tive inhibitors for the enzyme (*7*). Williams has accounted for the great catalytic efficiency of cupric chelates on theoretical grounds (*32*). He postulates the *d*-orbitals of divalent metal ions as forming strong, continuous, overlapping molecular orbitals with the π- and σ-orbitals of certain ligands. We may extend this picture to include the substrate and acceptor in the present case. Electrons, either singly or in pairs, may then be capable of being transferred directly from the former to the latter. The metal is pictured as (i) providing a locus of physical attachment for both moieties of the catalytic complex, (ii) polarizing the electrons, to be transferred, away from the substrate by virtue of its strong electrophilic character, and (iii) permitting the actual interpenetrations of orbitals which we have alluded to. The somewhat greater liability to dissociation from the protein of the singly linked copper within the ternary complex may provide an explanation of two phenomena previously observed with other copper proteins—the exchange of radioactive copper with the copper of ascorbate oxidase, which occurs only in the presence of substrate and oxygen simultaneously (*33*), and the "reaction inactivation" common to many different cuproenzymes (*28*).

A somewhat similar picture has already been proposed to account for a large number of observations in the metalloflavoprotein series (*34*). Its possible extension to other metallodehydrogenases, such as other cuproenzymes and the zinc-pyridino-proteins, is now under investigation in this laboratory.

References and Notes

1. W. Wiechowski, *Beitr. chem. physiol. Pathol.* **9**, 295 (1907); F. Batelli and L. Stern, *Biochem. Z.* **19**, 219 (1909).
2. D. Keilin and E. F. Hartree, *Proc. Roy. Soc. London* **B119**, 114 (1938).
3. J. N. Davidson, *Biochem. J. London* **32**, 1306 (1938); *ibid.* **36**, 252 (1942); C. G. Holmberg, *ibid.* **33**, 1901 (1939); K. I. Altman, K. Smull, E. S. G. Barron, *Arch. Biochem.* **21**, 153 (1949); E. Leone, *Biochem J. London* **54**, 393 (1953).
4. F. Felix, F. Scheel, W. Schuler, *Hoppe-Seyler's Z. physiol. Chem.* **180**, 90 (1929); W. Schuler, *ibid.* **208**, 237 (1932).
5. E. Praetorius, *Biochim. et Biophys. Acta* **2**, 602 (1948).
6. R. Bentley and A. Neuberger, *Biochem. J. London* **52**, 694 (1952).
7. H. R. Mahler, G. Hubscher, H. Baum, *J. Biol. Chem.* **216**, 625 (1955).
8. H. Baum, G. Hubscher, H. R. Mahler, *Biochim. et Biophys. Acta,* in press; G. Hubscher, H. Baum, H. R. Mahler, *ibid.*, in press.
9. We wish to express our sincere appreciation to David E. Green, director of the Institute for Enzyme Research, for his encouragement of this investigation. It was supported by grants-in-aid by the American Cancer Society (on recommendation by the Committee on Growth, National Research Council) and by the National Institutes of Health, U.S. Public Health Service, to one of us (H. R. M.).
10. F. Kubowitz, *Biochem. Z.* **292**, 221 (1937); **299**, 32 (1938).
11. A. Albert, *Biochem. J. London* **54**, 646 (1953).
12. I. M. Klotz, in *The Mechanism of Enzyme Action,* W. D. McElroy and B. Glass, Eds., (Johns Hopkins Press, Baltimore, Md., 1954), p. 257.
13. A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds* (Prentice-Hall, New York, 1952); R. J. P. Williams, *J. Phys. Chem.* **58**, 121 (1954).
14. S. G. Waley, *Biochim. et Biophys. Acta* **10**, 27 (1953); M. Dixon, *Biochem. J. London* **55**, 161 (1953); V. Massey and R. A. Alberty, *Biochim. et Biophys. Acta* **13**, 354 (1954); C. Frieden and R. A. Alberty, *J. Biol. Chem.* **212**, 859 (1955); K. J. Laidler, *Trans. Faraday Soc.* **51**, 528, 540, 550 (1955).
15. J. Schubert, in *Chemical Specificity in Biological Interactions,* R. N. Gurd, Ed. (Academic, New York, 1954).
16. D. Keilin and E. F. Hartree, *Proc. Roy. Soc. London* **B119**, 141 (1936).
17. We are indebted to P. P. Cohen for generous gifts of the 2-C^{14} and 8-C^{14} uric acids and to A. Neuberger for his generous gift of C^{14}-diaminouracil sulfate that was used as the precursor of 6-C^{14} uric acid (*18*). The substituted purines were kindly provided by G. B. Brown.
18. C. E. Dalgliesh and A. Neuberger, *J. Chem. Soc.* **1954**, 3407 (1954).
19. E. S. Cannelakis and P. P. Cohen, *J. Biol. Chem.* **213**, 385 (1955).
20. F. Bergmann and S. Dikstein, *J. Am. Chem. Soc.* **77**, 691 (1955); L. F. Cavalieri *et al.*, *ibid.* **76**, 1119 (1954); D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta* **9**, 199 (1952).
21. J. Bjerrum, *Metal Amine Formation in Aqueous Solution* (Haase, Copenhagen, Denmark, 1941).
22. N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.* **71**, 3089 (1949); N. J. Leonard and W. V. Ruyle, *ibid.* **71**, 3094 (1949).
23. F. Brown and R. Hammick, *J. Chem. Soc.* **1949**, 659 (1949).
24. B. R. Brown, *Quart. Revs. London* **5**, 131 (1951); J. Hine, *Physical Organic Chemistry* (McGraw-Hill, New York–London, 1956), pp. 283–291.
25. H. Biltz, *Ber. deut. chem. Ges.* **47**, 460 (1914).
26. R. Behrend, *Ann. Chem. Justus Liebigs* **333**, 153 (1904); W. Schuler and W. Reindel, *Hoppe-Seyler's Z. physiol. Chem.* **208**, 248 (1932); *ibid.* **215**, 258 (1933).
27. F. W. Klemperer, *J. Biol. Chem.* **160**, 111 (1945).
28. See, for example, the discussion by T. P. Singer and E. Kearney in *The Proteins,* H. Neurath and K. Bailey, Eds. (Academic, New York, 1954), vol. II-A.
29. L. Michaelis, in *The Enzymes,* J. B. Sumner and K. Myrback, Eds. (Academic, New York, 1952), vol. II-1.
30. B. Chance, in *Techniques in Organic Chemistry,* S. L. Friess and A. Weissberger, Eds. (Interscience, New York, 1953), vol. VII.
31. B. Chance and A. M. Pappenheimer, Jr., *J. Biol. Chem.* **209**, 931 (1954); H. Theorell and B. Chance, *Acta Chem. Scand.* **5**, 1127 (1951).
32. R. J. P. Williams, *Nature* **177**, 304 (1956).
33. M. Joselow and C. R. Dawson, *J. Biol. Chem.* **191**, 1, 11 (1951).
34. H. R. Mahler and J. Glenn, in *Inorganic Nitrogen Metabolism: Function of Flavoproteins,* W. D. McElroy and B. Glass, Eds. (Johns Hopkins Press, Baltimore, Md., 1956).

Amedeo Avogadro

Two thousand years ago Lucretius in Rome expounded the doctrine of atoms. He expressed in immortal language the speculations of the Greek philosophers, and he described with the vividness of a great poet the movements, the unions and separations of the tiny corpuscles of which he conceived all things to be composed. The atoms had many qualities which modern science assumes even today. Vigorous motion under the appearance of rest, penetration of heat and cold depending on this movement, hooks for attachment to others, and even an unpredictable "clinamen" or swerve, which is a sort of fantastic anticipation of the uncertainty principle of quantum mechanics.

This was magnificent and represented a wonderful intuitive insight into the working of nature, but it was not science. There was no link with quantitative experimentation, the construction of which connection was lacking until modern times. Then, one might say suddenly, the science of chemistry was created by the vision of a few great men, among whom was Amedeo Avogadro.

The recognition by Avogadro of the distinction between atoms and molecules was the key which opened the treasury of structural chemistry: a treasury whose riches are not yet exhausted. The establishment of the true doctrine about the nature of the particles of the elementary gases rendered possible the development of the kinetic theory and the understanding of the energy relationships of these particles.

On this basis was founded the study not only of the structure of substances but of the functional relationships that govern chemical change: chemical kinetics. A true doctrine of molecules was the necessary precursor of what may

This article, by Cyril Hinshelwood, and the following one, by Linus Pauling, are based on addresses given in Rome on 6 June, when the Accademia Nazionale dei XL commemorated the centenary of the death of Avogadro. At the ceremony, a new medal, commemorating Avogadro, was presented by the Accademia, for the first time, to Sir Cyril and to Dr. Pauling.

truly be called both the anatomy and the physiology of chemical compounds.

There is irony in the fact that the importance of Avogadro's work was not understood for 40 years. This has of course happened to other men of science, and it should perhaps remind us that the advance of knowledge is in some measure an impersonal thing. However this may be, there is no doubt that one of the best ways of honoring the memory of the great scientists of the past is by considering the progress that has been made on the basis of their original labors.

In the century since the death of Amedeo Avogadro chemistry has undergone a marvelous transformation. Structural chemistry has now elucidated the architecture of substances the complexity of which would have seemed scarcely imaginable to the early chemists: the coloring matters of flowers, the proteins of animal and vegetable cells, constituents of all the varied and manifold products of nature. Perhaps the most remarkable advance of all is the synthesis of molecules to a defined purpose, as happens in the great industry of plastics, where molecules of enormous length rival or surpass both in size and in subtlety those of nature itself.

In this field of colloids one must of course incidentally allude to the wonderful result whereby molecules, consisting of so many thousands of atoms that they are actually visible in the ultramicroscope, obey the law of Avogadro—a principle upon which, as everyone knows, is based the determination of one of the most important of all physical constants, Avogadro number.

Today perhaps one of the greatest problems of structural chemistry is that of the nucleic acids, and of the wonderful relationships which exist between their configurations and those of the proteins, with which in the process of autosynthesis of living matter they are mysteriously and yet certainly linked. It was a long road from the simple diatomic molecules of hydrogen and oxygen to here.

Nevertheless, chemistry does not deal with static systems but with dynamic systems. Not only are the maps and plans showing how atoms are joined important, but also a knowledge of the forces which unite them and of the mode of operation of these forces.

By the time of Avogadro the valences of the chemist had not changed much from the hooks of Lucretius. Since his time, however, they have changed out of all recognition. The electrical theory of matter first revealed that the union of atoms is determined by electrons. (Indeed, it is upon the electronic charge and the value of the faraday that the best value of Avogadro's constant now depends.) The interpretation of the mode of action of electrons in effecting chemical union has led us very far from the simple realistic representations of Avogadro's day. This mode of action is understandable only in terms of quantum mechanics and the Pauli principle; and indeed in the last analysis there is nothing to explain the existence of the bonds between atoms except an abstract principle about the observability of particles. As the material victories of science multiply, the principles upon which our understanding of it is based seem to vanish into abstractions. Yet the work of Avogadro remains.

Structures and forces are still not the whole of chemistry. The processes by which atoms and molecules combine, separate, and rearrange themselves constitute a problem of fascinating diversity. Chemical kinetics is the vision of Lucretius, rendered precise and affrontable by experiment on the basis of the doctrine of Avogadro.

Chemical kinetics has itself evolved through the study of simple systems to the study of the formation of vast polymerized molecules, and from the study of isolated reactions to that of the complex mutually interdependent systems which determine the characteristic properties of the living cell. Some of these properties, such as adaptability, can be given an explanation in terms of chemical kinetics.

Perhaps, however, when we think of Avogadro it is to the simpler molecules that our attention should most be given, for, after all, a reaction system such as

$$H + H \rightleftharpoons H_2$$

is that which most readily comes to mind when his name is mentioned. It would hardly have been realized, however, in his time what intricate problems the kinetics of such reactions present.

The union of two atoms to form molecules requires, as is well known, the presence of a third body to remove the energy liberated.

$$H + H + M \rightarrow H_2 + M$$

But the efficiency with which the third body performs this function is very variable and is governed by factors only partially understood. By a thermodynamic necessity this efficiency parallels that with which the molecule M can transfer vibrational energy in a collision between H_2 and M. This in turn depends on the extent to which the proximity of M modifies the potential energy curve of the molecule H_2. Numerous studies of such transfers by indirect methods, including the study of supersonic dispersion and of photolysis by very intense, transitory illumination, have been made and continue to be made. A certain chemical affinity between the two colliding molecules favors the energy transfer; so also does the complete identity of the two molecules. In general, energy transfers between like molecules occur much more readily than those between unlike molecules, a fact for which the explanation must be sought, not in affinity, but in the exact fulfillment of quantum conditions.

The converse process—that is, the dissociation of a diatomic molecule—requires the correct energy transfer, after which the decomposition ensues at once. But even here there are complexities. The separated atoms may recombine, a process that is not at all likely in the gas phase but is more so in the liquid phase. As has recently been pointed out, the probability of the recombination—that is, the "reactivity" of the atoms—diminishes steadily to a limiting value during the time following their formation, as more and more inert molecules come between them. This fact is of some importance in the consideration of photochemical dissociations.

When the molecule becomes even a little more complex the problem of dissociation reactions becomes still more interesting. The energy required for dissociation—the so-called "activation energy"—must be communicated in a suitable collision. This process, as has already been explained, is one of considerable specificity. The energy then needs to be concentrated with sufficient intensity into the bond which has to be ruptured, for example, in the dissociation

$$N_2O \rightarrow N_2 + O$$

into the bond between N and O. The necessary redistribution of energy requires time. Thus, before it is accomplished the molecule may lose its energy in another collision. The result of this, as is well known, is that the first-order rate constant, k, of the unimolecular dissociation rises from zero at zero pressure to reach a limit k_∞ at high enough pressures. The value of k_∞ is often given nearly by

$$k_\infty = \nu e^{-E/RT}$$

where E is the activation energy and ν a vibration frequency. When this relationship is obeyed, the condition for dissociation is indeed the localization of the energy E in one bond. Sometimes, however, the factor multiplying the exponential term is much greater, showing that another, and possibly less mechanical, picture of the process must be adopted. The details of this picture are not yet quite clear.

The form of the curve showing k for a unimolecular reaction in the gas phase as a function of p, the pressure, has occasioned much discussion, in which theory has sometimes outrun experiment. It is curious that one feature of this curve has long escaped recognition. And yet I believe it to be of fundamental importance and to have a relatively simple explanation.

Although the subject is a little specialized, I shall mention it now as part of this homage to Avogadro, because in honoring the great men of the past who have pursued truth, it is well, if possible and in however humble a manner, to bring something that is new, and what I shall describe does, after all, relate to a simple molecular phenomenon.

The phenomenon in question may be exemplified by measurements on the chemical reaction

$$N_2O \rightarrow N_2 + O$$

recently reinvestigated very thoroughly by Lindars, in my laboratory. Similar effects are observed in several other reactions.

The curves of k as a function of p_{N_2O}, the initial pressure of the nitrous oxide, or as a function of p_X, the pressure of an added foreign gas, do not in rising from zero to k_∞ follow the course predicted by the standard theories but follow a quite different course.

They show, in fact, a series of changes of slope, separated by regions of more nearly uniform slope. The curve of k against p_{N_2O} rises at first from the origin; it then bends in such a way as to suggest that will soon become horizontal. It does, however, nothing of the sort but continues upward until at a much higher pressure it again shows a diminution of slope.

To understand the explanation, first consider the classical case. This involves the processes

$$\text{Normal molecules} \underset{1'}{\overset{1}{\rightleftharpoons}} \text{activated molecules} \xrightarrow{2} \text{reaction products}$$

These are two extreme conditions. If 1 is rate-determining (at low pressure), k is proportional to p_{N_2O}. If 2 is rate-determining and 1 and 1′ are nearly in equilibrium, k reaches the steady value k_∞. The change in slope of the k, p_{N_2O} curve occurs where the one rate-determining process gives place to the other.

If, as occurs, there are several regions where the slope changes, there would seem to be more than one change in the nature of the process that determines the rate. What does this mean? If we have the sequence of processes

$$\text{Normal molecules} \underset{1'}{\overset{1}{\rightleftharpoons}} \text{energized molecules type 1} \underset{2'}{\overset{2}{\rightleftharpoons}} \text{energized molecules type 2} \xrightarrow{3} \text{products of reaction}$$

then the rate-determining process may be 1 or 2 or 3. If 1 and 1′, on the one hand, and 2 and 2′, on the other hand, are specifically influenced by the pressures, and if further the transformations 2 and 2′ may be either spontaneous or pressure-induced, then the form of the curves can be fully accounted for. The changes in slope, in fact, occur where one rate-determining process is replacing another.

What then is the nature of the transformation from the energized molecule of type 1 to that of type 2? With the N_2O molecule it is probably the passage from the singlet to the triplet state. The fact that the direct transition of N_2O into $N_2 + O$ would be a violation of a spectroscopic rule was long ago realized, but the application of this fact in explanation of the relationships between k and pressure was not recognized.

Since there can be several triplet states, there can be more than one extra "bend" in the k, p_{N_2O} curve, as indeed experiments at higher pressures show to exist.

Whether the explanation in terms of singlet-triplet transitions applies also in the other examples, such as the thermal decomposition of saturated hydrocarbons, is a very interesting question, the answer to which must be awaited.

Thus it can be said that the problems raised by the association of atoms into simple compound structures, the fundamental conception of Avogadro, still have their mystery. To adapt the old Latin saying: *ex chemia semper aliquid novi.*

For centuries atoms lay concealed behind the tenebrous theories of the alchemists; even after Dalton, the diatomic molecules of simple gases long went unrecognized. In more than a century of the atomic theory, D_2O existed undiscovered in ordinary water. The triplet states of some simple molecules have apparently been unacknowledged participants in their chemical transformations. And so it must go on. But no discovery will ever excel in simplicity and beauty that which was made by Amedeo Avogadro.

CYRIL N. HINSHELWOOD
Physical Chemistry Laboratory,
Oxford University, England

Avogadro's work forms the basis of the whole of theoretical chemistry, and especially of the structure theory of chemistry. The first step in understanding the physical and chemical properties of substances in terms of their structure, the problem to which Avogadro was devoted throughout his life, is that of finding out how many atoms of different kinds are involved in the molecules or crystals of the substances. It was this problem, the discovery of the correct molecular formulas of substances, that was largely solved by Avogadro in his great paper of 1811 and the papers that he published during later years. Avogadro was the first man in the world to know that water is H_2O, composed of 2 atoms of hydrogen and 1 atom of oxygen; that hydrogen itself is H_2, and oxygen is O_2; that ammonia is NH_3; that ethane is C_2H_6; that camphor is $C_{10}H_{16}O$.

It was impossible for the idea that atoms are held together by chemical bonds to be developed and to be given adequate experimental support until the correct formulas had been discovered for a large number of substances. It was impossible for the idea of chemical valence to be developed until the correct formulas of molecules had been discovered.

Avogadro began to write the correct molecular formulas for gaseous substances in 1811. From that year on until about 1860, when his system of atomic weights and chemical formulas was finally adopted by chemists all over the world, Avogadro was always far ahead of any of his contemporaries. There was never a time, after 1811, when any other scientist proposed a system of atomic weights of elements that contained fewer errors than the system contemporaneously used by Avogadro.

His first paper on this subject was "Essai d'une manière de determiner les masses relatives des molécules élémentaires des corps, et les proportions selon lesquelles elles entrent dans ces combinaisons," published in the *Journal de physique, de chimie, d'histoire naturelle et des arts* [**73**, 58 (1811)]. In this paper (I shall use modern nomenclature in describing his results) he assigned the formulas H_2, O_2, N_2, and Cl_2 to these elementary gases, and the formulas H_2O, NH_3, CH_4, SO_3, SO_2, CO_2, CO, HCl, NO_2 to the corresponding compounds. He also discussed the atomic weights of some metals, but without success, in the absence of information about vapor densities.

In 1814, in a second paper in the same journal, he discussed H_2S, PH_3, F_2, HF, and a number of other substances, including boron trifluoride and silicon tetrafluoride.

He returned to the problem again in 1821, when he published his third paper "Nouvelles considérations sur la théorie des proportions déterminées dans les combinaisons, et sur la détermination des masses des molécules des corps," a paper of 162 pages published in the *Memorie della Reale Accademia delle Scienze di Torino*. In this paper he discussed, in an entirely correct manner, the gas densities of cyanogen, C_2N_2; hydrogen cyanide, HCN; cyanogen chloride, NCCl; phosgene, $COCl_2$; and a large number of other substances. In particular, he returned to the problem of the correct atomic weights of boron and silicon. He showed that boron compounds have formulas such as BF_3, B_2O_3, H_3BO_3, and that compounds of silicon have formulas such as SiF_4 and SiO_2. Berzelius had used the formulas BO_3 and SiO_3 for the oxides of these important elements, and in consequence all of the formulas written for the borates and silicates were wrong. During the same year Avogadro also published a significant paper on the composition of organic substances.

Avogadro's discoveries of the correct atomic weights and the correct molecular formulas of compounds might well have been adopted by chemists and physicists throughout the world shortly after the publication of his third and fourth papers on this question, in 1821. We may ask the question: Why was the acceptance of Avogadro's system delayed for nearly 40 years, until Gerhardt and Cannizzaro presented Avogadro's arguments again, in a forceful way?

If Avogadro's ideas had been accepted in 1821, the history of chemistry, and the history of the world too, would without doubt have been much different. I am sure that within a few years of using the correct molecular formulas some chemist would have introduced the idea of the chemical bond, some chemist would have recognized that carbon is quadrivalent, some chemist would have begun to write structural formulas for organic substances—that it would not have been left for Frankland, Kekulé, and Couper to do this in the years 1852 to 1855. With the development of structural chemistry at this early time, chemists would have been stimulated to carry on many original investigations, as they were in the years following 1855. Someone else than van't Hoff and LeBel would have discovered the tetrahedral arrangement in space of four single bonds formed by a carbon atom, someone else than Werner would have discovered the coordination polyhedra of inorganic complexes.

It cannot be contended that Avogadro's ideas were not clearly expressed in his 1811 paper and the later papers. His argument in these papers is presented in a straightforward and logical way. His ideas are clearly expressed.

The suggestion has been made that Avogadro was such a modest man that he did not think that it would be proper for him to strive to obtain the acceptance of his ideas by other scientists. I have formed the opinion, from reading his papers, that this suggestion is not correct. Avogadro may well have been a modest man; but he was not restrained by his modesty from making a vigorous attempt to convince his fellow-scientists about the correctness of his hypothesis and of the system of atomic weights and molecular formulas that he had built with its use. Every few years throughout his life he published a paper devoted wholly or in part to the discussion of this matter.

For example, in the third of his six long papers on atomic volumes, published in 1843, he begins with a statement that he had a long time ago (1811, 1814, 1821, 1824, and later years) presented arguments showing that equal volumes of gases of different substances, under the same conditions of temperature and pressure and sufficiently removed from their condensation temperatures, contain the same number of molecules. He goes on to say "Ce principe est aujourd'hui assez généralement admis, ou explicitement ou implicitement, par les physiciens and les chimistes." In 1838 he had published a very clear discussion of his hypothesis, in 38 pages, in his four-volume book on the physics of ponderable bodies. In 1840 he gave a discussion "Sul principio che volumi eguali di gas contengono egual numero di atomi." In 1849 he published in the *Archives des sciences physiques et naturelles* (Geneva) [**11**, 285] a note about atomic volumes in which he stated again that his postulate must be accepted, in order to explain the results about combining volumes obtained by Gay-Lussac, and that indeed the hypothesis had been accepted by all physicists and chemists who make application of the theory.

Perhaps Avogadro himself was in part responsible for the delay in the acceptance of his ideas. First, I think that Avogadro could not imagine how great the value of his discovery was. We now can see, in retrospect, that almost the whole of the development of the science of chemistry has followed from the acceptance of the correct atomic weights and the subsequent development of chemical structure theory. It would have been difficult, however, to have foretold the course of events. If Avogadro could have foreseen how important his hypothesis would be in the history of science he would, I am sure, have devoted himself wholeheartedly to this field of work, and to the effort to obtain general acceptance of his system. Instead, he made a vigorous effort to understand the densities of substances in the liquid and solid states of aggregation. His extensive work along these lines has turned out to have little value. This work is described in six papers, totalling 680 pages, published in the years between 1826 and 1852.

I should like to compare the argument used by Avogadro in the discussion of his hypothesis about gases and that used in his discussion of molecular volumes in solids. In his discussion of gases he pointed out that there are two alternative explanations of the Gay-Lussac law of combining volumes. The first is that equal volumes of gases of different substances under the same conditions contain the same number of molecules. The second is that equal volumes of gases of different substances contain numbers of molecules that are in the ratio of small whole numbers; that is, that some molecules occupy twice or three times as large a volume as others. Avogadro considered that it was unreasonable that molecules of different kinds should occupy different volumes that were nearly exactly in the ratios of small integers to one another, and that accordingly it was reasonable to accept the first explanation. This is Avogadro's hypothesis, which is, of course, now called Avogadro's law.

However, for a reason that is discussed in his papers but that is far from convincing, he adopted essentially the second alternative in treating the molecular volumes of solids.

It is evident that Avogadro was a man with an intense curiosity about nature. He believed that a scientist should try to *understand* the world, and should not be content to tabulate the results of experiments—that is, simply to *describe* the world. For example, in his paper of 1843 on molecular volumes he discusses the work of Hermann Kopp. Kopp had calculated the atomic volumes of the elements, by dividing the atomic weights (as given by Berzelius) by the densities of the solid or liquid substances. The values that he obtained, corrected to the system of atomic weights of Avogadro, differed widely from one element to another. Avogadro says that Kopp did not try to *explain* the fact that the atomic volumes of different elements are different. All of Avogadro's work was an effort to explain the world.

In his effort to obtain a systematization of the densities of solid and liquid substances he rejected the hypothesis that atoms of the elements have essentially constant volumes, so that the molecular volume of a condensed substance may be expressed as the sum of the atomic volumes. Instead, he made the hypothesis, obviously suggested by his hypothesis for gases, that all molecules of solid and liquid substances have essentially the same volume, but that some deviations are shown from the standard molecular volume, as determined by the nature of the molecules. In particular he attempted to correlate the molecular volumes of substances with their electronegativities.

The soundness of Avogadro's intuition is evident. There is no doubt that many of the properties of compound substances are determined by the difference in electronegativity of the elements composing the substances. The modern electronegativity scale of the elements was formulated from the heats of formation of compound substances in which the bonds are single bonds. Schomaker and Stevenson have pointed out that the interatomic distances of pairs of elements are determined to some extent by their difference in electronegativity. If Avogadro had accepted the idea that molecular volumes may be represented approximately as a sum of atomic volumes, he might well have used this starting point, and have introduced a refinement involving a correction determined by the electronegativities of the elements.

Instead, however, he preferred to make the postulate of a standard molecular volume. He soon found, of course, that the molecular volumes, as calculated by taking the molecular weights of substances in the gas phase and dividing them by the density in the liquid or solid state, showed great variations, and no correlation with electronegativity or electropositivity of the substances. He then made a decision that was unfortunate. He decided to assume that the molecules in solids or liquids either might be identical with the corresponding gas molecules or might be different in size: one-half as great, or one-quarter, or one-eighth, or perhaps twice as great, or three times. This assumption permitted him to introduce an arbitrary factor (a small integer or a simple fraction) for each substance. He introduced this factor in such a way as to obtain corrected molecular volumes that could be correlated with the electronegativities of the substances or with the heat capacities or some other physical property.

The degree of success achieved by Avogadro is indicated by the table in his 1843 paper. In this table values are given of the atomic volumes for 25 elements, in the solid or liquid state. The atomic volumes cover a range from 0.4 to 1.5, and the elements arranged in order of atomic volumes, as calculated by Avogadro, are also roughly in the order of their electronegativity, beginning with chlorine and ending with sodium. Avogadro obtained this correlation, however, by taking for chlorine an atomic weight one-quarter as great as that corresponding to the formula Cl_2 for the gas, and for other elements values one-quarter, one-half, or twice the standard atomic weights. For example, he obtained nearly the same atomic volumes for sodium and potassium, as solid substances, but only by the device of taking the atomic weight of potassium one-half as great as the correct atomic weight.

Why did this clear-headed, imaginative, and able scientist make this assumption, which seems to us to be unreasonable? I think that we must remember that chemical theory was in a confused state 130 years ago. The idea that atoms of different substances have different combining powers, valences, had not yet been formulated. The concept of valence involves the introduction of integers, one, two, three, four, five, six, describing a difference in behavior of different elements. An indication of valence was provided by the difference between the chemical equivalents of substances and their atomic weights. Small integers were involved in formulas such as H_2O, CO_2, NH_3. I think that Avogadro was searching for some way to introduce a new set of small integers into chemistry, and that he had the misfortune to select a wrong way of doing it.

Nevertheless, even though Avogadro's studies on molecular volumes, acidity and alkalinity, heat capacity, and other properties of substances were unsuccessful, he was attempting to follow a procedure that has been valuable throughout the development of chemistry, and that permitted him, in his formulation of his hypothesis for gases, to make one of the greatest contributions to chemistry that has ever been made. This is the procedure of formulating an imaginative, new principle, in the effort to bring the facts of chemistry, discovered by experiment and observation, into a system. The hypothesis that Avogadro made about molecular volumes of solids turned out to have no value. In fact, by suggesting that the molecules of a gas may split into smaller molecules when the substance condenses to a liquid or solid, Avogadro may well have helped to confuse his fellow-scientists about the significance and reality of the gas molecules, and have helped to postpone the general acceptance of his postulate about gases and his system of atomic weights and chemical formulas.

There seems to be no doubt about Avogadro's own convictions. Even in his papers on molecular volumes in solids he mentions from time to time the use of gas densities in order to determine the *correct* molecular formulas of substances, and he almost always uses, in these early papers, the formulas that are now accepted as the correct ones.

While reading the papers by Avogadro on molecular volumes of solids, I have been led to make a comparison between this unsuccessful effort by Avogadro to understand the properties of solid substances and my own effort, during the last 20 years, to understand the properties of metals and alloys. I ask that you allow me to refer briefly to this effort.

It is well known that, long after the structure theory of organic chemistry had been developed, beginning 100 years ago, and the structure theory of general inorganic chemistry had been developed, especially in the period around 50 years ago, no chemical theory of metals and alloys had yet been formulated. In 1938 I published a paper on the valences of metals and the structure of intermetallic compounds. In this paper and succeeding ones there has been described a chemical theory of metals and alloys.

One might say that chemistry has now been swallowed by the physicists, through the development of quantum mechanics. Dirac said, some time ago, that the Schrödinger equation encompasses the whole of chemistry. It is true that theoretical physicists have attempted to describe metals and alloys by use of approximate solutions of the Schrödinger wave equation. They have found, however, that the job of solving the Schrödinger equation for a metal or alloy is such a difficult one that it cannot be carried out with much accuracy, and I believe that there is still room in this field for the application of the old chemical procedure, that of attempting to obtain by induction, from a great mass of experimental facts, a simple empirical theory that compasses these facts. This is what Avogadro was trying to do in his discussion of the molecular volumes of solids.

In my discussion of metals and intermetallic compounds I was led to assign metallic valences to metals that seem strange. For example, iron, cobalt, and nickel were assigned the metallic valence 6, as were also chromium and manganese. The valence 6 for chromium is, of course, a reasonable one—this is one of the standard oxidation states of chromium. Also, 6 may not be unreasonable for manganese. But iron, cobalt, and nickel usually have smaller oxidation numbers in their compounds, and the valence 6 may be considered to be surprising.

Still more surprising is the result of the consideration of the properties of copper and zinc, as metals and in intermetallic compounds. Copper in its ordinary compounds is assigned the oxidation number $+1$ or $+2$, and zinc always has oxidation number $+2$. In metallic copper and metallic zinc the valences of these elements are indicated to be $5\frac{1}{2}$ and $4\frac{1}{2}$, respectively. Similarly gallium is assigned the metallic valence $3\frac{1}{2}$, and tin, the congener of germanium, has the valence $2\frac{1}{2}$ in the metallic form, white tin.

Moreover, in connection with these valences, the postulate was made, as an explanation of them, that there is one orbital, or, rather, three-quarters of an orbital, for each atom in a metal that serves some special purpose, and is not to be assigned electrons in the usual counting up of orbitals. This orbital is called the metallic orbital. That a metal must have about three-quarters of a metallic orbital per atom in order to have metallic properties is a pure postulate, indicated by some facts, by some properties of metals, but not derived from the Schrödinger equation or from any other theory. This postulate of the metallic orbital may be compared with the postulate that Avogadro made, that the molecules in solids are one-quarter or one-half as big, or perhaps twice as big, as the molecules in gases. Avogadro was led to this incorrect postulate by the success of his gas-volume postulate. I have been led to apply ideas about valence to metals by the success of valence theory in organic chemistry and ordinary inorganic chemistry.

I do not know whether the system of metallic valences that I have formulated, and the postulate of the metallic orbital too, will have the same fate as Avogadro's assumption about molecular volumes of solids. Perhaps someone will think of a completely new way of handling the problem of the structure of metals and alloys. Perhaps the idea of valence should not be extended from the compounds of organic chemistry and ordinary inorganic chemistry to metals and intermetallic compounds. Nevertheless, I feel that there is still reason to attempt to apply the old methods of argument that have been used by chemists especially, including Avogadro, during the past 200 years, in an effort to discover laws of nature by induction from a great mass of experimental and observational information.

Avogadro was a great man. He was a thinker—a man who tried to understand the world.

Although he seems to have departed from the faith in being willing to split molecules in solids, I think that Avogadro really believed in molecules. In 1839 he gave a clear discussion of isomerism in terms of molecular structure. He described two isomers as substances which present different arrangements of the atoms out of which their molecules are formed. It is unfortunate that he was not led by considerations of this sort to ask what the forces are that hold the atoms together.

A description that he gave of a molecule in 1849 seems almost modern. He wrote: "It seems to me that one can think of the combination of several atoms of different kinds only as their union into a single molecule, in which one can no longer distinguish the parts of the volume that belong to the individual atoms. The atmospheres of imponderable bodies that surround the atoms in the separated state, and that hold them at a certain distance from one another, and thus determine the volume, should interpenetrate and become combined, in such a way as to form only a single atmosphere for the entire molecule, surrounding the individual atoms, and bringing them rather closer together than are the resultant molecules themselves, and thus determining the molecular volume of compounds." This sounds much like a modern description of a molecule, with imponderable bodies replaced by electron clouds.

I do not know whether Avogadro would be happy in the modern world, or unhappy. Chemists know too much now; perhaps we should say that physicists have discovered too much. It is hard for a chemist now to find a part of chemistry where hypotheses, chemical hypotheses, can be made. I almost feel that Schrödinger did the chemist a disservice when he developed the wave equation. But biology still offers a great opportunity for theoretical discovery, for the development of new hypotheses. Perhaps Avogadro, if he were living now, would be trying to think of a new Avogadro's hypothesis, a hypothesis relating to the gene, perhaps, to enzymes, to viruses, to the nature of life.

We are fortunate in having the example of Avogadro and the hypothesis that he made in 1811, to show us clearly how great is the value of hypothesis in science.

LINUS PAULING
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena

---

A. J. Carlson

The death of A. J. Carlson on Sunday morning, 2 September 1956, in Chicago, was not a surprise to anyone who knew of his illness but was a shock to everyone acquainted with him. A man so strong in body and soul, so permanent in his influence, so timeless in his outlook, partook sufficiently of the stuff of immortality to seem to belie a vulnerability to disease and death.

Appropriate though the appellation "Ajax" may have seemed, I somehow never much fancied it. Perhaps it was because Homer's Ajax, the embodiment of strength and courage, was yet second to another—Achilles—in these attributes. Dr. Carlson had no Achilles. I preferred "Carlson," a common enough name but one encompassing all strength and courage, dignity and distinction. In any academic or scientific gathering, there was never any doubt about the identity of "Carlson."

Strong and *powerful* are words that belong to Dr. Carlson. His powerful physique supported an intensely active life of full 81 years. His sturdy integrity knew no compromise with the right and the good. His strong mind cut straight through to the truth. But with all his strength, he relentlessly fought the abuse of power. Tyranny was his enemy, whether it was economic or political, scientific or academic.

He lent his strength where it was needed. At whatever session of a scientific meeting one of his graduate students appeared on the program, Dr. Carlson was sure to be on hand, usually in the front row, to encourage and support. Woe betide the unfair critic who rose to an unwarranted attack upon the graduate student's paper.

Behind an austere or even forbidding aspect, Dr. Carlson was a staunch friend; he was loyal, warm, encouraging, inspiriting to his graduate students. His conscience about teaching was boundless, almost a religion. He wanted everyone to understand something about man's body in health and disease. Scores and hundreds of medical students remember Carlson as the greatest influence in their scientific experience. He was a superb teacher of college freshmen, whose instruction he was unwilling to relegate to junior staff members.

Unerringly, he could place a finger and say of a research project, a reasoned argument, a conclusion drawn, "thou ailest here, and here, and here." His penetrating incisiveness was liberally peppered with a ready wit.

His prodigious work-drive, guided by a disciplined intellect and fired with imagination, shed new light upon the operation of virtually every organ and system of the body. Nerve conduction, the heartbeat, digestion, hunger, thirst, thyroid function, diabetes, lymph formation, nutrition, the parathyroid glands, salivary secretion, and a score more, in