Pauling's Left-Handed α-Helix

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On February 28, 1951, his fiftieth birthday, Linus Pauling (Figure 1) submitted to the *Proceedings of the United States National Academy of Sciences* a paper entitled "The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain".[1] This paper can be regarded as a milestone in twentieth century science: One of the structures proposed there was the α-helix. Its formulation was the first and is still one of the greatest triumphs of speculative model building in molecular biology; it is the forerunner of the vast investment in computer-assisted molecular modeling in present-day research in structural chemistry. Nowadays, almost everyone is aware that the α-helix is right-handed (that is to say, if the thumb of the right hand points along the helix axis, then the helix turns in the direction indicated by the fingers of the right hand). Imagine my surprise when, a few months ago, I noticed that in the illustration of the *Proceedings* paper (Figure 2) the helix is drawn left-handed! This is not an error. The choice of a left-handed sense of helicity was made arbitrarily. As written in the paper:

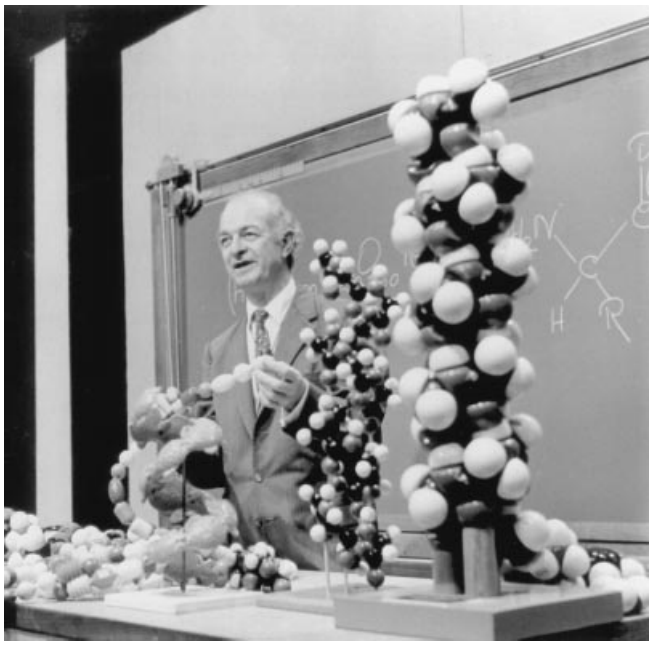

Figure 1. Linus Pauling (1901–1994) surrounded by molecular models, sometime during the 1960s, from the Ava Helen and Linus Pauling Papers, Oregon State University Special Collections.

> *"For glycine both the 3.7-residue helix [later named the α-helix] and the 5.1-residue helix [later named the γ-helix] could occur with either a positive or a negative rotational translation; that is, as either a positive or a negative helix, relative to the positive direction of the helical axis given by the sequence of atoms in the peptide chain. For other amino acids with the L configuration, however, the positive helix and the negative helix would differ in the position of the side chains, and it might well be expected that in each case one sense of the helix would be more stable than the other. An arbitrary assignment of the R groups has been made in the figures."*

The text speaks of an arbitrary assignment of the R groups, and the modern viewer will recognize that the amino acid residues in the Figure are drawn with the opposite configuration to the natural series. Around each asymmetric carbon atom C(α), the C(α)–N, C(α)–C(O), and C(α)–C(β) bonds are in clockwise sequence when viewed along the C(α)–H bond. In the naturally occurring "laevorotatory" L-amino acids this sequence is anticlockwise.[2] Thus the "arbitrary assignment of the R groups" in the Figure happens to be the incorrect one for

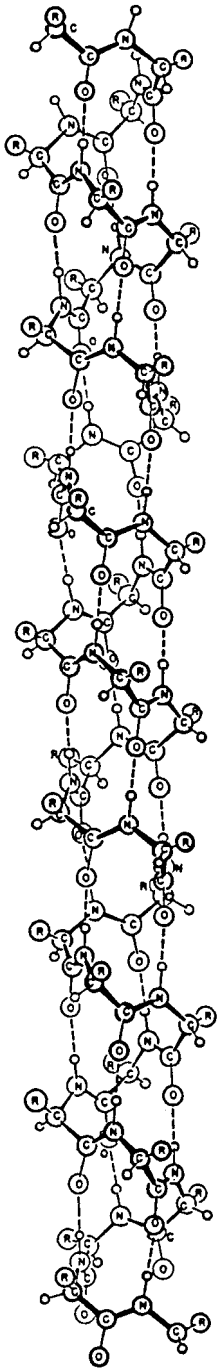

Figure 2. The helix with 3.7 residues per turn (the α-helix), as shown in figure 2 of ref. [1].

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the natural amino acids. Note also that Pauling does not commit himself about the sense of helicity; for a given configuration of the amino acids "one sense of the helix would be more stable than the other" but it is not stated which. Thus the drawing of the α-helix is based on two arbitrary choices: the configuration of the side chains (wrong) and the relative orientation of the side chains in the helix (correct). The structure depicted is the mirror image of the α-helix as it is found in protein structures. Others have certainly noticed this before and possibly drawn their own conclusions about how it came about. The question that intrigues me is this: When Pauling wrote the paper, was he unaware that the absolute configuration of the natural amino acids was already known with a high degree of certainty? It was no longer necessary to make an arbitrary choice. Or was he simply not interested in the question of absolute configuration?

The year 2001 is not only the fiftieth anniversary of the α-helix structure, it also happens to be the fiftieth anniversary of the transformation of stereochemistry from a relative to an absolute basis. This achievement became known to general scientific circles through the paper "Determination of the Absolute Configuration of Optically Active Compounds by Means of X-Rays" published in August 1951 in *Nature* by J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel from the University of Utrecht.[3] Essentially the same information had been published by the same authors a few months earlier in the less generally available *Proceedings of the Royal Netherlands Academy of Sciences*.[4] In both papers it is explained how the absolute structure of a chiral crystal can be established from a special type of X-ray diffraction experiment involving the introduction of a phase-lag into the primary scattering process (anomalous scattering); in both papers, as first example of the use of the new method, the absolute structure of the anion in the crystalline double salt rubidium sodium (+)-tartrate (Figure 3) was described. In my student days I had been taught that a chiral crystal and its mirror image yield the same X-ray diffraction pattern, and hence the impossibility of determining the absolute structure of a chiral crystal by means of X-ray diffraction analysis. Yet here it was done! Previous to this, all stereochemical configurations of optically active substances determined by chemical means were assigned relative to an arbitrarily chosen standard. Thus, the assemblage of assigned structures was self-consistent; the individual structures were all, so to speak, consistently on one side of a mirror, but it was left undetermined as to whether these structures correspond to the real world or to a mirror-image world. As it turned out, the absolute configuration found for dextrorotatory tartaric acid (Figure 3) by X-ray diffraction happened to correspond to the one that had been arbitrarily chosen for this substance by Emil Fischer more than a half-century earlier.[5] It was therefore not necessary to rewrite all the stereochemical formulas in the chemistry textbooks. In particular, starting from the newly established (+)-tartaric acid configuration, the absolute configurations of the naturally occurring amino acids could be assigned with reasonable confidence as being the opposite of those depicted in the α-helix paper.[6]

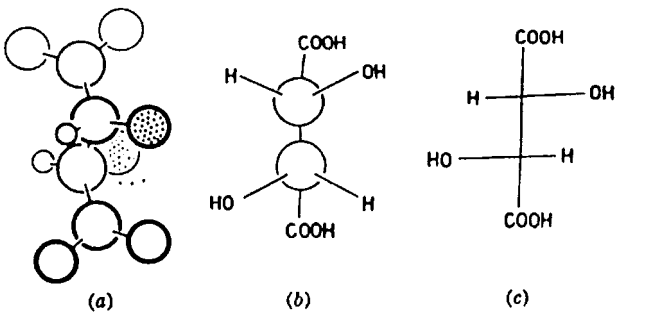

Figure 3. Absolute configuration of natural dextrorotatory tartaric acid. a) As determined by X-rays in sodium rubidium tartrate. b) In a normalized configuration by rotating around single bonds. c) In projection. Reprinted by permission from Nature 1951, *168*, 271–272, ref. [3]. Copyright 1951, Macmillan Magazines Ltd. with original explanatory text.

For those who may be interested in the physics of absolute structure determination using the anomalous scattering method, a few words on these topics may be in order; others may skip this paragraph. Our earlier belief in the "impossibility" of determining the absolute reference frame for describing a crystal structure determined by X-ray analysis had been based on the assumed validity of Friedel's Law, which states that the X-ray diffraction pattern of a crystal is centrosymmetric, whether the crystal itself is centrosymmetric or not. This "law" results from the assumption that phase differences between waves scattered at different points in a crystal depend only on path length differences, which is equivalent to the assumption that any intrinsic phase change connected with the scattering event is the same for all the atoms in the structure. It implies that reflections from opposite faces of a crystal have opposite phase but equal intensity. Since the phase is not observable, the diffraction pattern from a chiral crystal and from its enantiomorph would then be indistinguishable. However, the underlying assumption is not quite correct. When the frequency of the incident X-radiation is such that the radiation is strongly absorbed by one or more of the elements in the crystal, some of the photons scattered by those atom types experience a phase increment of $\pi/2$ with respect to photons scattered by the other atom types—it is *as if* the scattering by a strongly absorbing atom is slightly delayed compared with the others. This is what is called anomalous scattering, and the phase increment, which is independent of path length, leads to small differences in intensity between reflections from opposite crystal faces $\boldsymbol{H}(h, k, l)$ and $-\boldsymbol{H}(\bar{h}, \bar{k}, \bar{l})$ of a chiral crystal, which would otherwise have equal intensity. This is depicted diagramatically in Figure 4, taken from the original paper. Here the anomalous scatterer is rubidium. The resultant vectors $\boldsymbol{F} = \boldsymbol{F}_{\mathrm{Rb}} + \boldsymbol{F}_{\mathrm{rest}}$ for the h,k,l and $\bar{h},\bar{k},\bar{l}$ reflections have equal amplitude and opposite phase. Addition of the anomalous contribution $\Delta\boldsymbol{F}''_{\mathrm{Rb}}$ destroys this equivalence, and the pattern of such differences over many such pairs tells us whether the atomic positions in a right-handed coordinate system correspond to the set $\boldsymbol{X}_{\mathrm{i}}\{x_{\mathrm{i}}, y_{\mathrm{i}}, z_{\mathrm{i}}\}$ or $-\boldsymbol{X}_{\mathrm{i}}\{-x_{\mathrm{i}}, -y_{\mathrm{i}}, -z_{\mathrm{i}}\}$.[7] Indeed, the breakdown of Friedel's Law had been demonstrated twenty years earlier, when Coster, Knol, and Prins utilized it to determine the sense of polarity of zinc sulfide crystals.[8] It was Bijvoet (Figure 5) who realized that polarity is just one-dimensional chirality, and that the

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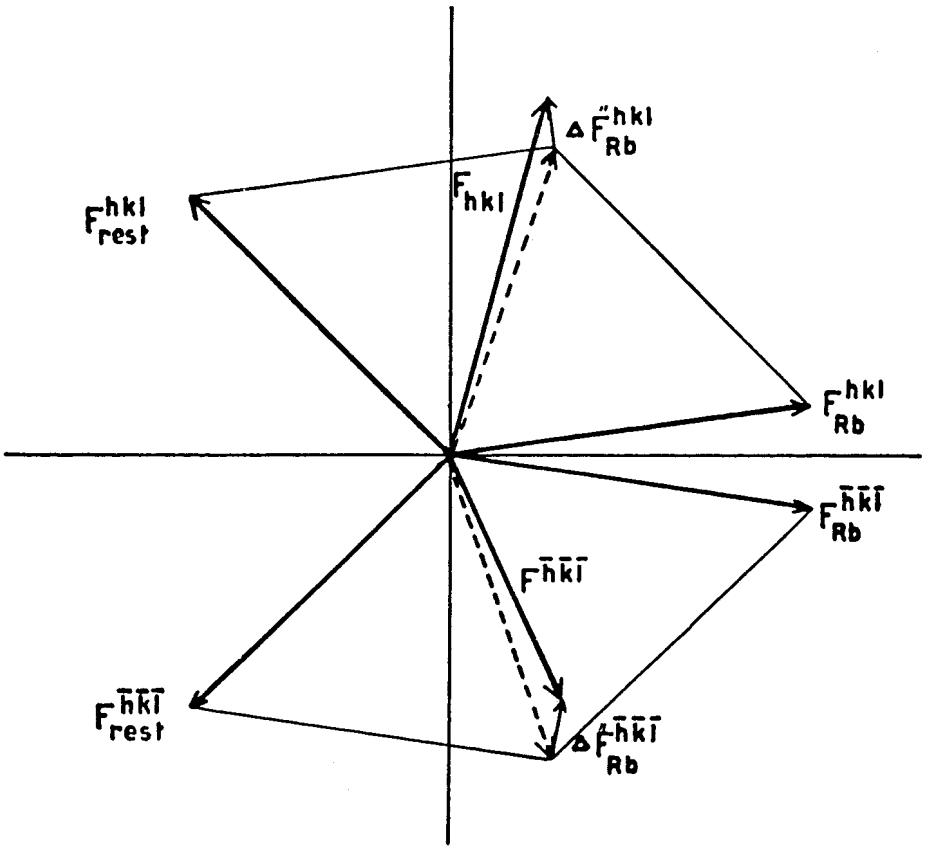

Figure 4. Diagram, reproduced from ref. [4], to illustrate these arguments for the case of sodium rubidium tartrate, where rubidium acts as the anomalous scatterer. The legend to the diagram read: The vectors $\boldsymbol{F}_{Rb}$ and $\boldsymbol{F}_{rest}$ are combined for the reflections *hkl* and $\bar{h},\bar{k},\bar{l}$ resp. neglecting the imaginary (anomalous) part of the structure factor of Rb. The resultant (dotted) amplitudes are of equal modulus but opposite phase. The introduction of the term $\Delta \boldsymbol{F}''_{Rb}$ with phase increment $\pi/2$ in respect to $\boldsymbol{F}_{Rb}$ is seen to destroy this equality of the resultant modulus.

determination of the absolute structure of a chiral crystal is no different in principle from the determination of the polarity sense of zinc sulfide. Any residual doubt that may have been entertained about the sign of the phase change involved in the scattering process was effectively eliminated twenty years later by the confirmation of the polarity sense of zinc sulfide by a most unexpected method—noble gas ion reflection mass spectrometry from opposite faces of the crystal.[9] And if even this were not sufficient, an elegant and convincing "chemical" confirmation of the absolute configuration of the α-amino acids was achieved a few year later by the use of "tailor-made additives" in influencing crystal growth by selective molecular recognition and absorption on opposite crystal surfaces.[10]

I have been wondering whether Pauling knew of the result of the Bijvoet experiment when he drew the left-handed helix with the wrong configuration of the amino acid side chains. On the one hand, the Pauling paper was submitted six months before the *Nature* paper appeared and four weeks before publication of the earlier *Proceedings* paper. On the other hand, just down the corridor from Pauling's office at Caltech was the office of John G. Kirkwood (Figure 6), who was then actively investigating the problem of absolute configuration by comparing observed optical rotations of optically active compounds with values derived from his theory of optical rotatory power based on group polarizabilities. Kirkwood, as I shall show, did know about Bijvoet's work and its implications by late 1950, well before the α-helix paper was submitted.

Figure 5. Johannes M. Bijvoet (1892–1980) taken in 1961 by his son.

During this period I was a postdoctoral research fellow at Caltech, and although my memory is notoriously fallible, especially about events that took place more than a half-century ago, I have a tenacious recollection that Kirkwood called me into his office one day to show me a letter he had received from a Dutch crystallographer who claimed to have found a method of establishing absolute configuration and to have used this method to determine the absolute configuration of tartaric acid; could I help to explain how this method worked? This, I am sure, was the first I had ever heard about the possibility of using X-ray diffraction to determine absolute configuration. My power to call up the past is inadequate to remember what I thought when I tried to absorb the contents of Bijvoet's letter or what I said to Kirkwood in my attempt to explain the new method. Quite likely I could see that when phase differences between waves

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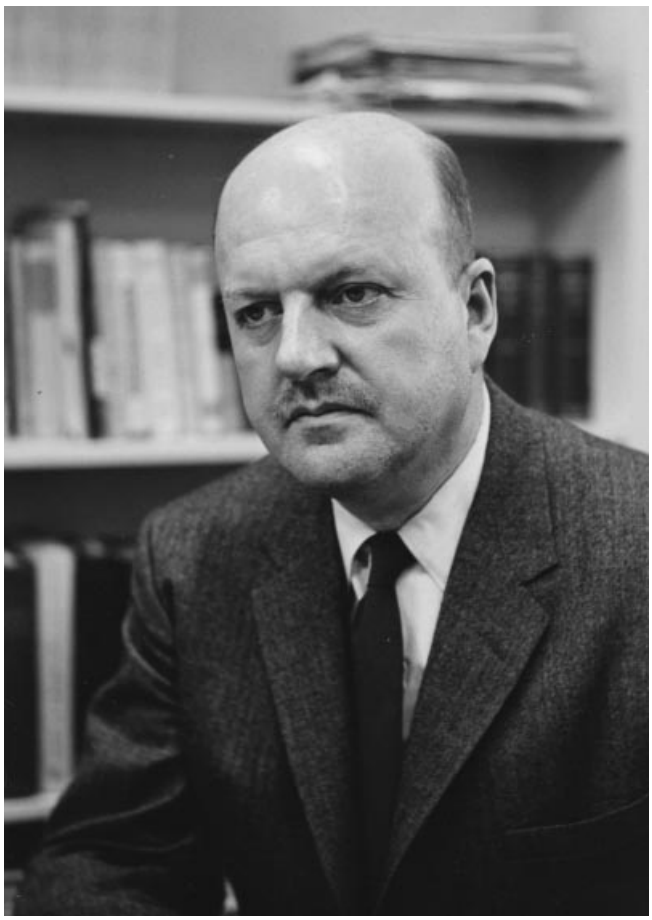

Figure 6. John G. Kirkwood (1907–1959), unknown date. Photographs of individuals maintained by the Office of Public Affairs, Yale University, Manuscripts and Archives, Yale University Library.

scattered from different atoms were no longer determined exclusively by path differences (as in "normal" X-ray diffraction), then, in principle, this would lead to a difference between the intensities of diffracted beams from opposite crystal faces and hence distinguish a chiral structure from its enantiomorph. But I am fairly sure that I could not at the time have been able to derive which enantiomorph was which. That would have been far too complicated for me. It is indeed a complicated matter, and it is easy to get mixed up and obtain the wrong answer by making a "trivial" error in sign—or rather by making an odd number of such errors. Fortunately, nowadays, the software in modern diffractometers and structure analysis and refinement packages makes it almost impossible to make a mistake. I have been able to persuade myself that these conversations with Kirkwood must have taken place sometime in 1950, in any case before Bijvoet wrote the Netherlands Academy *Proceedings* paper.

In July 1951, Kirkwood submitted a paper entitled "The Absolute Configuration of Optically Active Molecules" in which absolute configurations were assigned to the enantiomers of 2,3-epoxybutane and 1,2-dichloropropane from the good agreement between observed and calculated optical rotations.[11] Like the X-ray diffraction experiment, these results again confirmed Fischer's arbitrary assignment as the structurally correct representation of absolute configuration. A similar result was published shortly afterwards by Werner Kuhn.[12] Kirkwood's paper was submitted a month or so before publication of Bijvoet's *Nature* paper, but a footnote states that the result is consistent with that obtained by X-ray diffraction, referring to the Dutch *Proceedings* paper. Symmetrically, a footnote in the *Proceedings* paper states that the authors had learned from Kirkwood that his new calculations of rotatory power and the X-ray result were "concordant as to the assignment of absolute configuration". It is therefore evident that the Bijvoet group in Utrecht and the Kirkwood group at Caltech were in contact and knew about each other's work before the papers were sent off.

To return to Pauling: During the time when he was putting the finishing touches to his helical models of polypeptides, Kirkwood was almost certainly aware of Bijvoet's work on absolute configuration. In any case, Kirkwood was presumably fairly confident that the correctness of Fischer's configurational assignments had been confirmed by his own work.[13] While Fischer's initial assignments had been concerned with the structures of carbohydrates and related substances, the configurational relationships between carbohydrates and other classes of compounds, such as hydroxy acids and amino acids, had recently been settled with reasonable confidence by Christopher Ingold and collaborators.[6] Together with the result of Bijvoet's experiment, this made it highly probable that the natural levorotatory amino acids have the opposite configuration to that depicted in Pauling's paper (Figure 1).

Either Pauling was unaware of these developments when he wrote the α-helix paper, or he knew about them but was uninterested. The first possibility would imply that Kirkwood did not tell Pauling about Bijvoet's achievement or about his own recent work confirming Fischer's assignment and its consequences, or at least failed to draw Pauling's attention to the fact that the amino acids used in construction of the helical models had the incorrect absolute configuration. Since Pauling and Kirkwood spent their days in the same building, had nearby offices, and shared many interests, from quantum mechanics to the structure and properties of proteins, it may seem strange that there was such a lack of scientific contact between them. Although I have no evidence of this and am merely guessing, it seems highly likely that Kirkwood was present at Pauling's seminar in the biology department in the fall of 1950 when the results of the model building work were announced. Following Pauling's theatrical unveiling of his two spiral structures, did Kirkwood notice that the amino acid structural units had the wrong configuration? Possibly not. It is likely that in those days only amino acid specialists had such knowledge immediately at their fingertips, and even among them only the few with a decided inclination towards stereochemistry.[14] Or is it possible that he told Pauling about the discrepancy but in such a way or at such a moment that it made no impression? From conversations with mid-century Caltech survivors I have the impression that the relationship between the two men was not a particularly cordial one, not unfriendly perhaps but remote. Most likely there was too little communication between them.

I tend to believe that when they wrote the paper, or quite possibly even when they made the models, Pauling (or his colleague Robert B. Corey) simply picked one of the two

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amino acid configurations (as it happened, the wrong one) to illustrate the helical structures and did not give the problem of absolute configuration much thought. Very likely, neither they nor any of their co-workers were especially interested in this problem or in the various conventions current in organic stereochemistry at the time. Support for this view comes from the fact that the figures in the subsequent papers in the Pauling – Corey series are not self-consistent with respect to the description of the amino acid configuration. In the paper dealing with the helical structures of poly-γ-methyl-L-glutamate and poly-γ-benzyl-L-glutamate fibers,[15] the amino acid residues are depicted (figures 2 and 3 of that paper) with the correct (*S*)-configuration (CIP system). On the other hand, in the paper describing pleated sheet protein structures,[16] the amino acid residues are drawn (figure 3 of that paper) with the (*R*)-configuration. For good measure, in the first paper of the series,[17] atomic coordinates are given for the amino acid residues in the α-helix with the two alternative positions for the C(β) atom, with no indication concerning which position corresponds to the natural series and which to its mirror image. Further support comes from a 1953 paper by Jerry Donohue in which four additional polypeptide helices were proposed, all drawn left-handed in the figures.[18] Inspection of these pictures (and of the accompanying lists of atomic coordinates) reveals that in three of them the amino acid residues have (*R*)-configuration and in the remaining one they have (*S*)-configuration. Donohue, known in his generation as a stickler for exactness in thought and expression, was clearly not interested in the question of absolute configuration of the amino acids and did not consider it important. Only in the mid-1950s were the diagrams drawn to illustrate the α-helix consistently drawn with (S)-configured amino acids.[19] Yet another expression of Pauling's lack of interest in questions of absolute configuration comes from the 1960 3rd edition of his classic "The Nature of the Chemical Bond",[20] where the topic "absolute configuration" is not mentioned in the index and where the name "Bijvoet" occurs only with reference to his early structure determinations of simple inorganic binary compounds such as mercuric bromide.

While the Caltech crystallographers appear to have shown little interest in Bijvoet's determination of absolute configuration, its reception on the other side of the Atlantic Ocean was quite different. Already in the London Chemical Society's 1951 Annual Reports, Dorothy Hodgkin hailed this achievement as the outstanding event in crystallographic research of the year.[21] Similarly, among the crystallographers in the Cavendish Laboratory in Cambridge the Bijvoet experiment was immediately recognized as a major achievement in structural science. Daniel McG. Brown, to whom we owe the establishment of the 3′ – 5′ linkage in nucleic acids, has told me that soon after Bijvoet's result was published, the organic chemists in Cambridge were aware that the conventional configurational formulas for D-sugars and L-amino acids had been shown to be correct and were suitably reassured by this knowledge. Although the method by which this had been achieved was certainly not understood by all and had to be taken on trust by most, its significance was widely perceived. They knew at last on which side of the mirror they stood. In contrast to the uncertainty about the correct handedness of the α-helix structure, there was never any question about the right-handedness of the DNA double-helix structure proposed a couple of years later in 1953.[22] In constructing their models, Watson and Crick used Furberg's "standard configuration" of the β-D-deoxyribofuranose units and its substituents,[23] and found that the model could be built only with a right-handed sense of helicity. Furberg's structure was based on the standard chemical convention, and its correctness is implicitly assumed in the famous *Nature* paper.[22] In the following, more detailed description of the assumptions made in deriving the structure of DNA,[24] the Bijvoet experiment is mentioned in a footnote.

There is also the other question that Pauling left open; even when the configuration of the amino acids in the helix could be settled, "in each case one sense of the helix would be more stable than the other". That is to say, even when the naturally occurring amino acids in the protein chain are given the correct (*S*)-configuration, it is by no means obvious from model building that the α-helix should be right- rather than left-handed. Both models can be constructed and neither is obviously untenable. Referring to the poly-L-glutamate fiber structures, Pauling and Corey wrote: "It seems likely that a poly-L-glutamate helix would be more stable with one screw sense (right-handed or left-handed) than the other, and that helixes (*sic*) of only one kind are formed in significant number in the process of folding",[15] but they did not venture an opinion about which screw sense should be preferred. The main difference between the two structures is that in a right-handed α-helix built from *S*-configured amino acids, the direction of each side chain C(α)–C(β) bond has a component in the direction of the N–H bond, whereas in a left-handed helix the C(α)–C(β) bond points in the direction of the C=O bond. For a polyglycine helix, without the side chains, the left- and right-handed helices are exact mirror images and hence equienergetic. A few months after publication of the Pauling structures, Maurice L. Huggins noted that for amino acids with the correct absolute configuration—he was already aware of the Bijvoet result—a left-handed helix would lead to a C(β)$\cdots$O distance of only 2.64 Å.[25] He concluded that "*levo* polypeptides form right-handed spirals and *dextro* polypeptides left-handed spirals, whichever of these two types of structure is correct". The protein chain is, of course, a "*levo* polypeptide".

During the following decade, the existence of the α-helix as an important structural element of proteins became generally accepted, and there was much, mostly inconclusive discussion about whether it occurred in a left- or right-handed form or even as a mixture of these depending on local conditions. The crude energy estimates available at that time could not lead to any reliable conclusion. The best evidence came perhaps from X-ray diffraction patterns of synthetic polypeptide fibers. For fibers built from the natural series of *S*-configured amino acids, somewhat better agreement with the X-ray patterns was generally obtained with models based on right-handed helices, but the differences were not large and hardly conclusive.[26] As late as 1960, Pauling was apparently still not prepared to make a decision between the two alternatives. In the 3rd edition of his "The Nature of the Chemical Bond", the α-helix is illustrated (ref. [17], figures 12 – 18, p. 500) by drawings of

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both right- and left-handed structures built from amino acids with the correct (*S*)-configuration for the natural series, and the question of which helix is preferred is left unanswered—in fact it is not even mentioned.

Indeed, it was only in that year that an answer to the question was provided—by the structure analysis of myoglobin at 2 Å resolution.[27] In this first protein structure at such a high resolution, John Kendrew and his co-workers found that for many stretches of polypeptide chain the observed electron density closely followed that expected for an α-helix with the dimensions given by Pauling and Corey.[17] This was the first direct proof that α-helices are present in proteins. It was also found that the C(β) atoms of the side chains were consistently located in the direction opposite to the C=O bonds of the main chain. As mentioned above, this is the signature of a right-handed helix if the amino acid residues are assigned the correct *S*-configuration.[28] From these arguments, the electron density of the whole myoglobin molecule could be plotted in the correct absolute configuration. All the lengths of α-helix were found to be right-handed. Moreover, in satisfying agreement with this assignment, the molecule as a whole was found to be of the same hand as the four closely similar subunits in hemoglobin, for which the absolute configuration had been determined by anomalous scattering measurements.[29] Since then, α-helices have been recognized as an ubiquitous building element in countless protein structures. They are almost always right-handed, although short stretches (three to five residues) of left-handed α-helix occur occasionally.

I have given reasons for believing that Pauling, around mid-century, was not interested in the problem of absolute configuration or, as we would now put it, in problems of molecular chirality, including biochirality. This may appear surprising in view of Pauling's deep and intuitive grasp of the symmetry aspects of complex crystal structures. We must remember, however, that this was at a time when the word "chirality" had not yet found its way into chemistry, a time many years before we were inundated by conferences, symposia, and journal issues devoted to chiral separation of chiral drugs by chiral chemists using chiral recognition methods.[30] Richard Marsh, one of the few surviving crystallographers from that Golden Age in structural chemistry at Caltech, has explained to me that at that time the Caltech group were interested in details of molecular structure, in bond lengths and bond angles, in interatomic distances, in features that were just as relevant in a left-handed world as in a right-handed one. It was indeed the close attention to such details that allowed Pauling in the first place to build models of polypeptide chains that would satisfy the strict structural requirements that had emerged from such studies. Problems of absolute configuration received little or no attention because there seemed to be no need for them then. Perhaps they were even regarded as a distraction from the task at hand. Sometimes one can focus more clearly by closing one eye.

In collecting information for this article, I have been greatly assisted by correspondence and conversations with many colleagues, especially Richard Marsh at the California Institute of Technology, J. Michael McBride at Yale University, Francis Crick in La Jolla, CA, Daniel McG. Brown in Cambridge, Kurt Mislow at Princeton University, and Frederik Bos on the staff of the Koninklijke Nederlandse Akademie van Wetenschappen.

[1] L. Pauling, R. B. Corey, H. R. Branson, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 205–211.
[2] In the now widely accepted Cahn–Ingold–Prelog (CIP) specification system (R. S. Cahn, C. K. Ingold, V. Prelog, *Experientia* **1956**, *12*, 81–94; R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem.* **1966**, *78*, 413–447; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385–415), the naturally occurring amino acids with anticlockwise sequences as described above are defined as having (*S*)-configuration (except cysteine, where the sulfur linked to the β-carbon of the side chain takes "precedence" over the carbonyl oxygen atom). Those with clockwise sequence have (*R*)-configuration.
[3] J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature* **1951**, *168*, 271–272.
[4] A. F. Peerdeman, A. J. van Bommel, J. M. Bijvoet, *Proc. Konink. Neder. Akad. Wetensch. B* **1951**, *54*, 16–19.
[5] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1377–1683.
[6] The configurational relationships between carbohydrates, hydroxy acids and amino acids were published (P. Brewster, E. D. Hughes, C. K. Ingold, P. A. D. S. Rao, *Nature* **1950**, *166*, 178–179) in July 1950, only a few months before submission of the Pauling and Bijvoet papers, but one can assume that this accomplishment rapidly became widely known in stereochemical circles. Soon afterwards, in November 1950, the need for a self-consistent method of specifying molecular configuration was set forth by Cahn and Ingold (R. S. Cahn, C. K. Ingold, *J. Chem. Soc.* **1950**, 612–622). The sequence-rule convention proposed in this paper is the forerunner of the CIP specification system (ref. [2]). Although the Cahn–Ingold paper was still based on the then-accepted convention for D-glyceraldehyde as a standard substance, it contains the prescient observation: "The time will come when absolute configuration can be determined with certainty; and the 'standard substance' will be a redundant concept."
[7] Given a right-handed coordinate system to describe the crystal axes, there is never any question about which of the two opposite (*h*, *k*, *l*) faces is which, only the uncertainty about the sense of chirality of the atomic coordinates $\boldsymbol{X}_i$ or $-\boldsymbol{X}_i$. See J. D. Dunitz, *Acta Crystallogr. Sect. A* **1995**, *51*, 588.
[8] D. Coster, K. S. Knol, J. A. Prins, *Z. Phys.* **1930**, *63*, 345–369.
[9] H. H. Brongersma, P. M. Mul, *Phys. Lett.* **1973**, *19*, 217–220.
[10] L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, M. Lahav, L. Leiserowitz, *J. Am. Chem. Soc.* **1982**, *104*, 2075–2077; Z. Berkovitch-Yellin, L. Addadi, M. Idelson, M. Lahav, L. Leiserowitz, *Nature* **1982**, *296*, 27–34.
[11] W. W. Wood, W. Fickett, J. G. Kirkwood, *J. Chem. Phys.* **1952**, *20*, 561–568.
[12] W. Kuhn, *Z. Elektrochem.* **1952**, *56*, 506–524.
[13] Although mistakes could also happen here! In one of the footnotes of reference [7], several sign errors in an earlier paper (J. G. Kirkwood, *J. Chem. Phys.* **1937**, *5*, 469) are corrected.
[14] I am almost certain that I did not notice at the time! Indeed, I find it most unlikely that I would have been able to identify the conventional spatial arrangement of the natural amino acids then or for many years afterwards.
[15] L. Pauling, R. B. Corey, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 241–250.
[16] L. Pauling, R. B. Corey, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 251–261.
[17] L. Pauling, R. B. Corey, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 235–240.
[18] J. Donohue, *Proc. Natl. Acad. Sci. USA* **1953**, *39*, 470–478.
[19] See, for example, figure 4 in B. W. Low, J. T. Edsall, *Aspects of Protein Structure* in *Currents in Biochemical Research* (Ed.: D. W. Green), Interscience, New York, NY, **1956**, p. 398.
[20] L. Pauling, *Nature of the Chemical Bond and the Structure of Molecules and Crystals*, 3rd ed., Cornell University Press, Ithaca, NY, **1960**.
[21] D. C. Hodgkin, *Annual Reports on Progress in Chemistry for 1951*, The Chemical Society, London, **1952**, p. 361.

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[22] J. D. Watson, F. H. C. Crick, *Nature* **1953**, *171*, 737–738.
[23] S. Furberg, *Acta Chem. Scand.* **1952**, *6*, 634–640.
[24] F. H. C. Crick, J. D. Watson, *Proc. R. Soc. London Ser. A* **1954**, *223*, 80–96.
[25] M. L. Huggins, *J. Am. Chem. Soc.* **1952**, *74*, 3963–3964.
[26] See, for example, for poly-L-alanine fibers A. Elliot, B. R. Malcolm, *Proc. R. Soc. London Ser. A* **1959**, *249*, 30–41.
[27] J. C. Kendrew, R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Phillips, V. C. Shore, *Nature* **1960**, *185*, 422–427.
[28] In the meantime the correctness of the configurations of the natural amino acids as determined by their configurational relationships with other groups of compounds (ref. [6]) had been confirmed by X-ray analysis of L-leucine hydrobromide using the anomalous scattering technique (J. Trommel, J. M. Bijvoet, *Acta Crystallogr.* **1954**, *7*, 703–710).
[29] M. F. Perutz, M. G. Rossmann, A. F. Cullis, H. Muirhead, G. Will, A. C. T. North, *Nature* **1960**, *185*, 416–421.
[30] The use of the terms "chiral" and "chirality" in chemistry is of fairly recent origin. I first heard the terms in the early 1960s when my Zurich colleagues (Duilio Arigoni, André Dreiding, Albert Eschenmoser, Edgar Heilbronner, Vlado Prelog) used to argue interminably about stereochemical concepts and terminology. When we heard that Kurt Mislow was proposing the term "chiral" from Greek $\chi\varepsilon\iota\rho$ as a multilingually accessible synonym for almost untranslatable "handedness", we unanimously and enthusiastically agreed to use this term at every available opportunity. To the best of my knowledge, its first use in a chemical text is to be found in K. Mislow, *Introduction to Stereochemistry*, Benjamin, New York, NY **1965**, but the term goes back at least to Lord Kelvin (Kelvin, *Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light*, Clay, London, **1904**). See K. Mislow in *Topics in Stereochemistry*, *Vol. 22* (Ed.: S. E. Denmark), Wiley, New York, NY, **1999**, chap. 1 for further details. Following the downfall of parity at the level of the weak force in particle physics, the wider usage of the term "chiral" in a variety of mathematical, physical, chemical, and everyday contexts was urged by L. L. Whyte, *Nature* **1957**, *180*, 513; L. L. Whyte, *Nature* **1958**, *182*, 198.

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