion of sp^2 carbanion hybridization leading to a pi accepting orbital. Differences in the steric effects of the proton donors were well accommodated by this model, while differences in the electronic properties of the proton donor were ascribed to a later transition state.



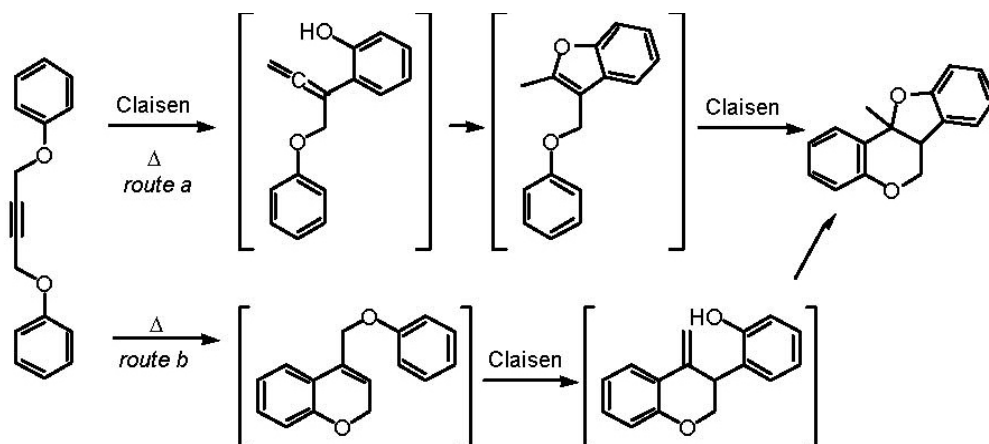
Scheme 5

In a supporting study, Professor Thyagarajan and Zimmerman compared the acidities of isopropyl- and cyclopropylphenylsulphone to examine resonance contributions to the stability of the conjugate bases of these species (scheme 6).¹⁵ The previously described study had suggested a limited resonance contribution from the carbanion into the sulfone moiety. Thus, the cyclopropyl analog was not expected to significantly stabilize the α carbon of the cyclopropyl species and the cyclopropyl analog was expected to be more acidic due to increased s-character of cyclopropyl C-H bonds. However, the acidities of the two species were very similar, suggesting that the resonance stabilization of the propyl analog approximately equaled the stability associated with the cyclopropyl anion. The two studies with Zimmerman required challenging syntheses, in addition to the development and careful execution of difficult monitoring protocols. These studies exemplified the inventive experimental design and superb laboratory skills that characterized the collaboration of Professor Thyagarajan and Zimmerman.¹⁶



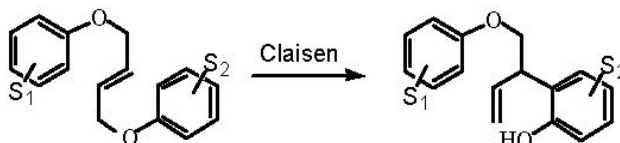
Scheme 6

Pericyclic reactions. Professor Thyagarajan examined the intricacies of Claisen rearrangements of 2-butyne- and buten-1,4-diyl bisaryl ethers as an independent investigator. For the former, it first appeared that a rearrangement was taking place that involved a double-Claisen mechanism¹⁷ (scheme 7, *route a*). However, some expert detective work revealed the true character of this reaction.¹⁸ The first intermediate of *route b* was synthesized and easily converted to product, while the second intermediate of *route a* resists any reaction when submitted to the normal conditions. Therefore, *route b* prevails, involving a single Claisen rearrangement and two addition steps. Considerable synthetic and analytical skills were employed to unravel this mystery.

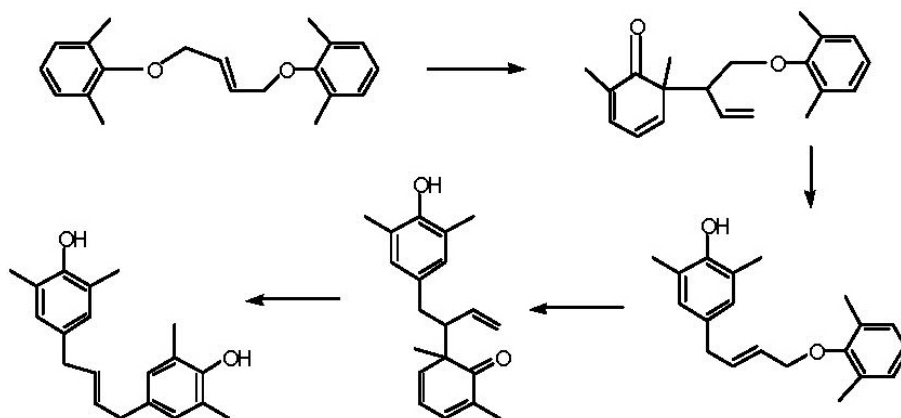


Scheme 7

The electronic influences in ortho Claisen rearrangements had been studied only under kinetic conditions before 1961. Thyagarajan designed the arylbutenyl ethers (Scheme 8) where two aromatic ethers, substituted with opposing electronic demands, were made to compete for the same alkene. Thus, the end product would determine which system would predominate.¹⁹ Interestingly, when the aryloxy groups are differentially substituted,²⁰ a clever method of determining the ratio of products was employed for quantification. The results were consistent with kinetic studies for these types of reactants. Thyagarajan and Balasubramanian also established for the first time a stereoselectivity in para Claisen rearrangements (Scheme 9).²¹



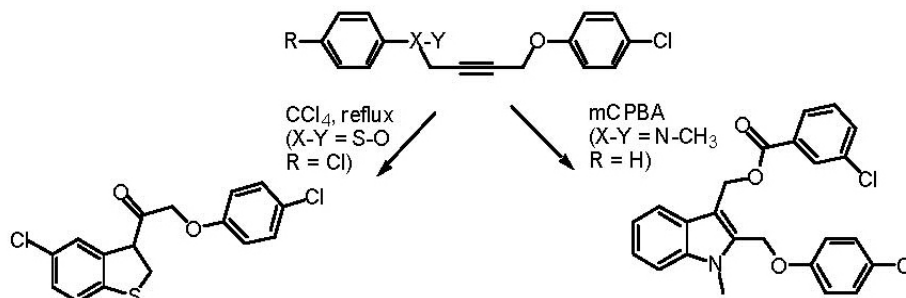
Scheme 8



Scheme 9

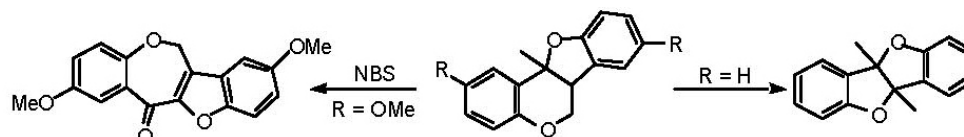
At the University of Idaho, Dr. Thyagarajan continued his adventures with rearrangement mechanisms engaging in heteroatom variations on the original butynyl theme. Substituting an *N*- or *S*-oxide for one of the oxygens of the butynyl bis(aryl ether) compounds illustrated below led

to useful indole²² or benzothiophene²³ derivatives, respectively (scheme 10). It is of interest to compare and contrast various mechanistic possibilities that can be offered to account for the course of the reactions shown therein. A wealth of additional synthetic work has been published that underscores the marvelous chemistry presented in these papers.^{23,24}



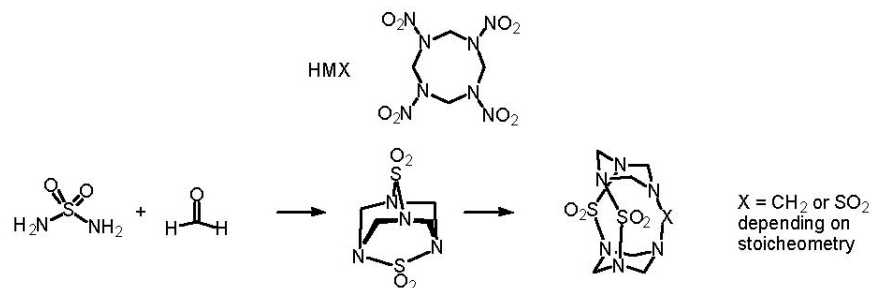
Scheme 10

Several of the products derived from earlier work were found to undergo further novel transformations of the ring expansion²⁴ and ring contraction²⁵ types (scheme 11).



Scheme 11

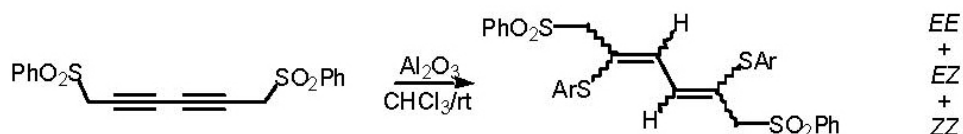
High energy materials. On contract with the US military, Thyagarajan discovered the only novel approach, in three decades, (despite efforts from Germany, France, Russia, England, Canada, and the USA) to the exclusive production of HMX (completely free from RDX). This is the currently employed manufacturing method for the solid propellant HMX.²⁶ The honoree is proud that his synthesis has provided materials that have made space exploration more accessible and reliable. In the course of this work, Thyagarajan developed new sulfonylurea-based polycyclic compounds (scheme 12).²⁷



Scheme 12

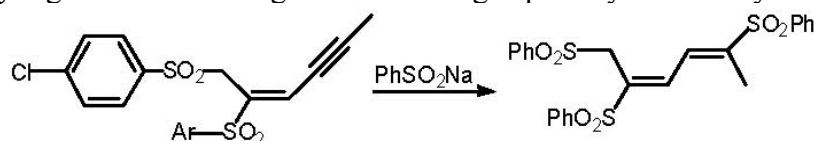
Thiol additions to butynes and hexadiynes. As part of his lifelong interest in the chemistry of sulfur compounds, an area for which he received an international award,²⁸ Thyagarajan

discovered the stereoselective, syn-selective nucleophilic additions to butynes in contrast to the previously established and widely accepted trans nucleophilic additions to alkynes. His group discovered that stereoselective addition of thiol to butynes gave the kinetically favored but less stable E isomer and the latter was then equilibrated to the Z isomer. In the hexadienes, once again, contrary to earlier theories, the kinetically preferred, less stable (E,E) isomer was formed predominantly. Equilibration among the three isomers, *viz.* (E,E), (E,Z), and the (Z,Z) led to the thermodynamically favored (Z,Z) isomer. Most interestingly, all of these isomerizations proceed via an entirely novel mechanism of elimination followed by re-addition of a sulfinate (scheme 13).²⁹ These equilibrations occurred under mild conditions. This also led to the discovery of a stereoselective syn reduction of an alkyne by sodium borohydride.³¹



Scheme 13

In subsequent work, Thyagarajan and coworkers disclosed results from an unusual, facile substitution and elimination in a related polyaryl sulfonyl enyne system³⁰ (scheme 14). In these studies, novel substitutions of vinyl and allyl sulfones were revealed. Mechanistic studies showed that the allylic sulfone is substituted prior to the addition of the sulfinate to the alkyne. The sulfinate addition is highly regioselective owing to the directing capability of the vinyl sulfone.



Scheme 14

OTHER ACTIVITIES AND INTERESTS

Several other areas of Professor Thyagarajan's leadership in chemistry are worthy of note. He published monographs on DMSO,³¹ cyanogen halide,³² and aromatic hydrocarbons.³³ Thyagarajan edited the series *Organic Spectral Data*,³⁴ four volumes of *Mechanisms of Molecular Migrations*,³⁵ and two volumes of *Selective Organic Transformations*.³⁶ The honoree chaired an international conference on DMSO chemistry³⁷ and served on numerous editorial boards of international journals.³⁸

Professor Thyagarajan has also been involved in service activities related to his local communities. In Madras, Dr. Ramachandran, Dr. Govindachari, and Professor Thyagarajan organized the Madras Science Society with the aim of promoting local science development. The group was instrumental in attracting eminent scientists to Madras, including Dr. Max Perutz, Dr. John Kendrew, Dr. Dorothy Hodgkins, Dr. Kathleen Lonsdale, Dr. William Bragg, Dr. Charles

Coulson, Dr. Linus Pauling, and Dr. S. Chandrasekar. These exchanges fueled a strong growth in scientific excellence in that region. In San Antonio, Professor Thyagarajan presented a local television show to popularize chemical discoveries of common interest. He also served as an American Chemical Society lecturer. These activities were supplemented by his role in attracting support for training high school students from the poorer areas of San Antonio. A number of former students from these humble roots completed undergraduate chemistry degrees. Several of his former students, now chemists, medical doctors, and lawyers, continue to have warm exchanges with their mentor.

Professor Thyagarajan continues to read chemistry journals voraciously, and is perhaps more free to do so since his retirement. A symposium entitled “Recent Advances in Heterocyclic Chemistry: Symposium Honoring Professor B.S. Thyagarajan” was held in his honor in October 2001 in San Antonio, Texas. Originally, 21 speakers from around the world were scheduled to present research talks, many of whom were suggested by the honoree. As one might expect, the choice of speakers reflected a broad array of forefront research, consonant with the vitality of the honoree’s vision of heterocyclic chemistry. Even the disastrous events of September 11, 2001, which caused last minute cancellations by seven speakers did not dampen the joy of the events.

On a personal level, Professor Thyagarajan was married and has three children. But his extended family includes many of his former students. He was particularly thrilled to see one of them mentioned in a *New York Times* article on the prospects of using the spin states of isotopically labeled compounds for information storage. At the symposium, this individual emotionally recalled the gift Professor Thyagarajan provided him: the love and wonder of chemistry. These sentiments are generally reflected in the several nominations and awards received by the honoree for his teaching and mentorship.

Professor Thyagarajan’s impact on students will continue into the future in several ways. There are now two endowed scholarships at the University of Texas at San Antonio that bear the Thyagarajan name. A scholarship dedicated to Professor Thyagarajan’s mother provides opportunities for deserving students in the several areas of physical science. A second chemistry scholarship bears Professor Thyagarajan’s name and honors his values and traditions. The recipients of these awards are required to reflect on the contributions of two of Thyagarajan’s heroes in the non-violent movements for social justice, the Mahathma Gandhi and Cesar Chavez.

Professor Thyagarajan is an avid reader in all areas and spends several hours per day reviewing a variety of sources. His name appears frequently in the local press as a contributor to the opinion page. He is a published poet and is particularly proud of the warm reception to his Haiku constructions, one of which appears under his photo, introducing this article. Like his science, his poetry reflects his belief that reality is something that must be grasped by each individual—“*The only thing that you really see is what you have found with your mind.*”

A lifetime in science is, perhaps, best reflected upon in the context of the legacy that remains when the professional career has waned. Clearly the honoree was a superb chemist with a reputation of industry and scholarship. A second indicator is the impact he has had on colleagues and mentored students. In that light, and entirely by chance, one of the co-authors of this tribute (MB) was trained by Professor Rajagopalan, Professor Thyagarajan's former doctoral student. MB is now working in the laboratory of the other co-author (GRN) who overlapped with Professor Thyagarajan in his later years at UTSA. Each of us has benefited, and will continue to benefit, from his wisdom, courage, and support. We look forward to continuing to learn from a distinguished mentor, and wish him good health and a long life.

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