Gopinath Kartha and the birth of chemical crystallography in India

P. Balaram

Gopinath Kartha was an extremely modest and soft-spoken scientist, whom I met only once when he visited the Indian Institute of Science (IISc), Bangalore, in the early 1980s. His reputation preceded him. His name was indelibly linked to the Ramachandran–Kartha triple helical model of the fibrous protein collagen proposed in the period 1954–1956. This model, one of the major scientific triumphs of newly independent India, has been celebrated in the decades that have followed, most notably by the christening of the large auditorium at the Central Leather Research Institute (CLRI) in Madras (now Chennai) as the Triple Helix Auditorium (Figure 1), its name visible as one drives along the busy road in front of the institution. I met him to discuss our mutual interest in the structures of peptides, in the hope that he would be interested in molecules being produced in my laboratory. He graciously agreed to study them and shortly after his visit I mailed promising crystals to his Buffalo, New York address. Some months later he requested more crystals which we mailed rather quickly, hoping that his skill in structure determination would provide us a view of the molecule. Sadly, he died suddenly, in 1984, even while he was engaged with this problem. At that time, I was unaware of much of Kartha's work, but realized over the years that he was undoubtedly one of the pioneers of chemical crystallography in India.

My interest in Kartha was further fuelled when I read the following paragraph in an article by Sivaraj Ramaseshan on Dorothy Hodgkin's Indian connection[1]: '*In the twenties, India had developed a fairly strong tradition in X-ray physics. The six-week visit of C. V. Raman to Europe in 1921 greatly changed his research interests. On seeing the blue of the Mediterranean, he started his researches on the scattering of light in liquids which finally culminated in the discovery of what is now called the Raman Effect. His encounter with Sir William Bragg and his work on naphthalene structure started three lines of research in India. First, Raman fabricated an X-ray tube and was amongst the earliest to use X-ray diffraction as a structural tool to study liquids. He showed that while in large-angle scattering the haloes reflected specific molecular sizes and packing shapes, small-angle scattering was directly related to the statistical fluctuation of density in a liquid. Second, Raman knew that Bragg's first structure of naphthalene was not consistent with its birefringence, while the second one was. With this as cue he and his school launched extensive studies on the optical and magnetic anisotropy of organic crystals to get vital information on the arrangements of molecules in the crystalline state. Third, one of his students, Kedareswar Banerjee, was amongst the earliest to probe into the problem of phase determination by direct methods and for this he used Bragg's data on naphthalene. Unfortunately, in spite of this early lead, it was not until 1951 that the first crystal structure was solved in India using Fourier methods by Gopinath Kartha.*' The last two sentences drew my attention. Banerjee was reinterpreting J. M. Robertson's analysis of Bragg's data on anthracene and naphthalene[2]. The statement that Gopinath Kartha solved the first crystal structure in India led me to ask myself: What was the molecule and where was it published? Should not this 'first' be celebrated? From the recesses of my memory, I could hazily recall hearing from friends in organic chemistry of another important Kartha structure, morellin, a complex natural product. Kartha, of course, was widely known, for his work on the collagen structure with G. N. Ramachandran at Madras University in 1954–1955, and his later structure determination of the enzyme ribonuclease, in David Harker's laboratory in Buffalo, New York. In the narrative that follows, I try to describe Kartha's trail of research and his impact on crystallography, in India and beyond, through his four molecules, all of them 'firsts' in different ways.

Barium chlorate monohydrate

The three-dimensional structure of $BaClO_3$ shown in Figure 2, taken from Kartha's Ph.D. thesis[3] submitted under the guidance of Ramachandran, is the first molecular structure determined by X-ray diffraction in India. Kartha's use of 'two dimensional Patterson and Fourier projections along three axes' and his application of the heavy atom method might rightly be considered as the first stirring of chemical crystallography in India[4]. In his report, Kartha notes that the intensities of the diffraction spots 'were corrected for Lorentz and polarization factors, according to Buerger & Klein (1945) in the case of the c-axis photograph and according to Kartha[5] for a- and b-axis photographs'. Seven decades later, reading these sentences and going back to look at the original papers, one can

Figure 1. ***a***, The Triple Helix Auditorium at the Central Leather Institute, Chennai. ***b***, A model of the Ramachandran–Kartha triple helix of collagen.

Box 1.
Biographical Note
Gopinath Kartha
(26 January 1927–18 June 1984)

Gopinath Kartha was born in Shertallay (now Cherthala), Alappuzha District in Kerala where he spent his childhood and had his early education. He studied at the Sanathana Dharma Vidyasala at Alappuzha, passing out in 1942. He was at the Maharaja's College in Trivandrum (now Thiruvananthapuram) for the Intermediate programme in 1942–1944. He graduated in 1948, with a B.Sc. (honours) degree in Physics and Mathematics, from Presidency College, Madras. He received an MA degree in Physics from Madras University and an M.Sc. degree from Andhra University, Waltair (Vishakapatnam), both in 1949. In the same year, he joined the Indian Institute of Science (IISc), Bangalore to work towards a Ph.D. degree in the Physics department under the guidance of G. N. Ramachandran. As IISc did not grant degrees then, he was registered at Madras University, and completed his work in 1953. He moved to join Ramachandran in Madras (now Chennai) in 1952. In 1955, he spent a year at the Cavendish Laboratory in Cambridge (UK), before moving to the National Research Council (NRC), Ottawa, Canada. In 1959, he moved to David Harker's laboratory at the Brooklyn Polytechnic, New York. Later that year he moved with Harker to the Roswell Park Memorial Institute, Buffalo, NY, where he would spend the rest of his career. He held appointments as research professor in the Roswell division of SUNY at Buffalo and as research professor at Niagara University. In 1961 he spent six months as a Reader at Madras University. He was at the University of Kyoto, Japan as National Research Professor in 1972–73.

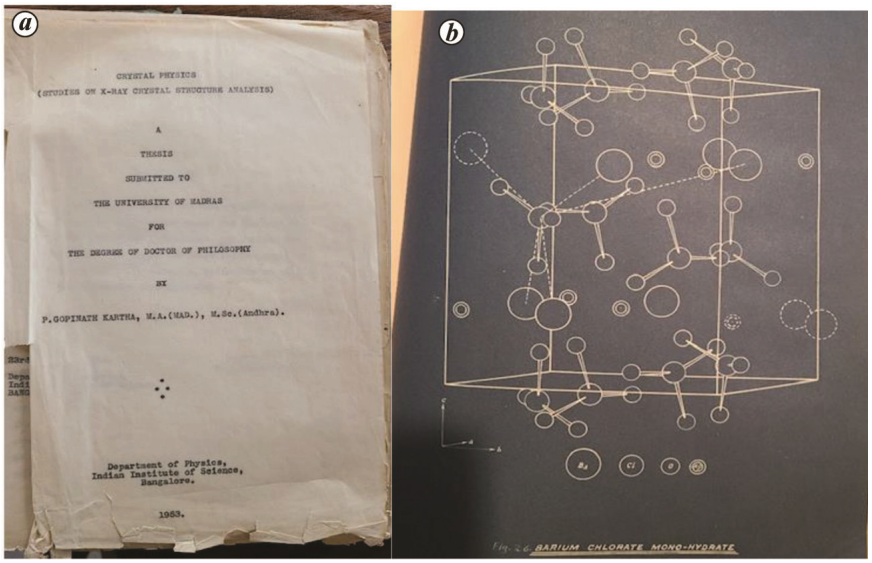

Figure 2. ***a***, Title page of the Ph.D. thesis submitted by Gopinath Kartha to Madras University in 1953 based on work at IISc, Bangalore. ***b***, Arrangement of atoms in the structure of barium chlorate.

only marvel as to how far the field has progressed. A cursory glance at the contents page of the *Acta Crystallographica* issue in which one of Kartha's papers appeared[5] reveals that he was in good company; J. Donohue and K. Trueblood describing the structure of hydroxyproline, R. Pepinsky and others reporting the structure of colchicine, R. E. Marsh on the structure of diphenyl diselenide and W. L. Bragg describing a device for calculating structure factors. Bangalore was beginning to make its presence felt in the world of crystallography. Would a student in 2021 consider barium chlorate an important molecule? Undoubtedly, not. Yet, it is these inorganic substances, containing atoms with high atomic numbers ('heavy atoms') that dominated the evolution of crystallography in its early years. Those readers who are historically inclined might do well to read David Harker's description of how he came upon the Harker sections, now famous in the lore of crystallography, while working on the structure of the minerals, Ag_3AsS_3 and Ag_3SbS_3, in Linus Pauling's laboratory in the mid-1930s (ref. 6). But even as he worked on his thesis, Kartha obtained crystals of a more complex molecule of unknown constitution, morellin, from P. L. Narasimha Rao's laboratory in the Biochemistry department of IISc.

Morellin

A yellow crystalline pigment, christened morellin, was first isolated in the laboratory of John Simonsen (1884–1957), then Chief Chemist at the Forest Research Institute and College, Dehradun, probably in the 1920s (ref. 7). Simonsen, whose lasting contribution to his field was his monumental five-volume treatise *The Terpenes*, published between 1931 and 1957, became Professor of Organic Chemistry at IISc in 1925, a position he held until 1929 (ref. 8). It was here that he suggested that a younger colleague, B. Sanjiva Rao take up the study of this novel substance isolated from 'the dry powdered pericarp of the seeds', of the evergreen tropical tree, *Garcinia morella*[7]. In the first report on the characterization of morellin, by Sanjiva Rao, a molecular formula of $C_{30}H_{34}O_6$ was deduced. The short report in the 1 January 1937 issue of the *Journal of the Chemical Society (London)* is replete with experimental detail, but the author concluded cautiously: '…the evidence at present available is insufficient to warrant the assignment of any structure to morellin…'. Narasimha Rao (1913–2013), who moved from the

Organic Chemistry department at IISc to the Biochemistry department, resumed work on morellin[9] reporting further chemical work aimed at determining the structure in the early 1950s (ref. 10). In their 1954 paper Rao *et al.* note: 'Although the elementary analysis of (*morellin*) is in good agreement with the previously assigned formula $C_{30}H_{34}O_6$, X-ray method (unit cell dimensions), a = b = 15.89 ± 0.04; c = 11.60 ± 0.02 A; density of crystals, 1.234 now gives a value of 544 ± 10 for its molecular weight. We like to reserve an explanation for this discrepancy.'[10] A footnote in their paper acknowledges personal communication from Gopinath Kartha, at Madras University, for the molecular weight estimation from unit cell volumes of morellin single crystals. Rao also noted the relatively unpromising antimicrobial properties of morellin.

In his first attempt at determining the structure of morellin, Kartha, then a student in the Physics department at IISc determined the unit cell dimensions of crystals provided by S. C. L. Verma, an associate of Narasimha Rao, who also determined the crystal density. Based on these observations, Kartha noted: '…we get the value 544 for the molecular weight. The value measured by chemical methods was 483 whereas the suggested formulae $C_{30}H_{34}O_6$ and $C_{29}H_{32}O_6$ give the molecular weight 490 and 476, respectively. The X-ray molecular weight 544 (which has an accuracy better than ±10) is thus definitely higher'[11]. The use of cell volumes and crystal density to estimate molecular weight (mass, in today's usage) of a complex natural product of unknown constitution might have been done for the first time in India, a rare incursion of physics into organic chemistry. This was the first sign that chemical methods may have hit a road block on the way to the structure determination of morellin. Kartha's paper was communicated in January 1954 from Madras University, with an acknowledgement to Ramachandran, to whose laboratory he had moved from Bangalore. A few months later another very brief communication followed in July 1954 on morellin this time with the IISc, Bangalore address in which limited progress had been made, permitting assignment of the space group, with the promise that 'detailed analysis is in progress'[12]. In the era before direct methods of phase determination revolutionized chemical crystallography, the structure of morellin from the available data would have been practically impossible. By 1954, Ramachandran and Kartha had begun their attack on collagen.

The research on morellin would get a boost, a few years later, with the entry of K. Venkataraman, who developed a major natural products centre at the National Chemical laboratory (NCL), Poona (Pune), with a focus on pigments. Morellin's colour may have undoubtedly attracted him. Venkataraman was one of India's foremost organic chemists at that time and the first Indian director of NCL. It is in Pune that a p-bromobenzenesulphonyl ester of morellin was prepared. The presence of the heavy atom bromine and the moderately heavy atom sulphur permitted structure determination using methods that had foundations in Ramachandran's theoretical work in crystallography[13]. The structure of morellin (Figure 3) revealed a complexity[14] which would have been extraordinarily difficult to unravel in the 1950s. The correct molecular formula for morellin was now established as $C_{33}H_{36}O_7$ corresponding to a molecular weight of 544, in complete agreement with Kartha'a initial 1954 estimate[11] of 540 ± 10. In a lecture presented a decade after the report of the morellin structure, Venkataraman presents a masterful overview[15] of all the chemical and spectroscopic evidence accumulated for morellin, whose interpretation is facilitated by the Kartha structure. Kartha had moved to the Roswell Park Memorial Institute in Buffalo, New York in 1959 and it is here that he completed the morellin structure, at a time when he was determining the structure of ribonuclease. The crystallographic section of the 1963 paper on morellin ends with a promise 'The absolute configuration has not yet been determined. The details of the structure analysis will be published elsewhere.' That promise was never kept.

Kartha was not a scientist who published prolifically. He drew his pleasure from solving problems. Morellin was a difficult one. It is to be hoped that this resurrection of the history of the structure determination of one of the most complex natural products of Indian origin and the first natural product whose structure was revealed in India by X-ray diffraction will challenge a new generation to revisit morellin and ensure that three dimensional coordinates become available. This would be a fitting tribute to Kartha and his dedicated collaborators. In the era of classical natural product structure determination, best exemplified by complex molecules like strychnine, total chemical synthesis and demonstration of the identity of the synthetic and natural substances was the final test. For morellin, this is a symbolic goal still to be reached, building on many efforts in this direction[16]. In reflecting on

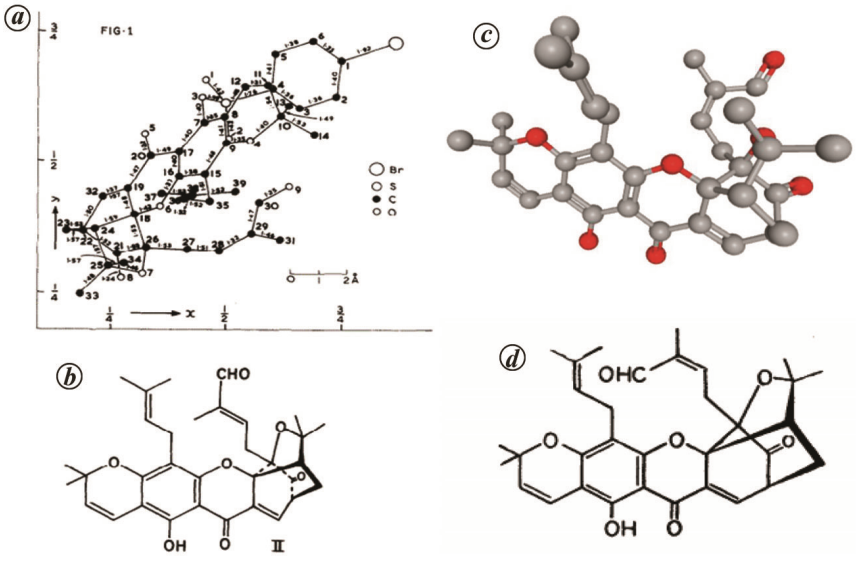

Figure 3. Views of the morellin constitution: ***a***, Projection of structure determined by X-ray diffraction[14]; ***b***, Chemical formula as drawn in ref. 14; ***c***, Three dimensional model generated using chemical structure on PubChem; https://pubchem.ncbi.nlm.nih.gov/compound/Morellin; ***d***, Chemical formula as drawn in ref. 15.

the heroic chemical work of Sanjiva Rao, Narasimha Rao, Venkataraman and their associates on morellin, it may be worth recalling Robert Robinson's words in his obituary of John Simonsen[8]: 'His scientific work was throughout of excellent calibre and absolutely reliable. He was in several cases unfortunately misled by unusual rearrangements and he did not have the advantage which certain modern techniques, especially infra-red spectrography and chromatography, have conferred on present-day workers in the difficult fields that he sought to cultivate.'

Collagen

The collagen structure is an important landmark in our understanding of the stereochemistry of proteins. Ramachandran and Kartha published their triple helical model[17,18] in 1954–1955, close on the heels of Pauling's single chain alpha-helix (1951)[19] and the iconic Watson–Crick double helix in 1953 (ref. 20). In many ways the collagen structure (Figure 1) may have been intuitively the most difficult, unconstrained as it was by multiple intra-chain hydrogen bonds, a consequence of the abundance and regular repetition of the imino acids proline and hydroxyproline in its sequence. This was the era of X-ray fibre crystallography, a technique which yields limited diffraction intensity data, diagnostic of the regular arrangements of the constituent unit along the repetitive polymer chains constituting the fibre. The key to structure determination is to build stereochemically acceptable models which can then provide a fit to the observed data, using the then known geometries for the monomeric constituent units of the biopolymer chain. For the alpha helix, Pauling had used two crucial pieces of structural information in constraining his model building; the planarity of the peptide unit and the formation of intrachain hydrogen bonds between the donor NH groups and the acceptor carbonyl groups repetitively present along the polypeptide backbone. The Watson–Crick story is too well known to bear retelling. The Chargaff Rules provide a dramatic constraint on possible models, now immortalized as Watson–Crick base pairs. Fresh from their triumphs, both Pauling and Crick turned to collagen. In Cricks words[21]: '*Misleading data, false ideas, problems of personal interrelationships occur in much if not all scientific work. Consider, for example, the discovery of the basic structure of collagen, the major protein of tendons, cartilage, and other tissues. The basic fiber of collagen is made of three long chains wound around one another. Its discovery had all the elements that surrounded the discovery of the double helix. The characters were just as colourful and diverse. The facts were just as confused and the false solutions just as misleading. Competition and friendliness also played a part in the story. Yet nobody has written even one book about the race for the triple helix. This is surely because, in a very real sense, collagen is not as important a molecule as DNA. Of course, this depends to some extent on what you consider important. Before Alex Rich and I worked (quite by accident, incidentally) on collagen, we tended to be rather patronizing about it. "After all," we said, "there's no collagen in plants." In 1955, after we got interested in the molecule, we found ourselves saying, "Do you realize that one-third of all the protein in your body is collagen?" But however you look at it, DNA is more important than collagen, more central to biology, and more significant for further research. So, as I have said before: it is the molecule that has the glamour, not the scientists.*'

Ramachandran moved to Madras University in September 1952, as the head of the newly formed Physics department at the young age of 30. Gopinath Kartha, his student in Bangalore moved shortly thereafter now in the role of a post-doctoral fellow. Years later Ramachandran would tell his biographer that Kartha was the best 'post-doc' he ever had. The collagen story in its entirety as seen from Madras is narrated with many insights in the Ramachandran biography by Raghupathy Sarma[22], who draws on Richard Dickerson's classic overview of the field of protein structures as seen in the 1960s (ref. 23). The first paper describing the three-chain structure appeared in *Nature* in August 1954 (ref. 17). The unit cell dimensions are reported and a nine amino acid model is constructed to fit the dimensions. This report reinterprets fibre diffraction data in the literature, differently from published interpretations by W. T. Astbury, Linus Pauling and R. B. Corey and R. S. Bear. The first fibre diffraction pattern of collagen from Madras appeared in November 1954, in this journal[24], which Ramachandran edited from 1950 to 1957. The *Current Science* paper reported the key diffraction data which led to the right structure. The authors, Ramachandran and his student G. K. Ambady, describe the earlier model as '*consisting of three cylindrical "ropes" each rope containing three helical chains*'. The imagery of the rope is striking. Many years later I heard Ramachandran in a lecture describe the moment that the coiled helix model struck him, as he watched his wife plait her hair in the traditional South Indian manner. I was reminded of the rope analogy when, in collecting material for this article, I corresponded with one of Kartha's associates, K. I. Varughese. He wrote: '*In 2007, during the meeting (honoring Dr. Kartha) at Vaikam, Kerala, I heard for the first time about a possible source of inspiration for the discovery of the triple helix. Earlier, the Alappuzha area where Dr. Kartha grew up was the center of the coir industry. A three stranded coir rope is like a coiled triple helix. I must add that Kartha had never mentioned this to me.*' The 1954 *Current Science* paper was quickly followed in September 1955 by the Ramachandran–Kartha paper in *Nature* which presents a more detailed and revised model of the triple helix, essentially the structure that has stood the tests of time[18]. Controversy soon followed as criticisms of this structure were levelled, most notably by Rich and Crick. An unexpected fallout of this turbulence of the mid-1950s, was that it spurred Ramachandran to embark on his now famous analysis of polypeptide conformations, resulting in the map that now bears his name, immortalizing him in the literature of biochemistry and structural biology. Some of the key insights into the discomfort that the Madras collagen triple helix, caused in Cambridge (F. H. C. Crick) and London (J. T. Randall) come from letters that Kartha penned to Ramachandran from the Cavendish laboratory (Figure 4). Collagen had placed Ramachandran and Kartha in competition with the most famous names in the field, Pauling, Crick and Randall, names which readers may recognize as characters vividly portrayed in James Watson's, controversial, but now classic, book *The Double Helix*. In one of the finest chapters of science in post-independence India, the Madras laboratory pipped Cambridge and Caltech to the post.

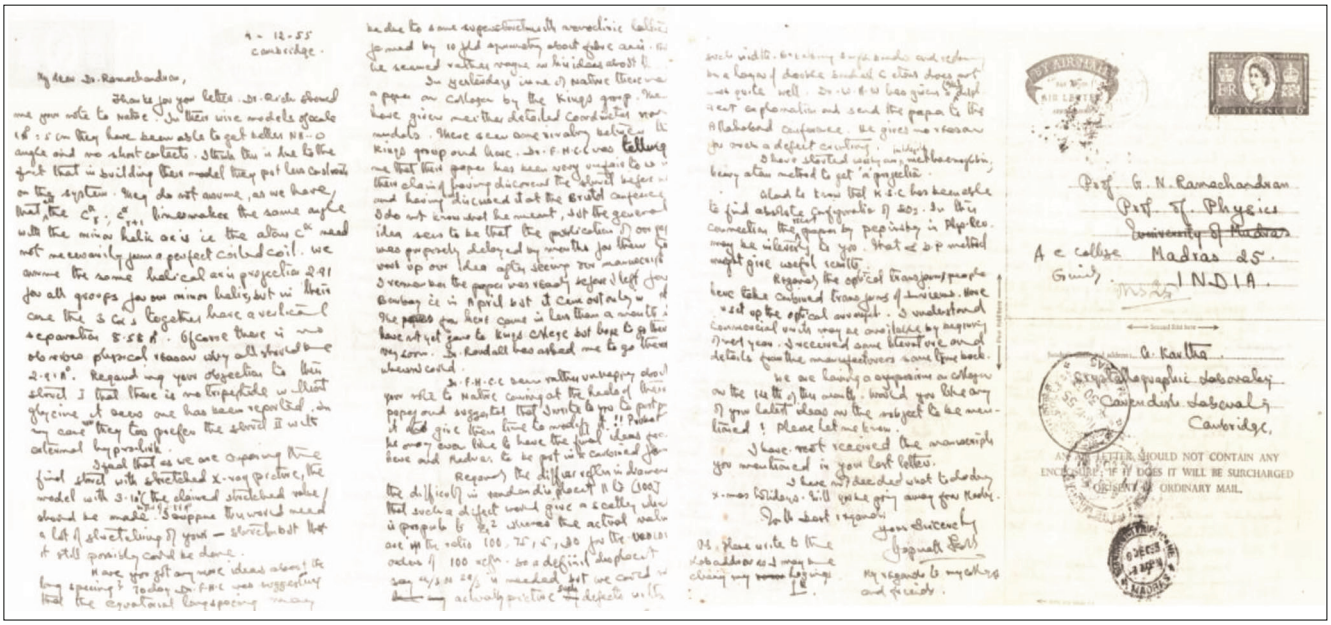

Figure 4. Letter from Gopinath Kartha (Cambridge) to G. N. Ramachandran (Madras) dated 4 December 1955.

Gopinath Kartha was indeed central to the collagen story.

Ribonuclease A

Ribonuclease, a remarkably stable and abundant pancreatic enzyme played a pivotal role in the development of protein chemistry and enzymology. The 1972 Nobel prize for chemistry[25] recognized Christian Anfinsen 'for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation'. The Anfinsen experiment established that code for directing three-dimensional folding of proteins was embedded in the sequence of the amino acids arranged along a polypeptide chain. The prize was shared by Stanford Moore and William Stein whose work on ribonuclease contributed 'to the understanding of the connection between chemical structure and catalytic activity of the active centre of the ribonuclease molecule.' The 1984 Nobel prize in chemistry[26] was awarded to R. Bruce Merrifield 'for his development of methodology for chemical synthesis on a solid matrix'. Undoubtedly, what persuaded the Nobel committee, on the utility of this fundamentally new method of synthetically assembling peptide chains, was Merrifield's monumental solid-phase synthesis of ribonuclease A, a chemical *tour de force*. Ribonuclease was also the first example of 'fragment complementation' demonstrated famously by Fred Richards and Paul Vithayathil, providing a dramatic example of the importance of long-range inter-residue interactions in maintaining three-dimensional structure and enzymatic function[27].

Why have I digressed? It is merely to emphasize the centrality of the molecule to the field of biochemistry and to revisit the first crystallographic structure determination of a protein in North America. When Gopinath Kartha, Jake Bello and David Harker reported the structure of ribonuclease on the pages of *Nature* in 1967 it was only the third protein to have been characterized at near atomic resolution[28], after myoglobin (John Kendrew) and lysozyme (David Phillips) and only the second enzyme to have its three-dimensional structure revealed. The ribonuclease project in North America was initiated by David Harker at the Polytechnic Institute of Brooklyn in 1950. It was here that Gopinath Kartha joined him. Harker, a student of Linus Pauling, was famous for his contributions to crystallography. Herbert Hauptmann, in his biographical memoir of Harker[6] notes that 'the Harker section made the Patterson function useful'. The Harker–Kasper inequalities, developed during the determination of the structure of decaborane ($B_{10}H_{14}$), would become the forerunner of the direct methods of phase determination, which would eventually be recognized by the award of the 1985 chemistry Nobel prize to Jerome Karle and Herbert Hauptman[29]. In 1959, Harker and Kartha moved to the Roswell Park Memorial Institute, Buffalo, NY. But much remained to be done before a final assault on ribonuclease. In Hauptman's words[6]: '*Due to the efforts of visiting crystallographers, a number of critical problems were solved during the Roswell Park years. M. V. King solved the problem of dyeing the protein molecules in crystals and he prepared ribonuclease in fourteen different crystal forms. F. H. C. Crick discovered the strong temperature dependence of the diffracted X rays from the protein crystals mounted in sealed capillaries and showed how to control it. V. Luzzati showed how the intensity statistics were related to the structure of the protein crystals and why the standard statistical methods could not be applied in these cases. A. Tulinsky worked out the exact structure of beryllium basic acetate and made it into a useful intensity standard. G. Kartha developed new ways of using the diffraction data from non-centrosymmetric crystals. A. de Vries showed how anomalous dispersion effects could help in determining the structures of crystalline proteins. J. Bello discovered new ways of labeling ribonuclease crystals with heavy atoms. T. C. Furnas, Jr., built their counter diffractometer, aided by that artist in instrument construction W. G. Weber. The stage was set to begin to collect X-ray crystallographic data from which the structure of ribonuclease*

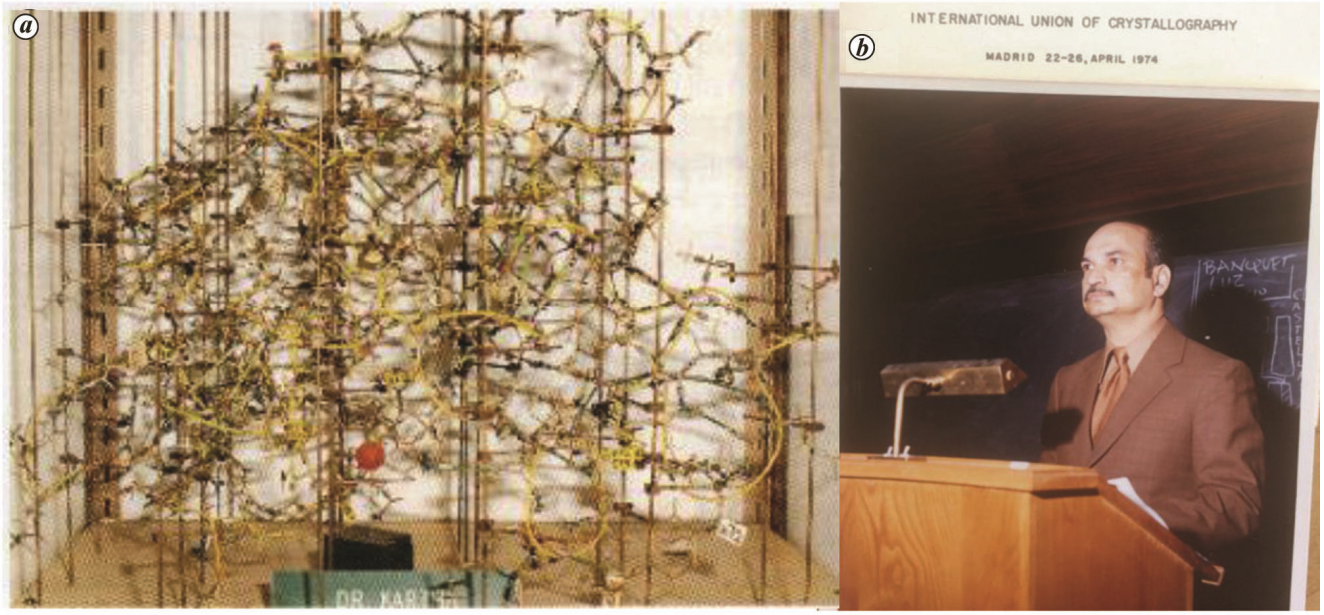

Figure 5. ***a***, A model of ribonuclease A from Kartha's laboratory; ***b***, Kartha lecturing at a conference in Madrid, Spain in April 1974.

could be determined.' It is that structure determination which was accomplished by Gopinath Kartha (Figure 5). Jake Bello, in an obituary of Kartha, notes: 'He was instrumental in resolving the structure of the protein ribonuclease.'[30] Wayne Hendrickson, in a tribute to Kartha, provides an assessment[31]: 'Kartha joined in the middle of David Harker's quest for the structure of ribonuclease, preceded by many others, but in the end it was just he with Jake Bello (crystallizer of the protein) who joined Harker in publishing the structure of ribonuclease A at 2 Å resolution.' In the first volume of the *Accounts of Chemical Research* in 1968, in an article simply titled 'Pictures of Proteins', Kartha reflected on many issues[32] that have occupied protein chemists over the years that followed: Are protein conformations in crystals and solution the same? Is there a connection between protein evolution and conformation? He was prescient in drawing attention to Anfinsen's Harvey Lectures in 1965–66. His conclusion anticipated the decades of discussion that would follow: '*Whether the conformation that the protein finally adopts is indeed a unique energy minimum or whether it is only one of the many local minima into which the protein chain can be coaxed by gentle prodding from one minimum to another is one of the as yet unanswered but hotly discussed questions in biology today.*'[32]

Finally, in acknowledgements Kartha not only credited his collaborators, on ribonuclease but thanked '*Professor M. F. Perutz, who first showed me how to take X-ray diffraction photographs of globular proteins, and, Professor G. N. Ramachandran, who initiated me in the application of X-ray diffraction methods to fibrous proteins*'. Reading Kartha's 1968 review may still be of benefit to students entering the field of protein chemistry today.

How then do I end this story of Gopinath Kartha? The four structures I have chosen to illustrate are all 'firsts' in many ways. They provide a view of the progress of crystallography in India in the 1950s and early 1960s. In reading Kartha's work, it is clear that he played a key role in the birth of chemical crystallography in India. How would we describe Kartha the man? I can do no better than borrow the words of Indira Kartha[33]: '….he was happy wherever he was; Presidency College, Indian Institute of Science, Cavendish laboratory in Cambridge, NRC, Canada. In each place the work was satisfying and the friends he had, understood him. It was difficult for most people to fathom him; for how could such a brilliant well-known person be so simple? Once when we were with a group of people, the evening wore off and Gopi Chettan was leaving. I heard another scientist a newcomer ask "Is that the real Dr. Kartha!" '. She goes on to quote James Bryant Conant, President of Harvard University for almost two decades: 'Each honest calling, each walk of life has its own aristocracy, based on excellence of performance.' Gopinath Kartha's molecules are a testimony to his excellence in his chosen calling, crystallography.

The stories of Ramachandran and Kartha take us back to a time when the shadowy world of molecules was beginning to be illuminated by the power of X-ray diffraction by crystals. It was a time when in the experimental sciences sophistication of technique appeared less important than the abilities to think analytically, imaginatively, independently and intensely. The problems pursued contributed to our understanding of molecules and nature; in Crick's words, 'mad pursuits'. The world of science has moved on but reflecting on past achievement can often be inspirational.

1. Ramaseshan, S., *Notes Rec. R. Soc. London*, 1996, **50**(1), 115–127.
2. Banerjee, K., *Nature*, 1930, **125**, 456.
3. Kartha, G., Ph.D. thesis, Madras University, 1953.
4. Kartha, G., *Acta Crystallogr*., 1952, **5**, 845–846.
5. Kartha, G., *Acta Crystallogr*., 1952, **5**, 549–550.
6. Hauptman, H. A., *Biogr. Mem., Nat. Acad. Sci.*, 1998, **74**, 127–140.
7. Sanjiva Rao, B., *J. Chem. Soc. (London)*, 1937, 853–855.

8. Robinson, R., *Biogr. Mem. R. Soc.*, *London*, 1960, **5**, 237–252.
9. Rao, P. L. N. and Verma, S. C. L., *J. Sci. Ind. Res*., 1951, **10B**, 184–185.
10. Rao, P. L. N., Krishnamurthy, D. V. and Verma, S. C. L., *Die Naturwissenschaften*, 1954, 66–67.
11. Kartha, G., *Curr. Sci*., 1954, **23**, 8.
12. Sundara Rao, R. V. G., Padmanabhan, V. M. and Kartha, G., *Curr. Sci.*, 1954, **23**, 2167.
13. Ramachandran, G. N. and Raman, S., *Acta Crystallogr.*, 1959, **12**, 957–964.
14. Kartha, G., Ramachandran, G. N., Bhat, H. B., Madhavan Nair, P., Raghavan, V. K. V. and Venkataraman, K., *Tetrahedron Lett*., 1963, 459–472.
15. Venkataraman, K., *Proc. Indian Natl. Sci. Acad*., 1973, **39**, 365–381.
16. Subba Rao, G. S. R. and Raghavan, S., *J. Indian Inst. Sci.*, 2001, **81**, 393–401.
17. Ramachandran, G. N. and Kartha, G., *Nature*, 1954, **174**, 269–270.
18. Ramachandran, G. N. and Kartha, G., *Nature*, 1955, **176**, 593–595.
19. Pauling, L., Corey, R. B. and Branson, H. R., *Proc. Natl. Acad. Sci. USA*, 1951, **37**, 205–211.
20. Watson, J. D. and Crick, F. H. C., *Nature*, 1953, **171**, 737–738.
21. Crick, F. H. C., *What Mad Pursuit: A Personal View of Scientific Discovery*, Basic Books, New York, 1989, p. 67.
22. Sarma, R., *Ramachandran*, Adenine Press, New York, 1998, pp 43–70.
23. Dickerson, R. E., In *The Proteins*, Academic Press, 1964, vol. 2, 2nd edn, pp. 603–778.
24. Ramachandran, G. N. and Ambady, G. K., *Curr. Sci.*, 1954, **23**, 349–350.
25. https://www.nobelprize.org/prizes/chemistry/1972/summary/
26. https://www.nobelprize.org/prizes/chemistry/1984/summary/
27. Richards, F. M. and Vithayathil, P. J., *J. Biol. Chem.*, 1959, **234**, 1459–1465.
28. Kartha, G., Bello, J. and Harker, D., *Nature*, 1967, **213**, 862–865.
29. https://www.nobelprize.org/prizes/chemistry/1985/summary/
30. Bello, J., *Phys. Today*, 1985, **38**, 135.
31. Hendrickson, W. A., In *A Tribute to Gopinath Kartha*, Indira Kartha and the Bahuleyan Charitable Foundation, Ernakulam, 2007.
32. Kartha, G., *Acc. Chem. Res.*, 1968, **1**, 374–381.
33. Kartha, I, in reference 31.

ACKNOWLEDGEMENTS. I am most grateful to Dr Indira Kartha and Dr K. I. Varughese for their help in taking immense trouble in providing me with old documents, related to Kartha's Bangalore days, for all details of his career and Figures 2 and 5. I am grateful to Dr N. Yathindra for the copy of the letter shown in Figure 4 and to Dr K. J. Sreeram, Director, CLRI Chennai for providing the photographs in Figure 1.

P. Balaram is in the National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bengaluru 560 065 and Molecular Biophysics Unit, Indian Institute of Science, Bengaluru 560 012, India.
e-mail: pb@iisc.ac.in

Edited by S. K. Satheesh, and printed & published by G. Madhavan for Current Science Association, Bengaluru 560 080.
Typeset by WINTECS Typesetters, Bengaluru and Printed at Lotus Printers Pvt Ltd, Bengaluru (Ph: 2320 9909)