15. *The Structure of Molecular Compounds. Part IV. Clathrate Compounds.*

By H. M. Powell.

It is shown that molecules may be firmly united to each other without the operation of strong attractive forces between them but through the enclosure of one by the other, of both by each other, or in more complex ways. The space arrangements are such that it is impossible to separate the different components without overcoming the strong attachment, *e.g.*, by hydrogen bonds of the molecules of one component only which are thus joined to form an enclosing structure around the others. The conditions of formation, the compositions, and some properties of such compounds are discussed. Among the examples given are those in which either two or more identical giant molecules interpenetrate and enclose each other, and others in which cage structures of suitable form imprison molecules of a second kind to give compounds of either fixed or variable molecular ratios. It is suggested that they should be named " clathrate " compounds (" clathratus," enclosed or protected by cross bars of a grating).

In addition to compounds whose existence is explained by the union of the components by chemical bonds of various types there are molecular compounds which do not require these bonds. In this class of compound molecules interact by attraction of their permanent dipoles, through dipole induction effects and through dispersion forces in varying degrees of importance (Briegleb, " Zwischenmolekulare Kräfte und Molekülstruktur," 1937). In crystalline molecular compounds the whole-number ratio of the two components, so far as it holds, is in part a packing effect, *i.e.*, it arises when the requirements of molecular size and shape can be satisfied by the formation of a crystalline compound containing the components in some simple ratio (Parts I and II, *J.*, **1943**, 153, 435). The present communication deals with a further general type of union which may lead to the formation of molecular compounds, sometimes of simple formula, through an association of different molecules without chemical combination in the usual senses, and although interactions of the other kinds mentioned above may play a rôle in particular cases, it is not *essential* for this type of union that there should be attraction between the molecules which are firmly held for other reasons.

A possible type of intermolecular compound formation involves the complete enclosure of a molecule by one or more molecules of another component in such a way that it cannot escape from its position unless strong forces holding its surroundings together are overcome. The enclosed molecule must then remain in association with its surroundings as firmly and as permanently as the parts of these surroundings are held to each other. This provides a means of uniting together different substances which may have very little attractive interaction. The form of enclosure required for such a compound is that of finite atomic groups or infinitely extended complexes that contain spaces of size great enough to hold a molecule of the second component. The spaces must also be bounded in such a way that escape of the enclosed molecule is prevented.

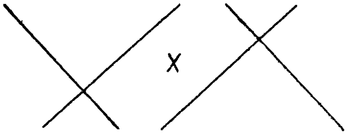
In order to determine the circumstances in which such a compound might be produced it is necessary to consider the conditions of formation of the surrounding structure which is to enclose the second component. Since it is assumed that there is to be little attraction between the enclosed and enclosing members, the compound is to be expected only when there is some special reason for the formation of the particular type of cage structure by the one component. In many materials the aggregation of the constituents is such as to give the best possible filling of space. Thus, in liquid mercury the atoms have on the average as many neighbours as possible, and many crystalline structures, *e.g.*, those of many metals, minerals, and complex ionic compounds, are formed of closest or nearly closest packed arrangements of spheres. Similarly, in many molecular crystals it is observed that molecules of very diverse shapes are arranged with the projections of one molecule fitting into the indentations of others so as to achieve a good degree of space filling; for adjacent atoms of neighbouring molecules not only are there no interatomic distances less than the van der Waals radius sum but also there are no distances greatly in excess of these equilibrium distances, *i.e.*, large vacant spaces are avoided. In molecular crystals this space filling is brought about by the residual attractions which bring the molecules to a state of lowest potential energy when the packing is as close as possible However, in structures where interatomic forces of several kinds are operative close packing may not be attained. Forces much stronger than the van der Waals attractions may impose an arrangement which is more open. Any attempt to alter the structure against these forces causes an increase of potential energy which will not be compensated by the comparatively small diminution due to a closer packing. In water the strong interaction through hydrogen atoms between one oxygen atom and its neighbours leads, owing to the directed character of the link, to a structure in which each water molecule has on the average about four neighbours only, and thus water has an open structure. For similar reasons open structures are found in the crystalline state, *e.g.*, in ice, owing to the directed OH . . . O bonds, in diamond on account of the directed tetrahedral C–C covalent bonds, and in α-resorcinol (Robertson, *Proc. Roy. Soc.*, 1936, **157**, 79) owing to a combination of two effects, the general shape of the comparatively rigid molecule as a whole and the requirement that the molecules shall be linked together through as many hydrogen bonds as there are hydroxyl groups, these hydrogen bonds being restricted to directions at approximately the tetrahedral angle to the C–O bonds.

Similarly, in ionic crystals the requirements of anion–cation contact may outweigh other effects, and for particular radius ratios may impose a structure of low co-ordination number which does not very effectively fill space.

The open structures already mentioned do not, however, enclose spaces of any great dimensions such as might contain a second atom or molecule. To obtain such large spaces it is necessary to increase the dimensions of the structural components, *i.e.*, instead of single atoms, extended groups of linked atoms must be held by strong attractive forces to their neighbours.

Some open structures result, in crystalline minerals, from the rigid form of silicon–oxygen frameworks and in the zeolites (Taylor, *Z. Krist.*, 1930, **74**, 1) there are spaces large enough to contain other loosely bound material. These spaces, however, are channels rather than complete enclosures, and the second component may be removed or interchanged for other materials since there is access to the surface of the crystals. Similar structures might be built up by use of the rigid linear metal–CN–metal sequence found in a number of complex cyanides. This may result in the formation of infinitely extended cage structures in which the cage bars have the length M–CN–M of 5 A. or more and are disposed in directions determined by the metal M, *e.g.*, octahedral M bonds may result in cube-shaped cages as probably occurs in Prussian-blue.

FIG. 1.



(*Schematic only.*) *The two molecules of arbitrary shape are imagined restricted by their neighbours to movement to right and left only. They are shown at the minimum separations possible between their projecting ends. Space is left for another small component at* X.

Structures of a more open character would result if a longer linear sequence of atoms were used as the cage bar, or if the bonds were disposed tetrahedrally around the metal to form diamond-like structures, but this does not necessarily mean that the conditions for enclosure of other molecules are thereby attained, since access to the outside of the enclosure will be made easier through a corresponding enlargement of the holes available for escape. In general, it may not be easy to construct by covalent bonds alone cages having suitable spaces combined with holes small enough to prevent escape of the other molecules that could occupy the spaces. A further difficulty is that of ensuring, in the conditions of formation of the bonds, that there is a second molecule in the right place to be trapped at the time when the cage is closed.

These difficulties may be overcome by selecting as the cage-forming components atoms covalently linked to form groups of appropriate superficial extension and binding each group firmly to its neighbours, at two or more points, by means other than covalent linkages. In two cases such an arrangement leads to inter-group cavities. In the first, the shape of the group is such that no packing can be made without this happening, as indicated schematically in Fig. 1. Rigid projecting portions of molecules or complex ions are so disposed that when closer approach is stopped by contact of these projections there remain spaces able to contain another molecule at van der Waals distances from its surroundings although these spaces cannot be used for better packing of the groups that enclose them. In the second, the packing is complicated by other conditions such as the directional requirements of hydrogen bonds linking the groups, and this may lead to cage structures similar to those resulting from covalent links alone.

This linking of the cage structure through covalencies combined with some other form of binding has many advantages. The component parts of the cage structure may be capable of separate existence as molecules or complex ions. They may be selected to be of suitable size and shape and their points of attachment to each other determined by the position of the hydrogen-bond-forming groups, or in the case of complex ions, by appropriate selection of the oppositely charged ions. Here, instead of a linear group of atoms as a cage bar, there is the whole covalently linked molecule or other group of atoms that may project over the faces of the cage. In this way large holes of exit may be blocked.

A molecule to be enclosed must be in the right place when the cage is closing and for a cavity formed without an enclosed molecule the difficulty of getting one in would be the same as that of getting it out. For a cage formed by covalencies alone it is not easy to avoid this, but if the cage structure is formed in solution or on a crystal surface by the ordered arrangement of a number of molecules or groups bound to each other at many points there will be a time before the space is completely sealed when the space is open to penetration by solvent or other solute molecules which may be present in relatively large concentration. The cage is also capable of re-opening, *e.g.*, when molecules or ions pass back into solution, and if the enclosed space is large the probability that the cage will close on an unoccupied space will be small.

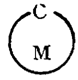
For an enclosed molecule to leave its enclosure it must overcome the attraction between itself and the cage, but even if it were possible for there to be no attraction, escape will be prevented by another process for some types of cage and enclosed molecule. When this molecule approaches a possible hole of exit its outward passage will be opposed by the repulsive forces that arise when any two atoms approach closely. These forces which are responsible for the approximate constancy of the effective atomic radii rise rapidly as atoms approach closer than the equilibrium distances. If the molecules forming the cage are subject to strong mutual attraction they will not be pushed apart readily, and if the holes of exit are sufficiently small the enclosed molecule will therefore be repelled inwards.

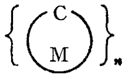
The process of escape of an enclosed molecule may be regarded as a type of dissociation reaction in which the rate of reaction depends on the activation energy. This activation energy is a measure of the work required to bring the enclosed molecule to the middle of an exit hole from which it may pass with equal ease into or out of the cage. It will vary greatly with the structural character of the molecular cage and the enclosed molecule and may be different for different holes of the same cage. For it to be high the requirements are that the escaping molecule must pass appreciably nearer than the normal van der Waals distances to the atoms forming the cagework, and it must be impossible for the component parts of the cage to be moved apart except against large resisting forces due to their attachment to each other. Whatever the precise distribution of energies among the enclosed molecules it is clear that the fraction of them having the amount necessary for escape will be very small if the activation energy is several times the average energy for the temperature concerned. In the extreme case in which all escape is effectively prevented except in conditions which destroy the cage structure a new type of compound is distinguished. The dissociation behaviour of this type of compound, once formed, is not determined by the attraction between the different molecules and the ease of dissociation bears as little relation to this attraction as the velocity of a reaction does to the affinity.

There may thus arise a structural combination of two substances which remain associated not through strong attraction between them but because strong mutual binding of the molecules of one sort only makes possible the firm enclosure of the other. It is suggested that the general character of this type of combination should be indicated by the description " clathrate " compound—" clathratus," enclosed or protected by cross bars of a grating.

For a full description the detailed structural arrangements must be given for each compound, but a convenient representation of constitution may be made by encirclement formulæ of the type (*a*), C giving the composition of the cage, M that of the enclosed component. When

(*a*.)





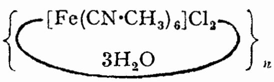
(*b*.)

the cage is an infinitely extended complex in a crystal the formula may be written as in (*b*). This method of formulation is easily extended to include other complexities as discussed below. Some examples of clathrate compounds will be described before the modes of formation, composition, and properties are considered further.

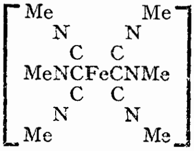
*Hexamethyl*iso*cyanidoferrous chloride trihydrate* (I). The complex ion (II) has six nearly linear $^-CN\cdot CH_3$ arms disposed octahedrally about the central iron atom. In the crystal structure (Powell and Bartindale, *J.*, 1945, 799) these ions are packed as closely as is possible in hexagonal layers with their terminal methyl groups in effective contact at 3·9 A. in any layer.

The closest packing of these layers is obtained by placing the downward-projecting arms of one complex ion to fit into the spaces between the three upward-pointing outspread arms of the ion

(I.)



$$\left\{\begin{array}{c}[\mathrm{Fe(CN{\cdot}CH_3)_6}]\mathrm{Cl_2}\\ \mathrm{3H_2O}\end{array}\right\}_n$$

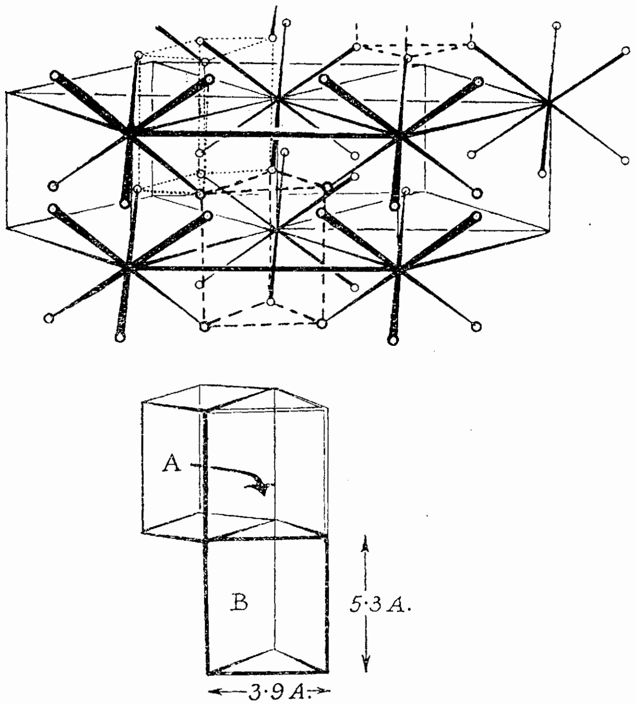


$$\left[\begin{array}{ccc}\mathrm{Me} & & \mathrm{Me}\\ \mathrm{N} & & \mathrm{N}\\ \mathrm{C} & & \mathrm{C}\\ & \mathrm{MeNCFeCNMe} & \\ \mathrm{C} & & \mathrm{C}\\ \mathrm{N} & & \mathrm{N}\\ \mathrm{Me} & & \mathrm{Me}\end{array}\right]$$

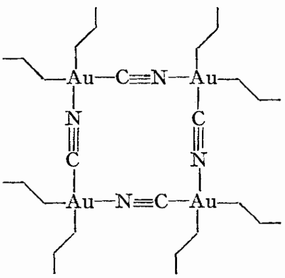
(II.)

below with a CH_3–CH_3 separation of 3·7 A. The general arrangement is shown in Fig. 2. Although it is packed as closely as possible, this complex group cannot fill the space owing to its shape, which is determined by the bond lengths and angles. It is important that the projecting portions of the molecule or complex ion that bring this about shall not be capable of rotations about single bonds in such a way that they will fold into positions that give a better packing.

FIG. 2.



Hexagonal packing of the complex ions [Fe(CNMe)$_6$]. *Small circles represent the terminal methyl groups. The spaces left when the methyl groups are in effective contact are shown by the broken lines above and in parallel positions below.*



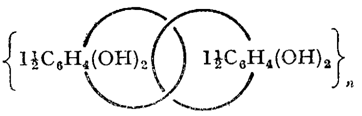
(III.)

The awkward shaped molecule (III) of di-*n*-propylmonocyanogold might be expected to give a similar open structure, but in its crystals (Phillips and Powell, *Proc. Roy. Soc.*, **1939**, *A*, **173**,

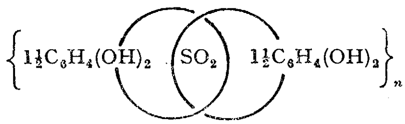
147) rotation of the propyl groups about the single bonds to the gold atoms makes it possible to form a complicated structure of low symmetry which, however, does not leave any large spaces. Such folding cannot occur with the complex ion (II) since the arms are linear. The spaces it leaves in the structure are of two kinds indicated in Fig. 2 by *A* and *B*. There is a set of these spaces with contiguous surfaces as shown in the lower part of the figure. To leave a space, an upward-moving atom must approach the atoms at the corners of the space to within 2·6 A. if it emerges from *A* or 2·2 A. if it emerges from *B*. Sideways movement from one space to another or through the surface of the crystal in the direction of the arrow does not require a closer approach than 3·5 A. to the terminal methyl groups of the octahedral complex ion. Movement could occur through all three side faces of the *B* space but only through two opposite faces of the *A* spaces, the other two sides being blocked by the octahedral complexes.

In the salt under discussion the three *A* spaces per unit cell are occupied by two chlorine ions and one of the water molecules, the arrangement being disordered so that for the structure as a whole each *A* position has statistically $\frac{2}{3}$Cl + $\frac{1}{3}H_2O$. The remaining two water molecules occupy the two *B* positions of the unit cell. The interionic attraction binds the complex ions and chlorine to form a strong cage structure and the water molecules cannot escape upwards, since their movement is barred by the methyl groups, or sideways, because the adjacent *A* spaces contain firmly fixed chlorine ions. It is observed that the water in these crystals can be removed only to a very small extent and this may be attributed to the imprisoning action. On prolonged heating of the crystals at a temperature slightly below 100°—higher temperatures are impracticable owing to decomposition of the substance with loss of methyl chloride—slight dehydration occurs, the crystals are seen to be crossed by faint white bands on the sides of the hexagonal prism, and they fall apart into slabs parallel to the hexagonal base. This suggests that the water may to a small extent emerge sideways but not upwards. This sideways movement is very much restricted since a molecule of water, having moved from *A* to *B* will usually find the two neighbouring *A* positions occupied by chlorine ions which prevent its further movement. The emergence with great difficulty of a small amount of water may be due to some molecules making their way through a few unblocked routes. There does not appear to be any other special reason why the water should be so tenaciously held in this compound; there is no evidence that it is strongly attached to any part of its surroundings, and the behaviour is therefore attributed to the imprisoning action.

Compounds of quinol with small molecules. Crystalline compounds of formula $M,3C_6H_4(OH)_2$, where M may be SO_2, H_2S, HCN, HCl, HBr, $H{\cdot}CO_2H$, $CH_3{\cdot}OH$, or $CH_3{\cdot}CN$, have been investigated by Palin and Powell (Part III, *J.*, 1947, 208). The imprisonment of one component by another is shown in a twofold manner in these structures. The quinol molecules link through hydrogen bonds directed at approximately the tetrahedral angle to the C–O bonds to form infinitely extended three-dimensional cageworks. Owing to the size of the covalently bound group of atoms connecting the two points of hydrogen bond attachment of each molecule, the resulting structure (see Fig. 13, Part III) is an extremely open one, and this extended cage structure would have a density of only 0·61 g./c.c., as calculated from its composition and dimensions. So great is the available space and so large the holes of entry to the cagework that it is possible to arrange a second identical cagework completely interpenetrating the first. This gives an association of two giant molecules which have no direct linkages but which are inseparable without the breaking of hydrogen bonds. Both molecules imprison the other by multiple enclosures. The constitution may be denoted by the encirclement formula (*c*). The



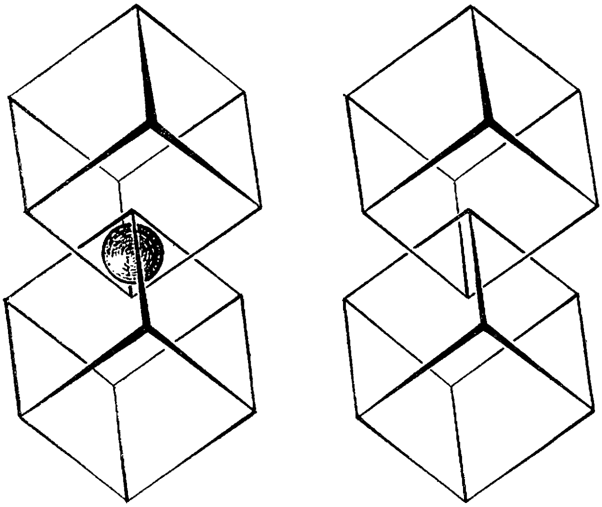
(*c*.)



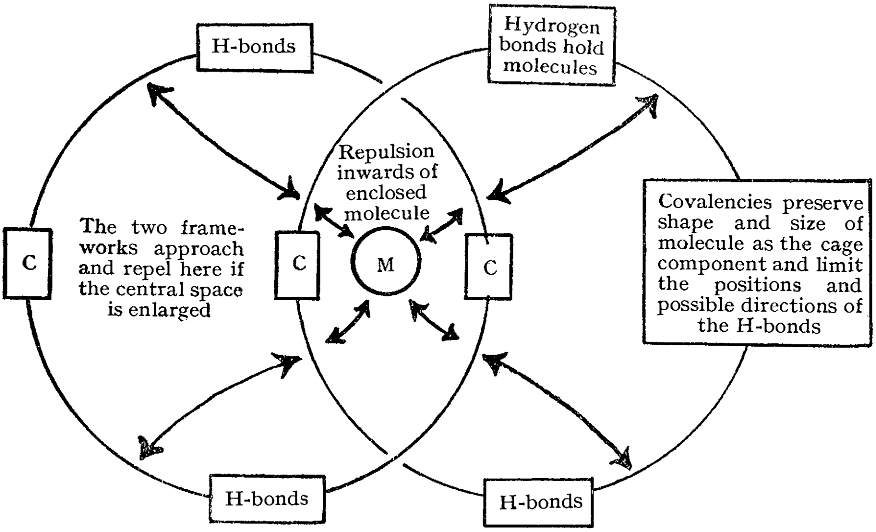
(*d*.)

interlocked rings denote mutual enclosure of two identical cageworks; the subscript *n* outside the brace shows that the cages are infinitely extended and that there is multiple enclosure of each cagework by the other. This arrangement of interpenetrating molecules still leaves unoccupied spaces able to contain the small molecules M. These spaces are bounded by parts of both the quinol frameworks and there are no holes of exit through which the enclosed molecule may emerge without close approach to the atoms of the framework. The general character of the enclosing action may be seen from Fig. 3. The sulphur dioxide, or other molecule M, is very firmly retained in spite of its volatile character in the free state, but it is readily liberated by any process that destroys the framework, *e.g.*, by addition in the cold of liquids that dissolve quinol, by melting, or to a small extent by grinding the crystals. The formula of the compound is determined by the ratio of available cavities to the amount of cage material. The constitution may be represented by the formula (*d*) which expresses the composition, and the enclosure simultaneously by two infinitely extended frameworks, although it cannot express the detailed structural arrangements.

FIG. 3.



Schematic representation of interpenetration of two cage structures. The quinol molecules are to be imagined as the edges of the cage. In the crystalline structure the corresponding cages are extended indefinitely in three dimensions, six quinol molecules being joined together at each corner of the figure. In the crystal the corners of one cage system fall at the centres of the other but in this figure they have been displaced in an arbitrary manner for greater clarity. On the left a small molecule is shown trapped between the two cages.



(*e*; C = covalencies.)

The precise nature of the restriction on emergence of the sulphur dioxide molecule is considered further in view of the explanation to be given for the next substance mentioned below. As indicated diagrammatically in (*e*), the enclosed molecule could escape by pushing apart the two independent portions of its cage, against their van der Waals attraction. This may be large but an indirect effect of greater importance is that the attempt to enlarge the holes of exit in this way necessarily brings the cages into closer contact in other places. The resulting large repulsions, which prevent the enlargement of the holes, are in their turn only possible if the hydrogen bonds hold the quinol molecules firmly together. Some bending of the hydrogen bonds is possible, as shown by the small differences in the shape of the cage for different enclosed molecules, but only a complete break will release the enclosed molecule. Finally, the hydrogen bonds are retained in their positions by the rigid structures of the covalently linked quinol molecules.

Quinol–formic acid–carbon monoxide. In an attempt to prepare formyl derivatives of quinol by heating this substance with formic acid in a sealed tube, Mylius (*Ber.*, 1886, **19**, 999) obtained a crystalline product of remarkable properties. On solution in cold water or other solvent it immediately liberated carbon monoxide and quinol could be recovered from the solution. It melted at 170° also with liberation of carbon monoxide. That it is not simply a compound of carbon monoxide and quinol was shown by analysis, by failure to prepare it when the mixture was heated in the same way but with an attachment to absorb water resulting from the decomposition of the formic acid, and by the detection of a small quantity of formic acid in it.

The properties of this substance may now be explained if it is assumed to be a clathrate compound of type $M,3C_6H_4(OH)_2$, where M is partly formic acid and partly carbon monoxide. Formic acid alone will form a similar compound but in the conditions used carbon monoxide will not. The absorption of water may have led to the decomposition of all the formic acid so that no medium remained in which quinol and carbon monoxide could be dissolved, but it is of some interest to consider an alternative explanation. It might be that a molecule small enough to escape from the cavities and therefore incapable of this type of compound could nevertheless be retained by a cagework which had some of its cavities already occupied by larger molecules such as those of formic acid, which block the exit of the smaller ones. From the fact that there is a measurable energy of activation for the diffusion of nitrogen into some zeolites which contain already a certain amount of water whereas there is no appreciable energy of activation for the same zeolite after more complete removal of the water (Emmett and DeWitt, *J. Amer. Chem. Soc.*, 1943, **65**, 1253), it has been concluded that water molecules fixed in zeolite channels may impede the inflow of nitrogen. Enclosure compounds are imaginable in which a similar obstacle prevents the emergence of a small molecule. The carbon monoxide molecule, not much smaller than that of hydrogen cyanide, which forms a compound, may be retained in the ordinary way without the need for formic acid but the implications of the alternative explanation are mentioned below since they may apply to other compounds.

The analytical results of Mylius (*loc. cit.*) show a variable carbon content. The hydrogen content does not vary in a systematic way with the carbon percentage and is approximately constant with a mean value of 5·3% as shown below for six different samples :

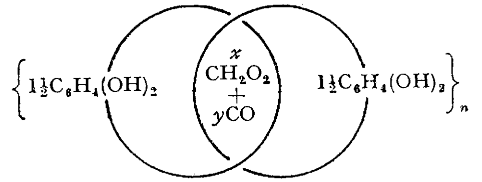
C, %	61·29	62·08	62·10	62·61	62·63	62·93
H, %	5·30	5·33	5·26	5·29	5·25	5·56

The requirements of the formula $3C_6H_4(OH)_2,(1 - a)CH_2O_2,aCO$, *viz.*, C, 60·6—63·7, H, 5·32—5·03 as a changes from 0 to 1·0, will account for the carbon percentages but not for those of hydrogen. The composition may be derived in the following way. It is supposed that the crystals are composed of quinol frameworks similar to those of the compounds previously mentioned, including the compound of quinol with formic acid. Between the frameworks some formic acid is enclosed, but in the temperature conditions of the preparation a certain proportion of the formic acid molecules are undergoing decomposition into carbon monoxide which may be retained by the further deposition of material on the crystal surface. Once enclosed by its own cage and possibly by the next deposited layer containing formic acid, it is retained in the manner described above, but there is a chance for it to escape before the next layer is deposited. If it escapes in this way after the cage has formed, the space cannot be filled by a formic acid molecule since the possible hole of entry is too small for this larger molecule. The resulting crystal therefore will have the composition $3C_6H_4(OH)_2,xCH_2O_2,yCO,z(\bigcirc)$ where $(\bigcirc)$ represents a vacant space, and $x + y + z = 1$. The introduction of vacant spaces makes it possible to vary the carbon content without appreciable variation in the hydrogen proportion, *e.g.*, the hypothetical series $3C_6H_4(OH)_2,(1 - a)CH_2O_2,\frac{1}{2}aCO,\frac{1}{2}a(\bigcirc)$ gives C ($a = 0$) 60·6, ($a = \frac{1}{2}$) 62·5, ($a = 1$) 64·5; H ($a = 0$) 5·32, ($a = \frac{1}{2}$) 5·28, ($a = 1$) 5·23. Mylius carried out determinations of the carbon monoxide and formic acid in addition to elementary analysis and his results can be explained on the formula $3C_6H_4(OH)_2,xCH_2O_2,yCO,z(\bigcirc)$ with $x = 0{\cdot}45$, $y = 0{\cdot}125$, $z = 0{\cdot}425$. This gives C, 62·9, H, 5·34 (Mylius: 62·93, 5·56) and for CO, 1·0, formic acid, 5·85 (Mylius: 1·0 and 5·7—5·9%). The complete figures are not available for all samples but the carbon and hydrogen contents may be explained by suitable variations of x, y, and z.

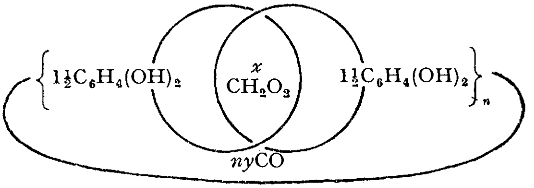
The large proportion of vacant spaces is not incompatible with the notion that the egress of the small carbon monoxide may be prevented by the presence of the larger formic acid. The only hole available for exit is the hexagon of side 2·7 A. formed by the hydrogen-bonded oxygen atoms (see Part III), and to escape from its enclosure a carbon monoxide molecule would be expected to pass by way of a channel parallel to the *c* axis of the crystal through a succession of such hexagons. A blocking of these escape routes may clearly be made with far less than the 45% occupancy of the cavities by formic acid. The figures as calculated show roughly half the spaces occupied by formic acid molecules, and of the rest about three-quarters are vacant and one-quarter occupied by carbon monoxide. A simplified picture of the enclosure in the channel may be shown by the sequence CH_2O_2 blank CH_2O_2 blank CH_2O_2 blank CH_2O_2 CO CH_2O_2 blank CH_2O_2 . . . which represents one of the possible ways of arranging the contents of a succession of cavities parallel to the *c* axis of the crystal. Other arrangements are possible, and although there is a certain probability of a carbon monoxide molecule being contained in a cavity which itself adjoins an empty cell, it is in any case bounded somewhere on both sides by occupied cells and there is a good chance that its two immediate neighbouring cells will both contain formic acid molecules.

Even if the explanation does not apply in the present case, it serves to show that by the process described it should be possible to combine together the most diverse substances provided that there is a means of getting the required molecules into position when the crystal is formed.

The quinol–formic acid–carbon monoxide compound is represented by the formula (*f*) if the formic acid is not necessary, but if the carbon monoxide is only retained by the combined caging effect of quinol and formic acid the alternative representation is (*g*). This shows a crystal complex of formula $\{3C_6H_4(OH)_2,xCH_2O_2\}_n$ which as a whole encloses *ny*CO. The formic acid is shown enclosed by the interpenetrating quinol cageworks but also as an essential part of the structure which encloses the carbon monoxide.



(*f*.)

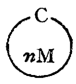


(*g*.)

Modes of formation of clathrate compounds. In the examples already discussed the essential condition that the cage shall form around the other molecular component is achieved by the building up of the cage bit by bit from small components capable of separate existence in the solution which also contains a large concentration of the molecules to be enclosed. The sulphur dioxide–quinol compound cannot be made directly by contact of its components at room temperature in the dry state. Apart from any other considerations this limits the possible partners in the compounds to those that can be present in sufficient concentrations in the same solution. High pressures might be used to increase the concentration of the second component, and preliminary experiments have shown that this method is successful in bringing about combination with a gas that does not form a compound at ordinary pressure owing to its small solubility. This suggests the possibility of forming a compound with an inert gas, *e.g.*, by crystallising quinol from a solution saturated with krypton at high pressure.

A method of preparation possibly applicable in a few special cases would be the formation of a compound from a substance that may be enclosed, followed by decomposition of the enclosed material. Thus the enclosed molecules might be decomposed by the action of heat, ultra-violet light, or *X*-rays, and, if the necessary condition is fulfilled that the cage remains unaffected, a molecule which could not otherwise be induced to enter the cage might be formed and retained in it.

Composition of clathrate compounds. The composition of these compounds may be reduced to a basic formula (*h*), which gives the amount of cage-forming material for every available cavity and the composition of the material enclosed per cavity, but ignores structural details which for some purposes may not be of great importance and in any case are only imperfectly described by more complex encirclement formulæ. In the formula *n*M there may be : (*a*) a whole number *n* of molecules of the second component M, (*b*) any fractional amounts of two or more enclosed molecules that together add up to a whole number, (*c*) fractional amounts as in (*b*) with the limitation that one of the enclosed molecules must be present in some minimum proportion needed to trap the other



(*h*.)

enclosed components, (*d*) fractional amounts that do not add up to a whole number. Case (*d*) may arise through some of the cavities being unoccupied. It could also occur in a structure with sufficiently large cavities occupied by more than one molecule when the determining factor would be the volume available and $M = X_nY_m$ where X and Y are moleules enclosed such that $(n + m)$ is not integral but the effective volume of X_nY_m is roughly constant.

For a given cage the type of molecule M is determined by volume considerations, not by the chemical nature of the molecule. In the examples given, the total volume of the enclosing parts is considerably greater than that of the enclosed component. Cavities which arise only from the impossibility of close packing of awkward shaped molecules must be smaller, and usually will be considerably smaller, than the cage-forming molecules themselves, and the presence in a molecular compound of a relatively small amount of one component, especially if the molecular ratio of the two components has no relation to the conceivable unions by other means, provides grounds for suspecting that the compound is of the clathrate type.

For cavities which arise from the directed character of the bonds linking the cage structure, the volume ratio of enclosed to enclosing material is not necessarily so small. Thus the material of the single quinol framework structure mentioned above has a less volume than the total available for enclosed material, as is clear from its enclosing not only an identical framework but small molecules in addition.

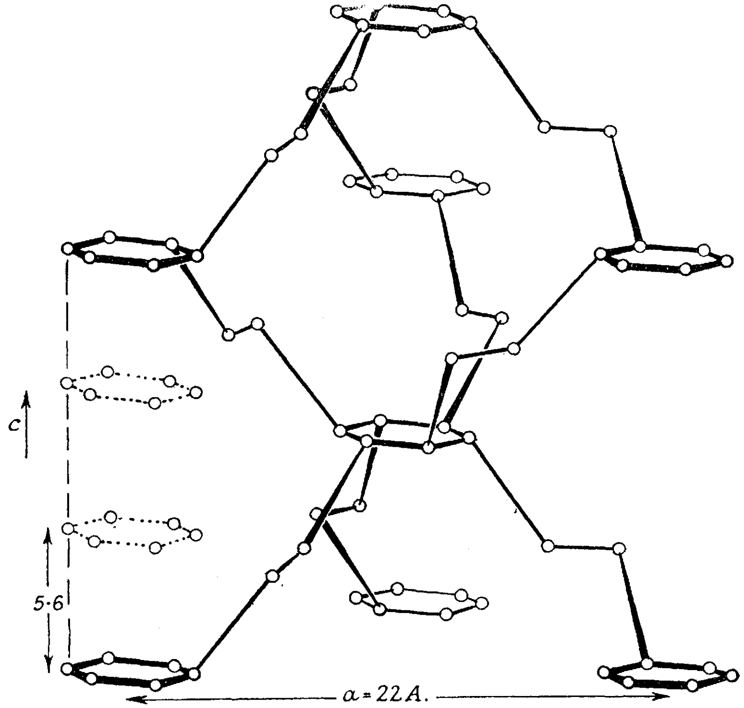
There will be a lower as well as an upper limit to the size of enclosed molecule that enters into combination with a given cage since a sufficiently small molecule would be able to pass through the escape holes without meeting the inward repulsion which is necessary to stabilise the compound. This explains the failure of water to form a compound with quinol. It might have been supposed that the various molecules which may be enclosed by quinol were attached to the framework, *e.g.*, by hydrogen bonds, but if this were the explanation water should be more firmly attached than some of the others, *e.g.*, hydrogen sulphide. But if any interactions between the cage and its enclosed molecule are insufficient to hold the components in the firm manner observed, and the factor determining permanence is the lack of access to the surface of the crystal, it follows that water is one of the molecules that will not form a compound, since it could pass out of the cage by way of the hexagons of hydrogen-bonded OH groups that link the quinol molecules. To do this it must approach to within 2·8 A. of the oxygen atoms, a distance very little less than the average separation, 2·9 A., of oxygen atoms in water. In contrast, the methyl alcohol molecule, which does not link more firmly to quinol for any other reason, is retained because the van der Waals equilibrium distance $CH_3 \ldots O$ is about 3·4 A. and the outward passage of the molecule is therefore prevented. Quinol crystallised from water forms a structure, not yet determined in detail, different from that found for the 3 : 1 compounds discussed above but containing similar cavities (see below.) This form, α-quinol, with unoccupied cavities, is also obtained from ethanol. In the series HOH, MeOH, EtOH the extreme members do not form the clathrate compound, their molecules being respectively too small and too large. This size factor accounts for the apparently erratic behaviour of quinol in giving compounds with a very varied set of molecules of about the same dimensions although it does not give similar compounds with molecules that are chemically closely related to one or other of the series.

Although structural investigations by physical methods are necessary for final decision, a preliminary assignment of a compound to the clathrate type may be made or rejected from consideration of the properties, molecular ratios, relative volumes of the components, and the behaviour of homologous or closely related substances. Some examples of this process are given below. The first of these is of particular interest since it shows how considerations of this kind may be used to determine what appears at first to be a very complex crystal structure, that of α-quinol itself.

α-Quinol. Quinol crystallised from water or ethanol gives crystals of the α-form which do not contain other enclosed molecules. The dimensions of the hexagonal unit cell are $a = 22{\cdot}07$, $c = 5{\cdot}62$ A. The lattice is not rhombohedral and there are 18 molecules per unit cell, twice as many as in the smallest hexagonal cell that may be chosen for the molecular compounds. The space-group is $C\bar{3}$ (Caspari, *J.*, 1926, 2944). The *a* dimension has no simple relation to that of the previously mentioned series of molecular compounds, but the *c* dimension agrees with those of the molecular compounds as closely as they agree with each other.

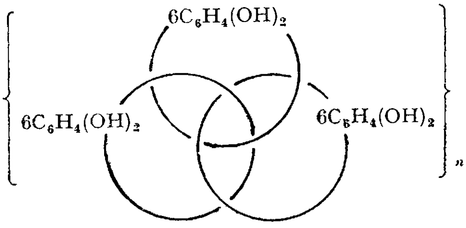
The structure is in course of detailed determination but may be predicted from the above facts and the behaviour (described below) with carbon dioxide as composed of independent interpenetrating giant molecules, probably three in number. Each giant molecule imprisons the others. The essential component of the structure is an interlocking group of quinol molecules enclosing cavities similar to those of the 3 : 1 molecular compounds. However, the quinol molecule links through hydrogen-bonded hexagons only at one of its hydroxyl groups, the other hydroxyl group being linked to its neighbours in such a way as to give a more compact arrangement of molecules than that imposed by the large hydrogen-bonded hexagons. There are thus only half as many cavities as in the 3 : 1 molecular compounds, *i.e.*, one cavity to six quinol molecules, and the density 1·33 is accordingly higher than that calculated for the quinol structure of the molecular compounds with vacant spaces, *viz.*, 1·22 g./c.c. The approximate relationship of the interpenetrating molecules may be seen from Fig. 4, and the encirclement formula may be written as in (*i*). These diagrams are for three interpenetrating giant molecules but may be easily modified for any other number.

FIG. 4.

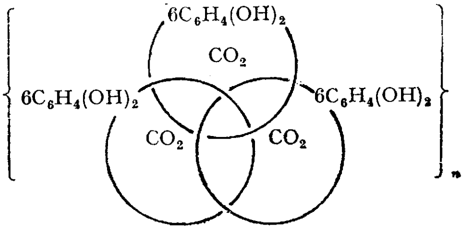


Possible structure for α-quinol. For clarity, only one of the interpenetrating giant molecules is shown, all benzene rings are omitted, and only the essential linkages of the cagework are shown. The small circles denote oxygen atoms. Each quinol is linked through one of its oxygen atoms by hydrogen bonds so that six oxygens form a hydrogen-bonded hexagon from which quinol molecules project alternately up and down. These molecules are denoted by long sloping lines which join the two oxygen atoms of one molecule. The second oxygen links to other molecules through hydrogen bonding but not in the open hexagon form. Enough links are shown to illustrate the formation of a cage structure. The cage is shown as having the height of three unit cells, and two hexagons shown by broken lines indicate the positions from which two structures identical with this cage are to be built up so that they interpenetrate the first cage and each other. Similar structures with different numbers of interpenetrating molecules may be imagined.

Quinol–carbon dioxide. It appears that clathrate compounds will also form with the α-quinol structure as the cage component. A carbon dioxide compound has been obtained by crystallisation of quinol from a benzene solution in presence of carbon dioxide at more than 50 atmospheres' pressure; it has a variable composition with not more than one molecule of carbon dioxide to six of quinol. Optical and *X*-ray examinations show that it has in the main the α-quinol type of structure, but there are further complexities which are still under investigation. It is a stable solid which liberates carbon dioxide when solvent is poured over it. The encirclement formula is drawn so that each circle passes over both the others and then under both. If the part of the circle which passes underneath at both ends is regarded as taking no part in the enclosure of an area, the state of the carbon dioxide molecules as enclosed simultaneously by any pair of the framework quinol structures is correctly depicted as in (*j*). Attempts were originally made to obtain a compound of quinol with carbon dioxide, since the size of the carbon dioxide molecule seemed favourable and this molecule differs from those already shown to form addition compounds in that it has no dipole moment which might be considered to play some rôle in the interaction of the two components. The general behaviour is outlined here without reference to the complexities mentioned above. At ordinary pressures of carbon dioxide an aqueous solution gives crystals of α-quinol containing no carbon dioxide. This is attributed to the low concentration of carbon dioxide, the quinol adopting the compact α-structure as it does when crystallised from pure water. At high pressures in benzene solution the compound already mentioned is obtained, but at moderate pressures Palin (private communication) has obtained from aqueous solution a compound $3C_6H_4(OH)_2,CO_2$ similar in structure to the sulphur dioxide compound. The first effect of pressure is therefore to increase the concentration of the carbon dioxide in solution so that formation of the 3 : 1 compound is possible, but too great a pressure results in the formation of the more compact structure, as might be expected, the pressure in this case preventing the formation of the more open structure and thus, in a sense, forcing the carbon dioxide out again. It appears at first surprising that under similar high pressure but with water as solvent the product contains no carbon dioxide, and does not have the compact α-structure. Instead, it has a low density and the structure of the very open double cagework found in the 3 : 1 molecular compounds. Since the effect of pressure cannot well be to produce this open structure which in other conditions appears to require at least a considerable proportion of its cavities filled by small molecules for stability, and since the observed effect of pressure in benzene solution is in fact to produce the compact form, the explanation must be sought in some specific behaviour of water. It has already been pointed out that water appears not to form a compound with quinol, and this has been attributed to the small dimensions of the water molecule which is not retained by the cageworks. Under pressure it will be possible for water molecules to pass freely through the quinol cage structure—it has been mentioned that the distance of a cage oxygen atom from a water molecule which enters through a hydroxyl hexagon is very little greater than that between two oxygen atoms in liquid water In these conditions the external pressure is rendered ineffective since it is transmitted also to the interior of the cages through water which occupies the spaces. The cavities that could otherwise be held responsible for the instability of the open structure are in this case filled even more effectively than by the sulphur dioxide or other molecule. It is not yet known with certainty whether all the water emerges from the structure when the pressure is removed. Benzene or other large solvent molecule cannot penetrate in this way and thus does not obscure the pressure effect.

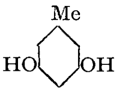


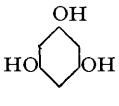
(*i*.)



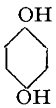
(*j*.)

Phenols and hydrogen bromide. A study of the behaviour of polyhydric phenols and their ethers with regard to the formation of addition compounds with hydrogen bromide has been made by Gomberg and Cone (*Annalen*, 1910, **376**, 237) with the following results. Orcinol (III) and phloroglucinol (IV) form compounds, HBr,2M, which are presumed to be of the same general character as the 3 : 1 compound with quinol (V) already known to be of the clathrate type. The other molecules (VI)—(XIII) do not form compounds with hydrogen bromide. Those without hydroxyl groups cannot link to form cage structures; those with only one hydroxyl group do not fulfil the requirement for the formation of a large space that they should be capable of attachment at two or more widely separated points. There is no relationship of number or position of the hydroxyl groups that correlates with the formation of compounds by (III), (IV), and (V) and the failure of (VI) and (VII) to give similar compounds. On the other hand, there is a close similarity of shape and size of molecules (III) and (IV) and the possibility of hydrogen-bond linking at two or more points with hydrogen bond directions restricted by the rigid framework of the molecules. The formula 2 molecules : 1HBr, like that of the 3 : 1 compound of (V), appears to be unrelated to any chemical characteristic such as the number of hydroxyl groups. The formation of compounds by (III) and (IV) is therefore provisionally explained by supposing that the requirements of the hydrogen-bond linking lead to a cage structure in the crystals with spaces large enough to contain a hydrogen bromide molecule which represents a small volume compared to that of the two molecules with which it is combined.

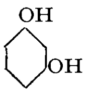

(III.)

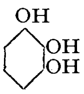

(IV.)

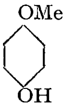
HBr,2M.

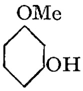

(V.)

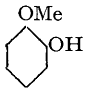
HBr,3M.

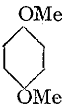

(VI.)

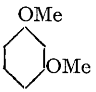

(VII.)

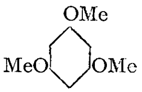

(VIII.)


(IX.)


(X.)


(XI.)


(XII.)


(XIII.)

Amines and aminophenols with sulphur dioxide. Lumière and Seyewitz (*Bull. Soc. chim.*, 1906, **35**, 1204) prepared addition compounds by the action of sulphur dioxide on aqueous suspensions of *p*-aminophenol, *p*-methylaminophenol, or *p*-phenylenediamine. The compositions, based however on determinations of sulphur dioxide content only, correspond approximately to the formulæ $10NH_2{\cdot}C_6H_4{\cdot}OH,H_2SO_3$, $6CH_3{\cdot}NH{\cdot}C_6H_4{\cdot}OH,H_2SO_3$, and $9NH_2{\cdot}C_6H_4{\cdot}NH_2,H_2SO_3$. These compounds do not lose their sulphur dioxide readily, melt (with liberation of sulphur dioxide) at or near the melting points of the parent amine or aminophenol, and have compositions which it is difficult to explain by ordinary constitutional formulæ. All three parent substances bear a close resemblance to quinol, being capable of hydrogen-bond formation through the oxygen or nitrogen atoms in *para*-positions to each other. It seems very probable that they form cage structures which enclose sulphur dioxide and perhaps water. Since the compositions may be variable in ways discussed previously, a more precise determination of the formula would best be obtained from crystal-structure examination. The melting points of these compounds may be those of the respective decomposition products. In this they resemble the compounds of quinol mentioned above, some of which have been shown to decompose into quinol at temperatures below the observed " melting points " which are very close to that of quinol itself.

Choleic acids. The choleic acids in which deoxycholic acid combines with a small proportion of fatty acid, hydrocarbon, or a variety of other substances bear some resemblance to clathrate compounds. It is clear from the so-called co-ordination numbers of deoxycholic acid per fatty acid molecule (Rheinbolt, *Annalen*, 1927, **451**, 256) which have the values 1, 3, 4, 6, or 8, increasing with chain length of the fatty acid, that the amount of material combined with the deoxycholic acid is determined by its volume, for if the formulæ are rewritten for constant amount of deoxycholic acid the numbers of combined fatty acid molecule diminish with increasing chain length. However, since molecules of very different lengths from 2 to 16 carbon atoms may enter into the compounds, the case is not exactly parallel to those discussed above. It is inherently more probable that the second component is here contained in extended channels formed by a structure of deoxycholic acid, rather than in closed cavities of limited dimensions; this is in agreement with available data on the crystal structures (Go and Kratky, *Z. physikal. Chem.*, 1934, *B*, **26**, 439; Giacomello, *Atti R. Accad. Lincei*, 1938, **27**, 101; *Gazzetta*, 1939, **69**, 790).

Decomposition by mechanical means. In the absence of any strong attachment of the enclosed molecules to their surroundings it should be possible to set them free by mechanical breaking of the cage. Crystals of the sulphur dioxide–quinol compound have been kept loosely corked for years and appear to last indefinitely when freely exposed to the air, but on being ground they liberate enough sulphur dioxide to be detected by smell. It is difficult to distinguish this from ordinary inclusions or from effects attributable to local heating, but that a noticeable amount of decomposition could occur is shown as follows.

For simplicity it may be assumed that the large crystals have been crushed to cubes of side a. The original surface is negligible compared to the new surface, and if all surface cages to a depth b are unsealed the volume of decomposed material for each cube is approximately $6a^2b$ when a

is large compared to b. The fraction of decomposed material obtained by dividing this by the volume of the cube is $6b/a$, *i.e.*, it is inversely proportional to the linear dimension of the fragment. Since the crystals are not cubic, the unit cell dimension depends on the direction considered, and a reasonable value for decomposition extending to one unit cell depth only is of the order of 10 A., or 10^{-7} cm. $= b$. If crystals are ground to a size $a = 10^{-3}$ cm., the proportion decomposed is thus 6×10^{-4}, or of the order of 0·1%.

Enclosure in solution and at surfaces. It has been shown (Lepenski, *Kolloid-Z.*, 1943, **105**, 144) from a study of the Plotnikow effect that quinol is strongly polymerised in ethyl-alcoholic or ethereal solution, and the possibility arises that cage polymers may be formed in solutions of this or other substances capable of hydrogen-bond formation. A space may be enclosed by a polyhedron having the molecules as its faces and OH . . . O bonds where the polyhedron faces meet at a corner. For a molecule which is not flat but has the general shape of a saucer with suitably placed hydroxyl groups on the rim it would be sufficient to link two only. Puckered ring systems with projecting hydroxyl groups are suitable. Such a union cannot be expected to occur in the presence of solvent molecules which would have to move away to form the empty space, but if solvent or other solute may be enclosed the complex will be stabilised. Enclosure of this type may explain why insoluble substances such as fats and hydrocarbons may be brought into solution in presence of deoxycholic acid. This molecule has hydroxyl groups that may lead to formation of enclosures somewhat different from those in the crystalline choleic acids. If the enclosures are of some permanence, the effective concentration of hydrocarbon molecules in solution in equilibrium with the solid or liquid hydrocarbon is much less than the total concentration which includes the enclosed material. Solution in this way is analogous to the solution of a normally insoluble salt by formation of a more complex ion.

Quinol and similar hydrogen-bond-forming molecules will attach themselves to surfaces, as is shown by the oriented growth of quinol on suitable crystal surfaces. When this occurs surface cages must be formed, and according to the conditions these could be of a permanent or a transient kind. The resulting proximity of any enclosed molecules may have an influence on reactions between the enclosed materials, the surface and the enclosing cage or between some of them, since it affects the chances of reacting substances being not only in the right places but also in suitable internal phases or states of activation. The restrictions on movement and possible packing positions of the enclosed materials could in some forms of cage lead to a preferential formation of particular isomers, including optical isomers. Loose compounds of this kind may play a part in reactions of biological importance.

Note added in Proof.—Since the prediction of the α-quinol structure was made, *X*-ray results have been obtained which do not agree with those previously reported. The structure therefore requires modification. It is more complex, but the c dimension is unchanged and there is little doubt of the validity of the main conclusion that an essential component is the interlocking group of quinol molecules enclosing a cavity.

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