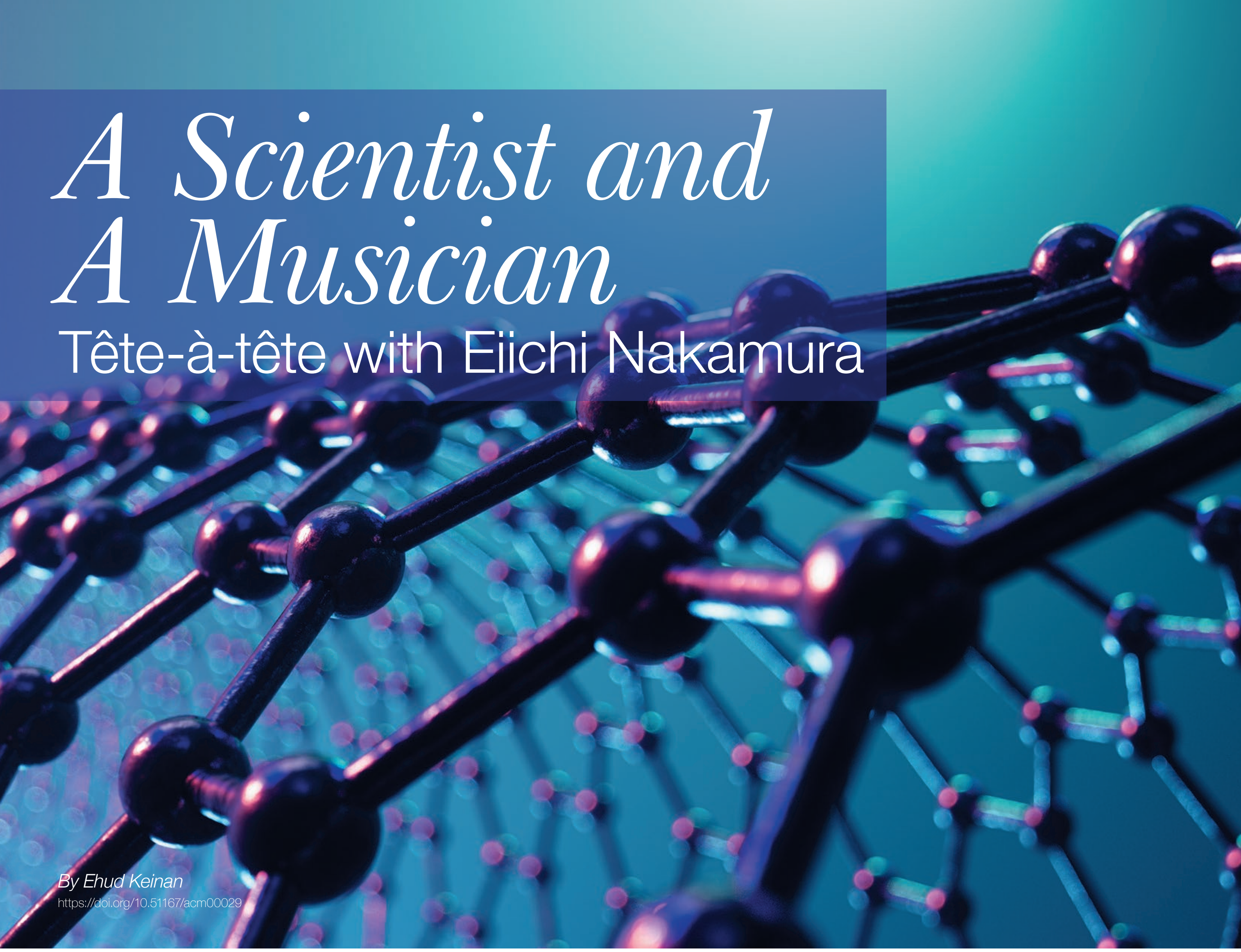


A Scientist and A Musician

Tête-à-tête with Eiichi Nakamura

By Ehud Keinan

https://doi.org/10.51167/acm00029

Ehud Keinan
Professor Keinan of the Technion is President of the Israel Chemical Society, Editor-in-Chief of AsiaChem and the Israel Journal of Chemistry, Council Member of the Wolf Foundation, and past Board Member of EuChemS. He was Dean of Chemistry at the Technion, Head of the Institute of Catalysis, and Adjunct Professor at The Scripps Research Institute in California. His research program includes biocatalysis, organic synthesis, molecular computing, supramolecular chemistry, and drug discovery. He received the New England Award, the Herschel-Rich Award, the Henri Taub Prize, the Schulich Prize, the Asia-Pacific Triple E Award, AAAS Fellowship, the ACS Fellowship, and the EuChemS Award of Service. Since 2022 he is IUPAC VP and President-elect.

Eiichi Nakamura is an old friend. We first met in 1977 at Columbia University when he had just started his postdoctoral research with Gilbert Stork, and I was on my way to Madison, Wisconsin, to begin my postdoctoral research with Barry M. Trost. Over the following 44 years, we have had many opportunities to meet in various countries. I have always enjoyed Eiichi's original science and Baroque flute music. He and his wife Yoko Nakamura visited my family at our home in Israel, and I had a chance to spend time in their beautiful home in Tokyo. Hence, I found it peculiar to conduct a friendly conversation over Zoom. But electronic communication has become an integral part of our life during the Covid-19 pandemic. It was a relaxed weekend in late October 2021, early morning in Israel and afternoon in Tokyo. It was as close as possible to a face-to-face meeting, spending a couple of hours together while staying in our home offices.

EK: As a science educator, I've always been looking for ways to attract the young generation to science. So, I am curious to know what had attracted you to science. I know that you came from a highly educated family, and your father was a mining engineer. Undoubtedly, you had a good start at home, and yet, much of the credit probably goes to your teachers who influenced you in elementary school, junior high, and high school. How early in your life did you decide to become a scientist, and why?

EN: First, I'll tell you the reason why I may not have become a chemist. When I was 20 years old, during my third year in college, I was so interested in studying railways that I almost decided to study railway history, particularly the British colonial railways. I thought of taking that as a serious hobby while making my living working in a chemical company as an engineer. This plan would not have allowed me to become a university professor. The second reason was my severe injury when I was a fourth-year undergraduate student in Mukaiyama's lab, just two months after joining him. I had a big explosion of silver perchlorate, and the whole flask exploded in my face. This unfortunate injury could be a good reason to abandon chemistry forever. Nevertheless, somehow these events worked in different ways.

Still, during my entire undergraduate years at the Tokyo Institute of Technology, I was not particularly attracted to chemistry, and I considered working at a chemical company, satisfying my intellectual curiosity by taking railway history as a serious hobby. And that idea was stimulated by my visit to Israel.

When I was a first-year M.Sc. student, I was still interested in chemistry and railway history to the same extent. I have realized that the two fields were not orthogonal to one another. For example, fieldwork with railways looked like scientific experiments. So, it was not difficult to switch from railways to chemistry. After the big explosion and severe injury, I thought it would be stupid to give up my chemistry career after suffering so much. So, I decided to study chemistry even more. During the three months in hospital and three months at home, I started reading chemistry books thoroughly, such as Cram's organic chemistry textbook.

EK: I try to understand your early decision as a young person to focus on the history of the railway system, which is not motivated by practical considerations. I remember that you told me about your trip to Israel, working as a technician at the Tnuva company in Tel Aviv. I guess that employment at a food company was not the actual reason for that visit. Was your interest in the British railways the main reason for coming to Israel?

EN: Not even that. I was interested in Roman and Greek architecture and art in my teens, and Israel has much of that. For example, there are old churches like the one in Bethlehem built around 300AD, and I wanted to look at these, although I am not Christian. Mr. Shiroki, an art teacher in my junior high school and high school triggered that interest. He fascinated me with stories about Chinese, Roman, Greek, European, Japanese arts, and architecture. I became particularly interested in Greek and Roman architecture and sculpture, which led me to Israel. I stayed in a small apartment next to the old bus station in South Tel Aviv, a walking distance from the ancient city of Jaffa. One day, close to my apartment, I found an old railway station on the Jaffa-Damascus line. I was astonished to discover that the distance between the rails was 1050 millimeters, whereas the Japanese railway's gauge is 1067 millimeters (3 ft 6 in). Soon, I realized that the 1050 gauge is peculiar to the Hejaz Railway systems. I traveled to Israel railway headquarters in Haifa, asking them to show me historical records. I kept in touch with them after the visit, and they sent me copies of plans of steam engines and passenger cars. I published the first research paper in my life, "Israel Railways, History and Status Quo" in July 1972.

EK: I see that your primary areas of interest as a young person were railway, ancient architecture, and probably Greek philosophy. But you became a chemist by pure chance. It reminds me of the Robert Frost famous poem "the road not taken." how come you finally became a chemist?

EN: Not by pure chance. There was a background for choosing chemistry, though. My father was a mining engineer, and he was involved with gold mining. There are not many gold mines to find pure, crystalline gold. The Nakaze mine, which is no longer active, about 50 kilometers away from Osaka, was fascinating. I remember the location in the mountains, where everything was covered by deep snow. My father specialized in mineralogy and kept beautiful crystals in many boxes at our home, repeatedly showing them to me. I remember the nice-looking blue crystals of copper sulfate. So, it became natural that I would be interested in chemistry. In those days, the regulations on chemicals were less stringent, and I could buy manganese oxide and hydrogen peroxide and generate oxygen by mixing them. When I did those experiments, I was 10-year-old. I still remember producing hydrogen gas by mixing zinc with acids, and I became very excited when the hydrogen flask exploded in front of me, fortunately with no injury.

EK: Well, I remember conducting even more ambitious experiments when I was 14-year-old, preparing gun powder, various improvised explosives, Molotov cocktails, and even primitive rockets. Luckily, I didn't kill myself when initiating these devices in our backyard. Fortunately, current regulations on chemicals forbid this kind of amateur laboratory practice.

EN: Well, my primary school teacher even helped me buy chemicals at a local pharmacy. I joined the Komaba Junior and Senior High School attached to Tsukuba University. Komaba, blessed with outstanding teachers, is still considered the top school in Japan. I had an excellent chemistry teacher, Mr. Fukuoka, who formed a chemistry club and taught us chemistry and many other things. We used to go together to the mountains, 3000 meters high in the Japanese Alps. He told us about the clouds and the water cycle, the Alpine flowers, and many other things not included in formal textbooks, including practical skills. For example, since preserved food was not too common those days, he told us to bring thinly sliced pork meat placed between layers of miso, which is fermented soybeans, used as a preservative. Those days, there was no instant dry food, and canned food was too heavy to carry. He also taught us

意味以前の存在、バッハの音楽のように言葉では置き換えられないリアリティ、
お二人の生き方にもこの映画そのものにも、たたずまいとしか呼べない在り方を感じます。谷川俊太郎

ナレーター／シシド・カフカ　出演／中村栄一 渡邊順生 中村洋子 渡邊慶子 水谷定徳 西田理恵 西田賢司 有村美智子
製作・配給:株式会社モンタージュ　〒156-0057 東京都世田谷区上北沢4-10-18 Tel/03-3303-9871 Fax/03-3303-9824 Mail/desk@montage.co.jp http//www.montage.co.jp
https://bunshi-no-neiro.com

©MONTAGE INC. 2021

many enjoyable things, like singing in the mountains, so everybody wanted to join the chemistry club. Mr. Fukuoka later published a book on the Alpine flowers.

EK: It sounds like a dream school. I can hardly think of a teacher in Israel who could have the liberty and talent to conduct such extraordinary programs. From your description, it sounds like the ideal chemistry teacher.

EN: Yes, we had several other ideal teachers besides the art and chemistry teachers. We also had an exceptional music teacher featured in a recent movie, "A Scientist and a Musician." Mr. Tada is the first-generation professional recorder and baroque flute player and the best throughout the 1960s and 70s. He regularly gave public concerts and invited his pupils to attend them. As a result, a few of my classmates eventually became musicians, including the professional harpsichord player Yoshio Watanabe, one of the movie's heroes. Although I kept playing music in public for nearly 40 years, only now to commemorate our 70th birthday, Watanabe and I played together for the first time. It was recorded in the movie.

In junior high school, we had two classes with 40 students in each, and when we continued in the senior high school, 160 students split into four parallel classes. The Komaba school still exists, affiliated with the President Office of Tsukuba University.

EK: As a private school that selects its students, I assume it does not need to report to the Japanese Ministry of Education.

EN: No, it is a National School under the control of Tsukuba University, which is a State University. The school is like an independent university department. It is not under the control of a municipal government or local educational committee, so the teachers had complete liberty to teach whatever they wanted. It is an autonomous operation, which gained a steady reputation over more than 50 years as the best school.


From the movie "A Scientist and a Musician." ©MONTAGE INC. 2021

EK: So, how does the school attract such high-quality teachers? What is the incentive for new teachers? Does the school offer them high salaries or something equivalent?

EN: The salaries are comparable with the teachers' salaries in ordinary schools. The incentive for good teachers has never been money but outstanding students. The school carefully selects the incoming students, which is still the same today. The school is relatively small but has produced a number of leaders of society and academia. The teachers tell the junior high students and parents not to study hard the school subjects, but to find what they are good at. Yet, many of them end up at the University of Tokyo.

EK: You have touched upon Japanese cultural issues, and I wish to follow up on that. On many occasions, I had opportunities to discuss Japanese culture and science. Western scientists tend to stereotype Japanese scientists as focused technocrats. Many perceive them as highly efficient but conservative professionals who prefer to narrow down their field of expertise rather than develop a broad perspective. They do not look at other fields or non-scientific disciplines, such as arts, literature, and music, and you don't fit this stereotype. I remember someone at Columbia University referred to you as "banana," which means yellow outside and white inside. Do you consider yourself a non-typical Japanese scientist or, perhaps, the stereotype outlined by many Western scientists is inaccurate?

EN: My grandparents used to do business in the Japanese territory of Dalian and survived the anarchy in the city after the end of the war. They respected Eiichi Shibusawa, the father of Japan's modern economy, whose name was given to me by Shibusawa's grandson. In 1971 when I decided to visit Israel for the summer internship, no one opposed it. It was a year before the Lod Airport massacre. Visiting Britain, Germany, Italy, France, Greece, Turkey, and Israel at the age of 20 changed my perception of the world.

EK: This does not seem to fit the Japanese stereotype.

EN: I agree. Professor Mukaiyama was not an average Japanese. When I joined his group as an undergraduate student, he always demanded in every group seminar to come up with a reasonable *Arbeitshypothese* and a new theory. He impressed me very much with that approach, and so did Prof. Kuwajima, a Mukaiyama student. I am pleased that most of the things I've done in my early career align with how Mukaiyama thought about chemistry. For example, during the second year of my graduate studies, I hypothesized that a fluoride anion might attack silyl enol ethers to generate a reactive enolate. I assumed that creating a bond between silicon and fluoride would release much energy to form a reactive enolate anion. I checked this idea, and we published it in JACS in 1975. When Prof. Noyori saw our paper, he was already working along the same line and proposed to Kuwajima to continue this research together. Noyori and Kuwajima have been good friends who worked together in Corey's lab. So, the collaboration came naturally. I worked with Prof. Noyori for two years on fluoride activation of silicon compounds, reinforcing my conviction that a hypothesis-driven, rational approach is the way to do science.

EK: What about modeling molecules and chemical reactions in those early days?

EN: In those days, I was not satisfied with the available molecular models such as the Dreiding Model, always trying to find better ways to explain mechanisms. As a graduate student, I participated in several summer schools and had a chance to network with eminent chemists. For example, I spent a week with Hisashi Yamamoto when he was very young and met Donald Cram just at the beginning of his recognition chemistry. He extensively used CPK models to explain the chiral environment of binaphthol and other molecules. I wrote him a letter indicating that molecular models were not helpful in my chemistry studies. But Cram wrote back that CPK models represent reality, telling us exactly what's happening, and they can predict the outcome of chemical reactions. I still remember his words: "I have considerable faith in CPK models for their predictive power."

EK: So, your frustration with the molecular models had eventually led you to pursue computational chemistry? Did you consider that time studying the complex mechanisms of organocopper and other organometallics reactions?

EN: In the mid-1970s, there were essentially no computers in chemistry. We were still using Bunsen burner to heat things, fractional distillation, and crystallization, and all that we had was a 60 MHz NMR machine in our department. For that reason, people were so impressed by the CPK models and used them to solve chemistry problems. And Cram said that CPK models are the reality. My interest in modeling continued until the late 1980s, when we got a mainframe computer. Although that colossal machine was much slower than today's iPhone, I immediately jumped into computational chemistry because I was eager to see events that happen in solution. I started collaborating with the late Prof. Keiji Morokuma in 1989, and that work eventually led me to transmission electron microscopy (TEM) in 2004.

EK: This story leads me to the next question. You have traveled to many territories in science, including organic synthesis, nanoscience, organic electronics, organometallics, theoretical chemistry, EM, dynamic EM, to name a few. I find it quite unusual for a Japanese scientist who usually focuses on one area of interest for the entire career. What was your motivation to switch from one field to many others?

EN: I have not switched the field. I have always stayed in physical organic chemistry but tried to explore new opportunities ahead of people. I'm not interested in synthetic chemistry by itself but getting the desired product in 100% yield suggests that you understand the mechanism pretty well. My main interest in mechanisms has taken me to all territories you've mentioned. In the 1970s, I was interested in molecular models, and after the 1990s, I went to computational chemistry. I started it in the late 1980s since Moore's law predicted that we could study realistic systems in the mid-1990s.

Similarly, when I started working on TEM around 2002, collaborating with Prof. Sumio Iijima, I hoped to study molecules at atomic resolution within 10 years. In 2015, we acquired a millisecond camera and the excellent resolution machine that we use now, and the camera was replaced by an even faster one in 2020. When I identify an opportunity, I tend to start preparing the background about five years ahead of others and wait for improved instrumentation and computer science. This way, as soon as the instrumentation and software become available, I can immediately do what I planned to do.

EK: I understand that what I saw as diverse fields are different manifestations of the same general interest in mechanisms. There are two different types of scientists or two extremes of a continuous spectrum: those who try to understand and decipher the clockwork of Nature and those who take advantage of the available knowledge to make something valuable and practical. For example, those who study methodology and reaction mechanisms in synthetic organic chemistry look at basic phenomena. In contrast, those who practice total synthesis exploit the available knowledge to make molecules for various purposes. Where do you place yourself on that spectrum?

Time may soon come that artificial intelligence tells us all what we need. Then we may need to accept it as the reality of chemistry in the years to come.

EN: Well, you may correctly put me in the first group because I am interested in fundamental research and mechanisms. However, I feel that I belong to both groups because I want to test my mechanistic hypothesis on something tangible like solar cells and iron catalysis. In line with the UN Sustainable Development Goals (SDGs), we cannot rely forever on precious metals like palladium. In 2004 I coined the term "element strategy", proposing a research initiative to the Japanese government. In the same year, I started our EM project. The generous funding of $15 million in our ERATO program led me to propose the teamwork of fundamental research and solar cells. We use functionalized carbon nanotubes as substrates to study chemical structures by TEM. But we also employ functionalized C60 for fabricating solar cells. Very recently, we have synthesized tiny blue quantum dots by self-organization approach. We did TEM video imaging at atomic resolution to precisely identify the whole structure of a single quantum dot.

EK: I feel that your fundamental research is much more rewarding and fruitful, even when aiming at practical research goals. I see that your hypothesis-driven study can lead to valuable results, probably more effectively than a trial-and-error search.

EN: Correct. Most achievements in the science of quantum dots resulted from the trial-and-error approach. Following empirical observations, people mixed various components making large and small dots with various ligands. That research has never been rational because they didn't know the actual structure. We can change this practice by using our atomic resolution EM technology.

EK: As for the empirical strategy, I remember attending a seminar by a famous Japanese chemist many years ago. He spoke about many successful palladium-catalyzed reactions. At the end of his lecture, I asked him about his efforts to explore the mechanism of the new reaction. He seemed puzzled when he looked at me, as if I was asking a silly question, and responded: "This reaction is very successful, and we get the product in nearly quantitative yield, so why should we waste time studying the mechanism?"

EN: I am not surprised by this story, which can fit a significant number of Asian scientists. Asian scientists may continue to be more opportunistic and risk-taking. On the other hand, I feel that the 19th-century European value of "rationality" is dying out these days. Perhaps, we have already stepped into a "post-causality era", as classical causal reasoning is not functioning anymore in this world of complexity. Time may soon come that artificial intelligence tells us all what we need. Then we may need to accept it as the reality of chemistry in the years to come.

EK: An interesting theory claims that the main difference between Western and Asian cultures goes back to the fundamental differences between wheat and paddy rice. Wheat-based agriculture involves low yields, is less nutritional, depends on rainfall irrigation and easy labor, and can support only a small population per square kilometer. As a result, Western culture people are more individualist, ideological, aggressive, and opportunistic. In contrast, paddy rice agriculture involves high yields, is more nutritional, intensive, and can support a dense population. It is also labor-intensive, requiring seasonal group efforts, planning, construction, and maintenance. As a result, people of the Asian culture are more socially responsible, pragmatic, tolerant, and flexible.

I assume that you value social awareness and social responsibility in light of these ideas. Also, I guess you agree that it is essential to improve the community, promote science teaching, and attract the young generation to choose a career in science and technology. Although these are non-trivial tasks, nobody can do the job better than scientists, certainly better than administrators and politicians. Have you invested efforts in these directions?

EN: I have been keen about this issue for a long time and have tried to influence society through research funding and undergraduate education. Together with my colleagues, we transformed our Department Chemistry at the University Tokyo into English teaching, first for graduate students and then undergraduate students. We invite international students to the third year of the undergraduate program to mix with the Japanese students, and we have recently hired Prof. Robert Campbell from the University of Alberta in Canada to be a regular faculty member. We have many non-Japanese junior faculty. Hopefully, what we have done in the past ten years could serve as a model for opening Japanese science education to the world. We are starting to utilize our “molecular movies” to make chemistry more familiar to school kids.

EK: The public looks at scientists as people who could help solve problems at national and global levels. In Taiwan, for example, the President and many Ministers regularly consult with top scientists at the Academia Sinica and other universities, not only on scientific issues but almost everything. They trust those professors for their knowledgeable and objective opinions. Similar consultations with the local academy also happen in Isreal, although to a lesser extent. Is something like this happening in Japan? Did you and your colleagues try to help your country and the world with novel ideas and capabilities?

EN: Unfortunately, the current Japanese government does not seem to respect scientists very much. In the past, the Prime Minister and cabinet members had communicated much with various scientists when reorganizing the Japanese system. For example, about 20 years ago, Prof. Noyori worked very hard with the Prime Minister. But in the past decade, that tradition has almost gone. I think that the main reason for that is the financial problems of our government. Due to extraordinary social and national security expenditures, they are running out of money. People are aging, and tensions are increasing in the seas around our country.

> Perhaps, I am opening up a new era of “cinematic chemistry” for studying and teaching chemistry by using motion pictures at atomic resolution.

EK: It’s a global phenomenon that politicians think they are brilliant and know better than others, so they don’t need to consult with anybody. Regardless of their field, all scientists can serve as a think-tank, producing new ideas and participating in brainstorming sessions. And we know that global problems cannot be solved by politicians but by scientists and engineers through international collaboration. How open are the Japanese scientists to international cooperation?

EN: I think Japanese scientists are very open to international collaboration. The question is how we define international? I don’t believe that collaboration among European countries is truly international. If we consider only trans-continental and trans-cultural cooperation, Japan is quite international. Of course, there’s a language barrier, and Japanese scientists are very close to each other historically and structurally. Still, we are ready to accept any talented professor and student, and I don’t think there are any barriers. The Japanese system is very open now, and you can see many Chinese professors as faculty in Japanese universities. So, nationality doesn’t matter in Japan. The situation is the same as in Germany, where you need to communicate in German for teaching at the undergraduate level. And research rapidly becomes more international with joint programs with many countries.

EK: Let’s talk about your music. I know that music is essential for you, and it is a very significant part of your life. I watched the recent movie “A Scientist and a Musician” which focuses on you and your friend Watanabe and realized that you take music very seriously. I know very few scientists worldwide who adopted such a “schizophrenic” lifestyle of science and music, and you have done it very successfully. How do you share your attention between the two worlds?

EN: Unfortunately, I cannot afford to spend more than 5% of my time on music. Every day I spend at least ten hours on chemistry and only 15 minutes on music. Admittedly, I make many mistakes when playing music, and I’ve never thought I’d become a professional musician. In addition to music, I did oil painting, but this art is very different from music. One needs a story and logical thinking for painting, whereas music is more sensational.

Painting requires logic and a plan to convert the 3-dimensional world into a limited 2-dimensional space. Probably because of this complexity, I cannot relax with painting or drawing, but I can relax by playing music. For me, music is like going to the mountains. I can liberate myself and forget about science. I focus only on music when I play my flute, totally forgetting about chemistry.

EK: So, where do you place your interest in railroads on that landscape of various hobbies?

EN: My interest in the history and technology of railroads has never been complementary to science. It has been an intellectual activity similar to scientific research, and this experience in my college years helped me a lot to do chemistry research later. Music, however, is entirely orthogonal to science unless you really go deep.

EK: Although music and science use the emotional and analytical halves of the brain, I can think of several known scientists who were also musicians. Albert Einstein was a violinist. Alexander Borodin was an organic chemist, a cellist, and a composer. Jean-Marie Lehn and Gerhard Ertl are talented pianists in our times, and I can add many more names to this list.

EN: Many scientists who do intensive intellectual work need relaxation and temporary escape mechanisms, so they go to the arts. But the arts are not one homogeneous domain. There are types of art that are more emotional and others more analytical. Some even require physical capabilities, like playing the piano, which sometimes seems like a sport.

EK: Let’s switch to your current science, where you focus all your energy now. The ability to watch molecules in action and see something that people have only imagined is fascinating. It opens new windows to inaccessible areas and may support or disprove many hypotheses on how molecules behave and look. Therefore, it is not too difficult to predict that your dynamic EM technology will result in global recognition. We know that once a new technology became widely available, like the case of the CRISPR gene-editing, it became so common that many people joined, including practitioners of theoretical, basic, and applied science.

Nevertheless, the dynamic EM may remain a scientific niche. You are the obvious pioneer and most active player in the field, but you don't want to remain lonely there. This situation raises several questions. First, what are the most significant achievements of your EM technology?

EN: What have I achieved? I am still wondering. Perhaps, I am opening up a new era of "cinematic chemistry" for studying and teaching chemistry by using motion pictures at atomic resolution. In this broad sense, we are among microscopists working on such instruments as environmental TEM and super-resolution optical microscopy–technologies, however yet to be suitable for molecular-level studies. We started our research in 2004 and reported the first result in 2007 in Science Magazine. We received a wonderful review comment, "The ability to image conformations of individual small molecules is "holy grail" of microscopy, and the authors present a convincing case that they have managed to do so." Our discovery is an ultimate form of a long-lasting endeavor in seeing minute matters by our eye since Hooke's Micrographia.

EK: How do you encourage others to join the field?

EN: This is a rather tricky question. Overall, our work initially created more skepticism than enthusiasm among chemists and electron microscopists. In addition, chemists at the beginning of the 21st century were still happy with cartoons and sculptures of molecules, not interested in "molecular cinemas". Instead, enthusiastic support came from school kids, laypeople, and scientists in other disciplines. Our most recent videos showing the time-course of "molecular shuttling", "flat molecule converting to fullerene", and "emergence of a NaCl crystal" have become a popular subject on Twitter and YouTube. The NaCl paper in JACS was viewed over 20,000 times within a few weeks after publication and has recorded the highest Altmetric score of >900 among all JACS publications.

Do you know the fifty-second film showing a steam train coming at some distance? "The Arrival of a Train at La Ciotat Station" by the Lumiere Brothers in 1895. This historic cinematograph opened up "the era of cinema". When this film was first shown to the public, the legend says the audience was so excited that they jumped out of their seats. After a hundred years, the era of the cinema is just coming to the world of chemistry.

EK: And how can you expand, popularize, and democratize your science? Your technology depends on prohibitively expensive infrastructure, which is not affordable to most people.

EN: Let's think about the cost. Take cryo-EM as precedence to our case. Thirty years ago, when cryo-EM was first introduced, EM was a complex instrument to operate, and it was costly. Now it is everywhere. Nowadays, the electron microscopes that we use are available in every major institution, and even an undergraduate can use them after a week of training.

We still see some problematic relationships between chemistry and electron microscopy. Chemists are not yet interested in using EM, and electron microscopists believe organic molecules are too unstable. Microscopists are afraid of contamination by the vapor of organic molecules, which is not at all a problem in our 15-year experience.

My group has essentially opened the door of EM-imaging to organic chemistry, particularly dynamic imaging of molecular motions and reactions. We demonstrated since 2007 that the observation of the dynamic behavior of single organic molecules in a carbon nanotube and studying it without decomposition is a norm rather than the exception. I say "without decomposition", meaning that any organic molecules would be stably observed for one to tens of minutes until a carbon nanotube container decomposes. Here, pi-electron-rich molecules may be slowly converted to something else. This phenomenon may seem like "decomposition" for physicists, but it is not. It is a perfectly rational behavior of such molecules reacting via excited state or radical cation. EM-imaging provides a new opportunity for a single molecule study of such species. You can draw a perfect analogy to a laser spectroscopic study of reactive species, except that we can see the reacting molecules one by one in real space and in real-time.

Like any microscopic research, the choice of the substrate that holds the specimen in place is crucial. In scanning probe microscopy, you need to literally immobilize the molecule on a substrate. We have discovered the use of a carbon nanotube as a "test-tube" and a "fishing rod". We used the tube as a test tube and put the specimen loosely in the interior. Or we installed a "chemical fishhook" on the pointed tip of the fishing rod to capture the specimen. In both cases, the molecules are half fixed, half free to move or to react. You can also use a thin graphene sheet as a "fishing net".

EK: It looks like comparing the motion of a free dog with that of a chained dog.

EN: This is a good metaphor. Ideally, we would like to watch the free dog, but that is impossible as the molecules will fly away into the vacuum. Therefore, we chain the dog and watch its movement. There is an additional essential function of our nanotube "fishing rod". This conductive rod connects the specimen molecule to the TEM instrument, which is grounded. The EM-imaging ionizes the organic specimens to form radical cations like in mass spectrometry experiments. The conductive nanotube supplies an electron to bring the radical cation back to the neutral molecules. The tube, therefore, protects the molecule from uncontrollable reactions, that is, decomposition. We have been working on this mechanism for six years and just finished the study's first phase under variable temperature/variable voltage conditions.

EK: It is precisely like the grounding technology in electrical engineering.

©MONTAGE INC. 2021

©MONTAGE INC. 2021

EN: Yes, grounding sounds like a perfect analogy. Only now, 15 years after our initial discovery, have we come to understand our system and can answer many of the questions raised by the referees of our 2007 Science paper. The carbon nanotube is an active participant rather than an inert bystander.

EK: It would be great if more people could join this line of research, which still depends on a $4 million EM machine. What can attract more chemists to join the club?

EN: I have a question for you. Why don't you study individual molecules like biologists studying individual animals and flowers? Chemists may be too accustomed to discuss their business using structural formulae and spectroscopic data. Why shouldn't they be proud of discussing and teaching chemistry using the movies of molecules in action? Chemistry has been so successfully built on the images of molecules that chemists have probably lost their naive interest in molecular reality. Abstraction is the power of science, but I sense that there is still a lot to learn from molecular reality. Please remember the enthusiasm shown by people worldwide for the NaCl movie. The movie has successfully visualized the chemical reaction that everyone has known since their primary school period. Chemists should share this naive feeling of people because "Scientific breakthroughs often build upon the successful visualization of objects invisible to the human eye"–– citation of the 2017 Nobel Prize for cryo-EM technology.

As to the instrument, most research universities already possess the necessary instrumentation in their analytical center. I know that you have excellent EMs at the Technion, so your colleagues can do similar experiments. It is up to you to approach electron microscopists and discuss your chemistry. Many people are already working in this field. The EM technology and infrastructure are rapidly becoming democratic, as once expensive NMR machines have become commonplace.

EK: From my perspective as an organic chemist, the turning point will be when the video analysis of single-molecule atomic resolution time-resolved EM (SMART-EM) crosses the barrier between organic chemistry and physical chemistry. Many will join once this technology becomes relevant to organic chemistry rather than just physical chemistry. I am sure this will happen one day, but how can you accelerate the process? Your work on the crystallization of sodium chloride inside a nanotube renders the technology highly attractive to experimental inorganic chemistry. But the key is the relevance to organic chemists. You know that organic chemists believe that they can do everything. If you show them something valuable that they cannot do, they will become highly interested.

Nakamura and Keinan floating on the Dead Sea together, October 2007.

EN: Indeed, things are moving fast in that direction. With Dom Lungerich of Yonsei, we have already reported a time-resolved evolution of the conversion of a flat $C_{60}H_{30}$ molecule to a spherical C60 molecule, where we identified several transient intermediates that other methods could have never identified. We are now finishing work on the aggregation behavior of daptomycin, a cyclic peptide that is effective against many drug-resistant bacteria. Using our SMART-EM, we could determine the structure of the products of their calcium-mediated aggregates at atomic resolution. We installed a fishhook using Jeff Bode's KAT ligation method. Our approach is the only way to obtain atomistic structural information on small and medium-size peptides or their aggregates, none of which is crystallize. Other people do in-silico studies of daptomycin aggregation, and we can provide them with the actual structure as a realistic reference point for their computations. We provide them with the reality for their molecular dynamics study. Altogether, we are getting closer to organic chemistry. We have started a collaboration project with Yoram Cohen of Tel Aviv University, studying the supramolecular chemistry of pillararenes. Another study focuses on the aggregation of amyloid-beta model compounds together with James Nowick of UC Irvine. With Tobin Marks of Northwestern, we are uncovering new reaction intermediates in heterogeneous Mo catalysis, and, with Toray people, intermediates in the formation on carbon fibers.

And for inorganic chemistry, we see various polymorphs of inorganic solids at a nanometer scale. We can see them as crystal nuclei and how they go from one polymorph to another. We can even study the relative stability of the polymorphs. Polymorphism has always been a fundamental phenomenon in science, but people could only study big crystals, averaged over many atoms. We can now see atom by atom in the initial stages of crystallization and start understanding polymorphs formation.

EK: The new applications of the EM technology are indeed mind boggling, and I am sure we'll see many people joining this technology soon. I wish to conclude our conversation by going back to the movie "A Scientist and A Musician." In one episode, you offer advice to the young generation: "Doing just what you like is wrong. It would be best if you did what you could. Find something that you like and can do and do it thoroughly." Would you please explain what did you mean?

EN: In the Japanese culture these days, and probably everywhere, most parents encourage their kids to do whatever they enjoy, and I find it wrong. I would better advise kids to find out what they can do best and then go for it. Kids may be very interested in something but cannot meet the requirements. For example, I may like baseball very much, but my body is too fragile to make a good baseball player. I wish I were Shohei Otani.

EK: In many cases, kids like what works for them at best, so the two issues eventually merge. If kids do something right and gain much satisfaction and external appreciation, they ultimately like what they do. So, being driven by what one wants and can do becomes the same thing.

EN: This is correct, and happy people succeed in doing what they like. But you need a certain level of human competence. Problems arise when people are interested in things they cannot accomplish. A temporary attraction to something unrealistic provides some short-living indulgence and transient satisfaction. But the following day, the kid may want something else.

In contrast, if they try to find out what they can do best, they can develop a successful, enduring career. I like music, but I know my limitations and abilities. However, my music progresses still at this age, as chemistry does the same.

◆

Opposite Page:

1. "The whale club" welcomed Ehud Keinan, March 26, 2004. From front left: Toshikazu Hirao, Masaaki Suzuki, Ehud Keinan, Tsutomu Katsuki, Koichiro Oshima. From back left: Eiichi Nakamura, Hisao Nishiyama, Ilhyong Ryu, Tamio Hayashi, Takao Ikariya.

2. In the TEM room in December 2020. ©MONTAGE. INC. 2021

3. Eiichi and Yoko Nakamura with the Keinan family, Bethlehem of Galilee, Israel, January 4, 2003.

4. Watching a quantum dot. ©MONTAGE. INC. 2021

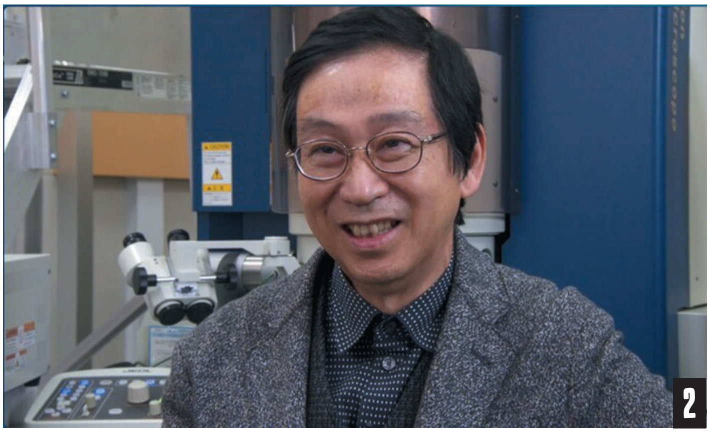
5. Playing the baroque flute in Keinan's home, Timrat, Israel, January 2003.

6. Nakamura with Gilbert Stork, Tateshina Meeting, November 2003,

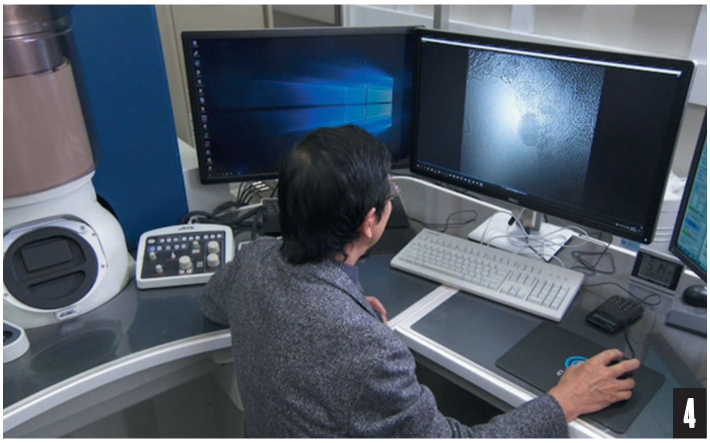
7. Nakamura with Keinan, Jiro Tsuji, Henry Kagan, and Keiji Yamamoto at the front gate of Tokyo Institute of Technology, July 1985.

8. Nakamura with John D. Roberts at the Tateshina Meeting, November 2003.


1


2


3


4


5


6


7

8