

THE TRANSITION FROM CRYSTALLOID TO COLLOID PROPERTIES WITHIN HOMOLOGOUS SERIES

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The properties of colloidal and crystalloidal solutions are generally discussed from the standpoint of their differences and less frequently from the standpoint of their similarities.² The former is done for convenience in presentation; the latter because they really are quite similar and as Einstein emphasized in a mathematical treatment of the subject,³ there is a gradual transition from crystalloid to colloid properties. There is in living organisms a special case of gradual transition from crystalloid to colloid properties within homologous series. This transition is not static but represents a dynamic equilibrium which is, so far, largely peculiar to the living organism and which seems to be an indispensable characteristic of life as we know it.

The biological aspects of the general problem of colloidal transition fall apart into three considerations.

(1) The factors that influence this transition in general with a given group of compounds.

(2) The condensation \rightleftharpoons hydrolysis equilibrium by which the transition is made from one end of the series to the other.

(3) The biological factors that sensitize and speed up this equilibrium.

In this paper we shall discuss this problem of transition mainly with respect to the first of these considerations in order to determine whether the relations involved can be considered in simple terms of chemical constitution, for instance. It seemed likely that to consider all solutions as a continuity would aid eventually in understanding certain aspects of many

¹ Contribution from the Otho S. S. Sprague Memorial Institute, Rush Medical College, Chicago, Ill.

² Zsigmondy-Spear: "Chemistry of Colloids," p. 23 (1917).

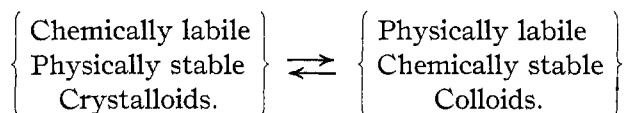
³ Einstein: Ann. Phys., (4) **17**, 549 (1905); **19**, 371 (1906); Zeit. Elektrochemie, **14**, 235 (1908).

biological problems such as diabetes mellitus for instance in which the organism can convert a colloid (starch) into a crystalloid (glucose) but cannot get it back again into the colloid state (glycogen) adequately.

The main components of living organisms (other than water) are the so-called biocolloids (lipoids, carbohydrates and proteins) and the simple molecules or crystalloids of which they are built up. These biocolloids as a group differ from other colloids in the degree to which they show certain typical characteristics of colloids. For instance they are in general more completely reversible than most other colloids. In fact they show two interesting kinds of reversibility.

(1) These colloids as a group may be taken out of or put into colloid-solution as often as desired, and in general if nothing is done to them that is incompatible with the life of the organism from which they are derived, they show little tendency to become irreversible. In any case the biocolloids are the type substances of the reversible colloids.

(2) In the living organism they exhibit a tremendous capacity for reversibility of the equilibrium represented thus:



A large portion of the physical chemical philosophy of the cell is graphically summarized in this equilibrium. The chemical processes of life take place in chemically stable colloidal systems built up from crystalloids by virtue of chemical transformations of other portions of the same crystalloids.

The formulation of this reversible equilibrium visualizes some interesting paradoxical situations. Both sides contribute indispensably to the joint result—namely, life—but from the viewpoint of either side of the equation the material on the other side is playing a passive rôle. Its effects are indirect. Assigning “social” attributes to the molecules in question we have here a kind of chemical “altruism.” Moreover the system contains both a dilute and concentrated solution since the

discontinuous phase contains a lower concentration of water (in biological systems) than the continuous phase. Therefore if condensation reactions thrive best in the more concentrated phase hydrolytic reactions should thrive best in the other. This discontinuity moreover gives rise to a differentiation in the energy components of the two phases the full consequences of which are yet to be appreciated and concerning which more will be said below.

These two types of reversibility so important to the chemical organization of life seem to fit these biocolloids peculiarly for their rôle in life processes as we know them. The chemist cannot aid materially in the dynamic interpretation of these processes until he can connect these two groups of spontaneous effects with the properties of the compounds in question and at the same time formulate his interpretation so that these transformations are seen to take place in accordance with the known principles of thermodynamics. Recent experience in the interpretation of the transformations of colloidal manganese dioxide¹ on the basis of equilibria sensitive to changes in temperature, in concentration and in the nature of the reagents suggested that perhaps the transition from crystalloid to colloid properties and *vice versa*, considered above, could be interpreted on the basis of chemical constitution. The results of such an inquiry are briefly stated in what follows.

The Fatty Acids

The commonest biocolloids constitute three complex homologous series—namely, the fats, carbohydrates and proteins—all of which are homogeneous or heterogeneous in their chemical components. For the sake of definiteness and simplicity it will be best to consider the fats first and these preferably in the form of their sodium and potassium soaps or salts. These compounds have the simplest chemical structure and within a truly homologous series show a strikingly definite transition from simple crystalloid qualities, in the lower members, to definite colloid properties in the higher members. The

¹ Jour. Am. Chem. Soc., 35, 1079 (1915); 39, 25 (1917).

main facts concerning this series will be recalled in connection with the brief review given in the following paragraphs.

(1) It is well known that after butyric acid the fatty acids rapidly become increasingly insoluble in water. Thus from complete miscibility in water for the lower acids there is a gradual passage to almost complete insolubility and immiscibility in the higher members.

(2) On the contrary the sodium and potassium salts of fatty acids are much more soluble, except the lowest members of the series, than the corresponding free acids. With increasing molecular weight the aqueous solutions tend to become more and more colloidal. Here, too, we have a gradually decreasing miscibility with increasing molecular weight manifested in a somewhat different way.¹ Thus the substitution of the hydrogen atom in the carboxyl group with potassium or sodium increases the range of solubility of the fatty acids and increases their capacity to take up water in the case of the higher acids in which colloidal solutions are formed.

(3) If we accept the main idea of the solvate theory of solution, namely, that solvent and solute interact in some way, then in the case of the fatty acid series the introduction of sodium or potassium in the carboxyl group increases the affinity of the molecule for water. Since a fatty acid is a constant (the carboxyl group) attached to a variable (the hydrocarbon group) it would obviously be unreasonable to expect the entire series of soaps to interact with water in exactly the same way. Now it is well known that water forms hydrates with formic and acetic acids and the alkali salts of lower fatty acids;² but the idea that these hydrates vary in complexity and stability for different fatty acids has not been much used as a working conception. Thus the long-known anomalous volatility of the lower fatty acids³ on distilling dilute aqueous solu-

¹ Cf., for instance, Mayer, Schaeffer and Terroine: *Comptes rendus*, **146**, 484 (1908).

² Jones: *Carnegie Inst. Publications*, No. **210** (1915); Cf. summary and list of earlier publications at the end. Turner: "Molecular Association" (1915).

³ Duclaux: *Ann. Chim. Phys.*, **2**, 289 (1874).

tions had no simple rational interpretation until recently the principle of decreasing stability of the fatty acid hydrates with increasing hydrocarbon function was used to supply one.¹

(4) The idea that these compounds interact with the solvent is supported by many well-known lines of evidence only a few of which will be mentioned.

If the growing insolubility of the acids in water is due to the increasing significance of the hydrocarbon function and this group and the carboxyl act in an opposite sense on the solubility as may be concluded from much data in the literature² then the substitution of hydrogen in water with hydrocarbon groups should increase the solubility of fatty acids in the solvent. Now it is well known that soaps and fatty acids give true solutions with alcohols to a higher point in the series and to higher concentrations than they do with water. Moreover if the presence of the hydroxyl group in water is associated with the favorable effect of the carboxyl group on the solubility of the fatty acid, then the introduction of hydroxyl groups in the hydrocarbon group of a higher fatty acid should favor solubility of the fatty acid in water. That the hydroxy fatty acids are more soluble and interact more strongly with water is well known.

Other effects of the hydrocarbon depending on the character of the carbon chain, the number of carbon atoms in it and the position of the substituents, all have marked influences upon the solubility, but these factors do not modify the minimal statements given above concerning the influence of the two component groups of a fatty acid upon its general behavior toward water.

Physical and Chemical Theories of Solution

In order to make this discussion of the problem of the transition from crystalloid to colloid properties within a homologous series concrete it seems necessary to compromise the immortal controversy between the physical and chemical

¹ Witzemann: Jour. Am. Chem. Soc., **41**, 1946 (1919).

² For example cf. Auwers: Zeit. phys. Chem., **42**, 542 (1902).

theories of solution.¹ After what was said in the preceding paragraphs it seems clear that whether the one or the other theory most nearly expresses the facts will depend upon the chemical constitution of the solvent and the solute in question. Thus hydrocarbons in hydrocarbons give solutions in which the two components of the two systems of molecules differ quantitatively in composition but not qualitatively. We should here expect a minimum of chemical interaction and many of the properties of the solution should represent the algebraic sum of those of the components. Such solutions would best conform with physical theories. With water and hydrocarbons we have no chemical resemblance and have no way of knowing *a priori* how these two substances will interact. Having found that they do not interact to form a solution we have two possible ways of modifying the mixture in order to attain solubility. We may chemically make the hydrocarbon more like water by putting a carboxyl or hydroxyl group into its molecule or we may make the water more like hydrocarbon by replacing a hydrogen atom with a hydrocarbon group. Both systems now interact and will conform more or less closely with the physical or chemical theory of a solution depending upon the nature of the groups involved, *i. e.*, in which component the concession to the chemical constitution of the other was made.

As a qualitative statement the above is probably generally accepted. The difficulties arise in attempting to apply quantitative definitions and are partly due to the fact that our qualitative conceptions are not yet sufficiently clear. Moreover there is a tendency to set up discontinuities in our consideration of these phenomena where gradual transitions only exist. In this way imaginary boundaries are set up which we find ourselves more reluctant to cross as the data in the two fields multiply.

¹ Cf. P. Walden; "Die Lösungstheorien in ihrer geschichtlichen Aufeinanderfolge," Ahrens Sammlung Chem. u. Chem.-Techn. Vorträge, 15, Nos. 8-18 (1910).

In a recent study of water in the state of vapor, Oddo¹ pointed out that the more rarefied water vapor becomes, or the lower the vapor pressure, the greater the percentage of water dissociated into H^+ and OH^- ions. On the other hand Oddo also found that after a certain vapor pressure was attained the percentage of ionic dissociation continues to decrease but that the percentage of molecular association rapidly increases. Oddo concluded that it seems that nature likes about so many particles of the constituents of water in a given volume and tends to break them apart or double them up in the attempt to maintain this number.

Jones² observed similar effects with mixtures of alcohol and water and acetic acid and water.

"An associated liquid tears down the molecules of an electrolyte dissolved in it, into simpler parts or ions; and it might be expected that such a liquid would tear down molecules of another associated liquid, a nonelectrolyte, not into charged parts or ions, but into simpler molecules. Alcohol and water are associated liquids, as has been shown by the surface tension method of Ramsay and Shields. Do these diminish the association of one another?

"That this is the case was shown by Murray.³ He worked with associated liquids, water, formic and acetic acids. He determined the molecular weight of each of these liquids in the other two and found that the molecular weight became smaller the more dilute the solutions. This showed that the solvent, i. e., the liquid present in the larger quantity, was tearing down the molecular complexes of the dissolved liquid or the one present in the smaller quantity."

Application of Le Chatelier's Principle

The above graphic statements of Oddo and Jones seem to resemble the qualitative statement of the second law of Thermodynamics known by chemists as the Theorem of Le Cha-

¹ Gazz. chim. ital., **45** I, 319 (1915).

² Carnegie Inst. Washington Pub., No. **210**, 163 (1915).

³ Am. Chem. Jour., **30**, 193 (1903).

telier, by physicists as the Theorem of De Maupertuis or the Principle of Least Action, by biologists as the Law of the Survival of the Fittest, and by economists as the Law of Supply and Demand.¹ If this apparently universal principle governing natural phenomena can be adequately applied to a formulation of the phenomena of true and colloidal solution it would constitute a simplification of the problem and an advance at the same time. The example cited by Jones will serve to discuss the proposition concretely and thus to test the applicability of this Principle of Le Chatelier of the problem of solution.

Pure liquid acetic acid and liquid water are largely dimolecular. When a little of the acid is dissolved in the water dimolecular acid and water break up and acetic acid hydrate is one of the products. The total number of dimolecular molecules is less than the sum of the dimolecular molecules originally present in the two component liquids. This distribution of acetic acid in water thus really involves two effects. (1) It involves the tendency on the part of the acid to distribute itself in the volume available as though it alone were present. This involves the breaking up of some associated molecules and some ionic dissociation analogous to what Oddo pictured for water. (2) It involves the interaction of these components of the acid system with the components of the water already present and this involves the formation of the various ion and molecule hydrates. The whole system of changes can be expressed in a series of equilibria² and the final condition of the system undoubtedly conforms with the Second Law of Thermodynamics, of which Le Chatelier's Principle is the qualitative statement.

When additional acid is added, the whole cycle of changes and adjustments is repeated until presently enough acid has been added so that it becomes obvious from molecular weight determinations such as those cited above that a smaller

¹ Paraphrased from a paper by W. D. Bancroft: *Jour. Am. Chem. Soc.*, **33**, 91 (1911).

² Cf., for instance, Witzemann: *Jour. Am. Chem. Soc.*, **39**, 25 (1917).

proportion of dimolecular acetic acid molecules is now being broken up. Into such a solution we could pass monomolecular acetic acid vapor and find it in the aqueous solution largely as dimolecular acid. Such a solution presents three kinds of acetic acid—ionized acid, monomolecular acid, and dimolecular acid—all in equilibrium with each other. The system is a completely reversible and reproducible one and may be prepared from any of the three acid components and water by adjusting the concentration of the water. Whether all three kinds of acid were present in the solution when equilibrium was attained after the first addition is probably not certainly known, but that as the concentration increases the dimolecular kind of acid increases faster than the other two kinds is clearly indicated by much experimental data. Since all of these kinds of acid are freely soluble in water the system is commonly considered to be homogenous. That it is not truly homogeneous is obvious.

The particular heterogeneity in which we are interested at this point is that involved in the formation of dimolecular acid from and in the presence of monomolecular acid within the aqueous solution. Here we have the spontaneous formation of a more condensed system within a less condensed one. Or using colloid chemical terminology a discontinuous phase (or concentrated solution of the colloidal substance) within a continuous phase (a dilute solution of the colloidal substance in the solvent). What may appear to be an unimportant distinction in the case of acetic acid as discussed ceases to be so if we take the sodium or potassium salts of the lower and higher fatty acids as well. One of the best-known facts of colloid chemistry is the fact that in passing up this series the significance of the ionized and monomolecular molecules diminishes more and more while the typical colloidal polymolecular molecules dominate more and more. Here we have developed for identical molecular concentrations of various salts the series of effects observed with variable concentrations of acetic acid.

The discussion in the preceding paragraphs confirms the

impression that the process of formation of both true and colloidal solutions, although not understood in its details, is obviously amenable to Le Chatelier's Principle. The molecular state of the fatty acids and their salts in solution presents no sharp break but rather a gradual transition from a less obvious to a more obvious heterogeneity. This change is seen to coincide with the increase in the hydrocarbon function of the molecule and since the other chemical function (carboxyl) is constant for the series the change must be definitely attributed to the constitutive influence of the hydrocarbon group. Consequently the decreasing dispersibility of these higher fatty acid salts is to be attributed to the increasing hydrocarbon function. Because of the chemical simplicity and stability of this group these salts and their derivatives should be expected to play the important biological rôle that they do.

Differentiation of Energy in the Two Phases

The fact that the soaps are not uniformly dispersed in aqueous solution but that the solution represents a concentrated solution suspended in a dilute one gives rise to an unequal distribution of energy between the two phases of the solution. The situation from the standpoint of energy is analogous to the behavior of compressed carbon dioxide. When the pressure is released the kinetically cool gas escapes into a warmer atmosphere. In expanding a portion of the gas is heated while the remainder is cooled. The end products are relatively warm carbon dioxide gas and cold carbon dioxide snow. A marked heterogeneity in the energy content of carbon dioxide was produced on releasing the relatively homogenous carbon dioxide into a similarly homogeneous atmosphere. A singularly parallel stepping up and down of the energy content of the component molecules of a quantity of soap occurs when it is dispersed in water. In the case of soap, however, we obtain a differentiated system that is stable in comparison with the carbon dioxide system. Since differentiation of heat energy content as in the case of carbon dioxide gives rise to unstable systems in which energy equalization occurs rapidly

if unhindered, it is obvious that the energy differentiation induced in these colloidal systems involves other kinds of energy than heat energy. The electrically charged colloidal particles (in so far as they are not due to ions) and the surface energies so pronounced in the colloidal state represent at least two known types of differentiation of other energies that are involved here.

This heterogeneity of energy distribution in colloids is conditioned by the orientation of the molecules within the system as a whole and manifests itself as surface energy only at the boundaries of the phases, as is shown by the interesting results of Harkins¹ for instance. These effects are particularly striking with simple compounds like the alkali soaps, the molecules of which have two ends of widely different chemical constitution. The same type of orientation probably is not conspicuous in the polysaccharides and proteins in which the active groups substituted in the hydrocarbon residues are rather evenly distributed through the large molecule.

Since the amount and kind of energy in the environment of molecules is an important factor in determining chemical reactivity, it is clear that such spontaneous differentiations of energies in colloidal systems would be desirable in the chemical organization of life because it would contribute so much to the chemical versatility of the organism. To have chemically cold, moderate and hot regions within submicroscopic distances of each other would be a great engineering advantage when the diversity of the chemical needs and processes of an organism are considered.

In summarizing for the fatty acid series we may say that increasing hydrocarbon function in this series gives rise to an increasing tendency to form two solutions in water at the same time (a concentrated and a dilute one) and that this material differentiation is associated with a differentiation in the amounts and kinds of energy present in the two phases of the

¹ Jour. Am. Chem. Soc., 39, 541 (1917).

solution. Moreover it is clear that these transformations are taking place in accordance with Le Chatelier's Principle. Such characteristics as these, together with the fact that these systems are self-reproducing from the components, admirably fit these compounds as biocolloids.

The Biocolloids Proper

In the above we have traced the transition from crystalloid to colloid properties in a simple homologous series of compounds. The even more typical biocolloids such as the hexose—polysaccharide series and the amino acid—polypeptide—protein series are not so simply constituted.

Both series are built by condensation reactions from simple crystalloids and thus show the same gradual transition from crystalloid to even more characteristic colloidal properties than are observed with the soaps, in passing up the series. Both series may be considered as substituted hydrocarbons and their differences may be ascribed to the degree and nature of this substitution. In the carbohydrate series the substitution consists mainly in OH groups and the compounds of the entire series are in general feebly acid in nature and generally not highly reactive chemically except under special chemical conditions. The proteins on the other hand are built up of crystalloid components in which the basic amino group balances the acid carboxyl group. When the protein molecule is synthesized from a variety of these compounds with a hexose, purine, phosphoric acid molecule, etc., introduced here and there we have *a priori* a system that will be chemically temperamental or stable, depending upon the quantitative chemical nature of its environment.

The constitutional reason for the colloidal state in the higher carbohydrates and proteins is not exactly the same as that given in the case of soaps. In the soaps we had but two groups—the hydrocarbon and the carboxyl groups—which, according to Auwers' classification of groups with reference to their effects upon molecular association,¹ have an opposite

¹ Zeit. phys. Chem., 42, 542 (1902).

effect upon molecular association of compounds in which they are substituted. In this series the increasing hydrocarbon function acts to decrease the affinity of the fatty acid for water and to increase its affinity for molecules of its own kind. In the case of the carbohydrates the increasing function is approximately CHOH of which group the OH , according to Auwers' classification, has distinct tendencies to facilitate molecular combination with other OH containing compounds, such as water. We therefore have greater solubility of the carbohydrate compounds than is shown by the corresponding hydrocarbons. That starch and cellulose are not freely soluble in water, however, shows that an unlimited number of OH groups does not secure unlimited solubility. In fact the facts in this connection are perhaps the best proof that the solvent interacts with the solute. It is a well-known fact that polyhydroxy compounds have a tendency to undergo condensation reactions by which two molecules react with the splitting out of a molecule of water giving rise to many simple and mixed complexes. Such condensations are however not limited to the kind just described. Anhydrides of some of these compounds are under some conditions more easily formed than the condensation products mentioned above. This is particularly true with γ -hydroxyorganic acids which give lactones so easily. The known chemistry of cellulose, for instance, is at present best explained by considering it as an anhydride of the γ -oxido form of glucose.¹ Compounds that so readily give rise to lactones and inner anhydrides have little tendency to add water at these points. In interacting with water they have a greater tendency to interact by means of their free OH groups to form hydrates than to add water at the anhydride oxygen rings and linkings. That is, the secondary valences of oxygen are more unsaturated toward water under these conditions than the anhydride linkages.

The same problem may be considered concretely in another way. The polysaccharide molecular complex contains many

¹ Hibbert: *Jour. Ind. Eng. Chem.*, **13**, 256, 334 (1921).

OH groups the secondary valence energy of which is saturated off by adjoining OH groups in the same complex. When this complex network of OH groups interacts with a simple set of OH groups like that of water $(\text{H}_2\text{O})_2$ the latter becomes molecularly dissociated and bound by the complex as hydration water without markedly dispersing the complex polysaccharide as a whole. Only as the final result of many such interactions with water molecules does a higher polysaccharide become dispersed in such solvents as water. Such a complex polysaccharide as starch should therefore be expected to swell and disperse slowly in water.

The process becomes still more concrete when pictured in terms of such simple electronic conceptions of valence as that of J. Stark,¹ details concerning which need not be given here.

In the protein molecule the changing functions, besides the hydrocarbon part, are the NH_2 and CO_2H residues which according to the same classification of Auwers also tend to facilitate molecular association with water. On the basis of the chemical nature of these groups the protein molecule interacts with water in some respects like the higher carbohydrates, but because the structural variety of groups in proteins is much greater the possibilities for sensitive influences become much greater. There is however no question about the gradual transition from crystalloid to colloid properties on passing up and down the series. Moreover it seems clear that if the above statements are of value in clarifying the relations in the fatty acid and carbohydrate series they are of value in the protein series although the relations are still somewhat more obscure on account of the more complex structure of these compounds and our ignorance of the influence of these various structural factors upon the properties of protein.

General Résumé

One of the most persistent problems of biological chemistry is the question as to how such chemical systems as con-

¹ Cf. P. Ruggli: *Ahrens Sammlung Chem. u. Chem.-Techn. Vorträge*, 19 (1912-3) for a review and refs.

stitute living organisms can come about. It is only as this question can be answered more or less clearly in chemical terms that the chemical dynamics of life processes become more amenable to attack with the conventional tools of chemistry. The above paragraphs constitute a partial answer to the question and state pretty clearly in terms of chemical constitution why the indispensable heterogeneity of the aqueous systems constituting living organisms exists and how it is spontaneously brought about. It is shown that the emulsoid structure of biocolloids constitutes a gross heterogeneity which is also present in a much less conspicuous form in the lower crystalloid members of the same homologous series. In this way it becomes clear that the particular properties of biocolloids arise from the cumulative effect of certain groups in the molecule. This effect of chemical constitution is especially easy to trace with the soaps and less easy with the carbohydrates and proteins.

The discussion also brings out the fact that there is associated with this material heterogeneity a well-known heterogeneity of energy. It is shown on the basis of a simple example how such heterogeneities may arise spontaneously upon releasing one system into another. The best known energy differentiation under these conditions is the much-discussed surface energy. In this discussion it appears that the surface energy phenomena in solutions are energy differentiations definitely associated with material differentiations and these in turn are due to chemical constitution and that changes in the latter necessarily involve the whole series of effects. Even the earliest students of chemical constitution knew that changes in constitution involved changes in solubility and therefore in the secondary effects of solubility. We however have been slow in following their lead particularly in considering the biocolloids.

So far as biological phenomena are concerned these two heterogeneities have in the past been regarded as associated with some vital force. But even now, when the aid of a hypothetical vital force is not so often called upon, these hetero-

geneities are frequently thought to be maintained in organisms by a constant expenditure of energy obtained from chemical reactions in the organism. Considerations developed in this paper indicate that certainly part of this heterogeneity occurring in the structure of organisms arises from a predisposition on the part of the component substances themselves to give rise to these effects. Such colloidal systems as those prepared from simple biocolloids are self-reproducing from the components: they arise spontaneously and require no unusual outlay of energy for their construction and maintenance.

Wm. Ostwald¹ has said that the two known laws of thermodynamics will take on a new comprehensiveness when we have learned to include the phenomena of biology among the data covered by what is still called thermodynamics. It is therefore particularly interesting to find that the qualitative statement of the second law known as Le Chatelier's Principle is so easily rediscovered in the phenomena of true and colloidal solutions so fundamentally involved in biological phenomena. This leads one to assert, whatever the errors made above may be, that the fundamental idea is right; since the most comprehensive statement yet developed concerning natural phenomena is so readily discovered to be operative in these phenomena of solution when the data are considered in this way.

¹ Cf., for instance, "Der energetische Imperativ," pp. 12-13 (1913).