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Obituary

Asher Mandelbaum (1934−2020)

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Asher Mandelbaum, Professor Emeritus of Chemistry at the Technion - Israel Institute of Technology, passed away on June 21, 2020. He earned the respect of colleagues and students for his impressive accomplishments as a scientist and gifted teacher, and likewise for his demonstrated integrity, modesty, and consideration for others. Before highlighting some of Prof. Mandelbaum's most notable lasting contributions to the field of mass spectrometry, we would like to offer a bit of lesser- known biographical information about his earlier years.

Asher Mandelbaum was born on December 27, 1934 in Krakow, Poland. At the age of five, he began a harrowing six-year period as he and his family attempted to evade first the Nazi restrictions against Jews, and later, their horrific extermination program. The family's struggles during that time are vividly described in his autobiographical notes (see the Supporting Information). He, his parents, and younger sister all miraculously survived the war, reunited, and three years later immigrated to Israel, arriving there just 1 day after the State was proclaimed.

After Asher completed his high school education and two-year stint of army service, he enrolled at the Technion - Israel Institute of Technology, in Haifa, intending to study chemical engineering. However, he took two organic chemistry courses taught in such a riveting way by David Ginsburg (who was well-known for his synthesis of morphine) that Asher decided to focus instead on pure chemistry. He pursued graduate studies under the supervision of Michael Cais, with research that led him to develop a new method for synthesizing triphenylenes (M.Sc., 1960) and to isolate and structurally identify components of the plant *Catha edulis* (D.Sc., 1963). His doctoral work involved mass spectrometric analysis and interpretation, although the spectra themselves were obtained in the Stanford University lab of Carl Djerassi because the instrumentation for measuring molecular weights of up to 1 kDa was not then available in Israel.

An organic mass spectrometry lab was established at the Technion as part of the Department of Chemistry shortly after Asher completed his graduate studies, and he accepted an offer to become a faculty lecturer and head of that lab. In that position, he used the first acquired instrument, an Atlas CH4, to investigate the mass spectral fragmentation of some substituted ferrocenes (reporting one of the first cases of electron ionization-induced rearrangements involving groups other than hydrogen) and of many morphine derivatives provided by Prof. Ginsburg, then Chemistry Department Dean. The analyzed morphine compounds included several pairs of stereoisomers whose respective members differed from one another only in their configuration at position 14. In accordance with the then-prevalent view that the high energy (usually 70 eV) of the electron ionization would cause the molecular ions to rearrange to a common structure, it was presumed that the respective mass spectra of stereoisomers would be similar to each other. Unexpectedly, those mass spectra differed markedly, pointing to stereospecificity in the fragmentation processes. In turn, that specificity suggested that structures of the molecular ions are retained, even though there is just a small difference in the respective energies of the stereoisomers. These observations and explanatory mechanistic arguments, published in 1965,[1] were among the first to disprove the previous assumption. That study spearheaded Asher's decades-long career interest in understanding stereochemical phenomena in mass spectrometry.

In those early stages of the organic mass spectrometry field, metastable peaks were crucial in identifying the correct fragmentation path when more than one option was possible. To find out which peak pair(s) could produce each of the metastable peaks in the mass spectrum, Asher devised a computer program to tabulate all the possible pairs, applying his creativity and problem-solving skills even outside his own immediate field. He wrote this program with a transistorized computer introduced not long before (1963) by Elliott Brothers Ltd. that had only 8 kilobytes of memory! One

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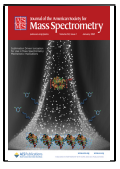

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example of the program's application was in helping to determine the structure of 31-norcycloartanol from a plant extract whose mass spectrum contained 90 significant peaks and over 30 metastable peaks.

Asher took leave from the Technion in 1966 for a research stint in the MIT lab of Klaus Biemann. One outcome of their work together was their challenging the opinion accepted at that time of "charge localization" at the site where a fragmentation occurred. In contrast to that view, they documented charge migration from the place where it induced fragmentation to another site of that fragment ion where it could produce further fragmentation.[2] This new concept was significant because it facilitated understanding of ion fragmentation in the gas phase and subsequent determination of structural information from mass spectra.

During his stint at MIT, Asher continued (by snail-mail) mentoring a Technion grad student on work that included a highly stereospecific retro-Diels–Alder (RDA) fragmentation accompanied by double hydrogen migration of certain polycyclic diketone adducts. The inconsistency of the RDA process in the gas phase whereby stereospecificity was exhibited in some systems and not in others was a subject that Asher and his lab group researched in depth over the following many years. Using carefully chosen model compounds, he showed that the RDA fragmentation is highly specific in many bi-, tri-, tetra-, and pentacyclic systems. The ions produced by the RDA fragmentation from the *cis*-isomers were very abundant while those fragments obtained from the *trans*-isomers were negligible. These results led him to suggest strongly that the RDA fragmentation of these compounds in the gas phase takes place by a concerted mechanism analogous to the ground-electronic-state RDA fragmentation in the neutral cyclohexene-containing compounds. Citing the many compounds that show a nonstereospecific RDA process, which implies a stepwise RDA fragmentation, he provided an explanation for the inconsistency based on energetic factors which are influenced by the degree of substitution at the bonds that are cleaved.

Based on other RDA-related studies, he offered mechanistic arguments that rationalized the highly stereospecific RDA fragmentations accompanied by the migration of two hydrogen atoms in some alicyclic systems and its dependency on the size of certain rings in the system. He also cleverly explained a surprisingly nonstereospecific RDA fragmentation accompanied by transfer of two hydrogen atoms in certain bicyclic anhydrides and the contrasting stereospecificity of such fragmentations in the related diesters. Furthermore, he proved that the RDA fragmentation exhibited stereospecificity under chemical ionization (CI) and collision-induced dissociation (CID) conditions in the compounds studied, similar to the results obtained under electron ionization conditions.

The above RDA processes occur in positive-ion mass spectrometry. In the mid-1970s, the RDA fragmentation of negative ions was considered unlikely to occur because C–C bond cleavage of the cyclohexene system was not likely in negative-ion mass spectrometry. Asher's lab was the first to report evidence of a highly stereospecific negative-ion RDA fragmentation process in which two C–C bonds are cleaved. In that 1992 paper,[3] he identified three systems that exemplify this process, and due to the high stereospecificity in each case, suggested that the RDA cycloreversion process occurs through a concerted mechanism in these negative ions as well.

Asher and his lab group also investigated instances of stereospecific elimination of alcohols, alkyl radicals, halogen atoms, and acetic acid under various ionization (EI, CI, CID) conditions. They identified systems in which the phenomenon occurs, and by designing and implementing elegant experiments involving site-specific deuterium labeling, they elucidated the underlying mechanistic intricacies. Their work convincingly proved that a "hidden hydrogen migration" was a necessary step preceding the elimination. While the proposed mechanisms are significant from a theoretical perspective (and corroborated by quantum mechanical calculations when performed), they are valuable as well for their diagnostic ramifications in differentiating isomers of the systems studied. For example, in certain cyclic and acyclic systems where an H-migration precedes stereospecific elimination of an alkyl radical, they provided proof that mass spectrometry can be used for configurational assignment of stereoisomers, a feature that is difficult to ascertain by other spectroscopic techniques.

Another series of Asher's studies was focused on causes other than H-migration for the stereospecific elimination of alcohols under CI and CID conditions. He demonstrated that in some systems the elimination can be explained as an effect of steric hindrance on the gas-phase protonation site. In other systems, it is caused by a concerted anchimerically assisted mechanism, which was proven by both experimental data and quantum mechanical calculations. Years before, Asher had shown foresight regarding the value of such calculations, as recalled by Yitzhak Apeloig, professor of Chemistry and former president of the Technion: "When I joined the Technion in 1976, the experimental community was still very skeptical about the ability of computational quantum mechanical methods to make useful predictions and interpretations. Asher was one of the first experimentalists to recognize the value of computational chemistry for studying reaction mechanisms in the gas phase and to collaborate with computational chemists, including my group."

The "even-electron rule" was yet another topic to which Asher's lab offered a significant and unusual kind of contribution. In the late 1970s, he and his graduate student, Miri Karni, identified a large number of organic compounds that do not obey the rule. That collection of data led to their convincing argument that while the rule was a "helpful guide" in explaining the mass spectra of many compounds, it could not be universally applied and therefore should not be deemed a mass spectrometry "rule" at all.

At the Technion, where he served as a classroom professor and a stint as Dean of the Chemistry Department, Asher was as committed to his teaching role as he was to his research, truly embodying the traits of a talented, dedicated, highly appreciated teacher. He offered countless Technion students engaging classroom presentations and wise guidance on lab experiments, all while kindly encouraging the students' self-confidence and emerging independence. In this regard, Jossi Deutsch, Professor Emeritus at the Hebrew University and Asher's first graduate student, commented that "Asher and I developed a very close mentor and student relationship that affected my life and my career." He noted his gratitude for Asher's kind support, particularly his sensitivity to Jossi's challenges as a recent immigrant, struggling to study and communicate in two new languages (Hebrew and English). Dr. Karni, currently a researcher at the Technion, recalled her own experience as Asher's student, commenting, "...in his instructive and patient way, he introduced me to the secrets of this field

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with a golden spoon...explaining the reactions that took place in the mass spectrometer based on the physical and chemical properties of the molecules." She also observed that "the atmosphere between the group members of his lab was very friendly, and I think this resulted from the friendship he bestowed upon us." She offered a "cherished" memory of his annual invitations for the lab members and their families to celebrate Chanukah with his own family, thereby "tightening the relations among the students...[who] remained friends long after we finished our studies." One of the present authors can vouch for the warmth and pleasure of those gatherings, which were enriched by the delicious, fluffy, powdered sugar-sprinkled "sufganiyot" (jelly donuts), homemade by Asher's wonderful wife of 61 years, Lea. To everyone who knew the Mandelbaum family, it was clear that Asher and Lea's closeness and friendship formed one of the most meaningful anchors in his life.

Beyond providing his many master's and doctoral students with gentle and astute mentorship, Asher was open-minded in extending the scope of his lab's research to accommodate a student's special area of interest. For example, one graduate student proposed a research topic that had mass spectrometric implications but did not specifically involve an investigation of gas-phase fragmentation mechanisms. Asher gladly agreed to support the project, and the student embarked on finding the pharmacologically active compound of a native Israeli plant (*Poterium spinosum*).

During the course of his career, Asher's broad-based knowledge and keen insights enabled him to write several valuable, widely cited reviews, book chapters, and encyclopedia articles devoted to the effect of stereochemistry on mass spectral fragmentations (e.g., ref 4). These writings are useful resources, containing thorough explanations of how thermochemical and kinetic factors underlie differences in the mass spectral behavior of stereoisomers, and the examples they provide of such stereospecific processes have become classics.

Professor Mandelbaum's expertise in organic mass spectrometry rendered him a widely acknowledged leader in the field. He was invited to join the Editorial Advisory Board of the journal *Organic Mass Spectrometry*, which later became the *Journal of Mass Spectrometry*, and he served on that board for more than 25 years. He was sought as a keynote speaker at mass spectrometry conferences worldwide and collaborated with a host of colleagues in France, Germany, Italy, Japan, the Netherlands, Switzerland, the United Kingdom, and the United States.

Over the years, he was a visiting scientist at the University of Cincinnati where he also taught a graduate course, Ciba-Geigy laboratories in Basel, Pierre and Marie Curie University in Paris, and the National Institutes of Health in Bethesda, MD. At NIH, although our lab projects were far removed from his primary interests, Asher participated actively in lab meetings. He was a most welcome advisor for all problems, both scientific and personnel-related, bringing insight and wisdom to thorny issues.

On many occasions, Asher's reputation led others in academic institutions, governmental agencies, and industry to solicit his help in elucidating the structure of various synthetic impurities or of isolated natural compounds. One of these projects, a 1990s collaboration with investigators at the Hebrew University and at the University of Aberdeen, resulted in the identification of the first known endogenous brain constituent—which the team named anandamide—that binds to the cannabinoid receptor.

The impact of Asher's scientific contributions cannot be overstated, but he is remembered equally importantly by his students, friends, family, and colleagues for his exceptional personal qualities. Perhaps the best summary of Asher's outstanding character was offered by Yitzhak Apeloig in 2011 when Asher was honored by the Israeli Society for Mass Spectrometry. Yitzhak said, "Asher is first and foremost a Mentsch [a Yiddish word referring to a person of integrity with the utmost consideration for others], a colleague of the kind that everyone wishes to have, and I was fortunate to have Asher as my senior colleague." Another way to describe Asher is to say he lived by the Biblical injunction, "love your neighbor as yourself" (Leviticus 19:18). His demeanor toward everyone with whom he interacted was consistently respectful, humble, gracious, and nonjudgmental. His calm, soft-spoken voice was more than his style of speech, it reflected his inner gentleness and attitude of kindness that permeated all his deeds.

Asher's passing is a deep loss not only for the close-knit Mandelbaum family, including his wife, children, grandchildren, and great-grandchildren, but also for all of us lucky enough to have had a meaningful personal and/or professional relationship with him. The scientific community has lost a preeminent world authority on stereochemical effects in mass spectrometry, a brilliant thinker, an inspiring teacher, and an exemplary human being.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jasms.0c00454.

Asher Mandelbaum's autobiographical notes (PDF)

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