The Chemistry of Intermolecular Compounds.

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THE production of new chemical compounds has for some time been guided by the concepts of the chemical elements and of the atom, and by the basic idea that new substances are formed when atoms of the elements unite or rearrange in various ways to give molecules or other aggregates.

Theories of chemical combination concerning the manners in which these changes occur derive some of their usefulness from the limitations that they set to combining power. Thus Dalton's laws, modified and re-interpreted but still not to be lightly disregarded by those who would make new compounds, state restrictions on the combining proportions of the elements. The electronic theory of valency may be summarised in a statement of the restriction that atoms unite only in ways that produce the comparative stability of certain electronic arrangements, notably those found in the inert gas atoms. In this theory each element has its electrons numbered and with that its valencies and its compounds are, in a sense, numbered. But the discovery of new atoms and new ways of holding them together seems continually to increase the number of compounds which have yet to be made. Amid the uncertainties that such developments introduce there remains the conviction that some things do not combine chemically and that, in particular, there are limitations on combination by simple addition of one substance to another. The paraffins, although capable of substitution reactions, do not add to other molecules; the noble gases remain chemically inert and the chlorine atoms of carbon tetrachloride do not donate their unshared pairs of electrons to form more bonds. If rules such as these are to be retained, account must be taken of a large number of crystalline intermolecular compounds which seem to disobey them. Table 1 gives some examples.

These substances, formed by simple addition of one compound to another, are sometimes distinguishable from ordinary chemical compounds with such difficulty that they have been mistaken for them. They include now even compounds of the inert gases argon, krypton, and xenon. They are attributable not to chemical bonding but to other forms of interactions, such as are sufficient to cause crystallisation of ordinary molecules. These substances may be isolated and characterised by their physical properties. They may be used in the traditional chemical processes of preparation, purification, identification, and quantitative analysis, and their chemical properties may differ to some extent from those of their components. Their existence has simplified some otherwise difficult chemical operations and many further applications will develop. Discussion as to whether they should be called compounds is profitless and any doubts are best not answered but evaded by the use of suitable qualifying words. In specimen tubes they look much the same as other crystalline compounds. Understanding of their nature is needed to explain their properties and behaviour and to control their effective use.

There have been descriptions of individual compounds of this kind for over a century but it is now desirable, and in a limited way possible, to supplement empirical knowledge by more general statements concerning what is here called their chemistry and to look for principles corresponding to the rules of interatomic chemistry. Such a system should say which molecules will unite and which will not. It should deal with combining proportions, the properties and conditions of formation of the intermolecular compound, and its stability and energy relationship to the components.

The advantage of a system for determining which pairs of substances will form addition compounds may be seen from consideration of all imaginable combinations. If each of the n possible different chemical molecules could unite with every other in one way only, the number of compounds formed would be approximately $\frac{1}{2}n^2$.

Any two approaching molecules experience attractive forces and in certain conditions very little attraction is necessary for intermolecular compound formation. Accordingly there is the hope or fear that many of the $\frac{1}{2}n^2$ possible compounds may exist. These feelings may be encouraged by the reflection that some of the known combining pairs such as urea and straight-chain paraffins seem, from the ordinary chemical viewpoint, most unlikely partners and may never have been brought together with intent. Further when any given pair of substances has at some time been in contact failure to form a compound may be due to unsuitable conditions. For example, quinol in aqueous solution is oxidised by atmospheric oxygen but a hot ethanolic

TABLE 1.

Molecular compounds, AB

A	B	Composition
Deoxycholic acid [1,2,3]	Fatty acids, *n*-paraffins, and some other substances	A_mB, $m = 1, 3, 4, 6,$ or 8 increasing as length of fatty acid molecule increases
4 : 4′-Dinitrodiphenyl [4]	4 : 4′-Substituted diphenyls	A_mB, $m = 5, 4, 3\frac{1}{2}$, or 3, being the larger the greater the length of molecule B
Urea [5,6]	*n*-Paraffins	A_mB, $m = 0{\cdot}6848(n - 1) + 2{\cdot}181$ where n is the number of carbon atoms
Thiourea [7]	Some branched paraffins and derivatives of *cyclo*paraffins	A_mB; m in general increases with the molecular length of B, but for some sets of three successive members of homologous series m may remain constant at integral values, *e.g.*, 6 and 9
Quinol [8]	MeOH, MeCN	A_3B
Quinol [8,9]	H_2S, SO_2, HCl, HBr, HCN, CO_2, C_2H_2, N_2, O_2, A, Kr, Xe	Limiting formula A_3B, but variable composition with less B
$Ni(CN)_2,NH_3$ complex [10]	Benzene, thiophen, and a few similar molecules, but not their homologues	AB
Water [11,12,13]	Gas hydrate-forming molecules, *e.g.*, A, Kr, Xe, CH_4, Cl_2, CH_3Cl, $CHCl_3$	$M,(H_2O)_m$, $m = 5$—8 or 16—18, the larger molecules having the higher hydrating numbers

solution subjected to a pressure of 50 atmospheres of oxygen deposits,[14] on cooling, the clathrate compound $3C_6H_4(OH)_2,O_2$. Similarly urea and paraffins do not unite merely on contact, but will do so in presence of methanol. It is not immediately obvious which molecules will unite in this way, but large numbers of related compounds may arise from the discovery of the manner of formation of one of them. Many such series of compounds remain to be found.

Of outstanding importance is a study of the crystal structures of these molecular compounds which may not exist apart from the crystalline state. It is found by this means that the components of some intermolecular compounds are not joined by chemical bonds of any kind. The distances between adjacent atoms in neighbouring molecules are too great. They correspond to non-bonded distances. Thus in the argon–quinol compound the smallest argon-to-CH distance is 3·8 Å. The energy of formation confirms this. Evans and Richards,[15] from the heats of solution of β-quinol and argon–β-quinol clathrates of various compositions find $\Delta H = 6$ kcal. for the heat of formation from gaseous argon and solid β-quinol. This is perhaps larger than would be expected for van der Waals interaction but is explained by the very large number of contacts made by one argon atom with the surrounding structure.

Thus it is certain that from a mixture of A and B molecules which are incapable of chemical union, in certain cases there will be formed a molecular compound of the two in preference to pure A or B. It is perhaps normally expected to be otherwise. A set of molecules, all capable of mutual attraction which is not markedly directed in space seem likely, in general, to crystallise in a close-packed structure as the most stable form. This is in accordance with experience concerning the structures of pure substances, and it may be thought that good packing is achieved most readily when molecules of only one sort are deposited from a mixture. But in some circircumstances crystallisation of the pure components may be expected not to occur. Either A and B are strongly attracted or there may be difficulties of packing. The two effects may operate together.

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[1] Rheinbolt, *Annalen*, 1927, **451**, 256.
[2] Go and Kratky, *Z. physikal. Chem.*, 1934, **26**, *B*, 439.
[3] Giacomello, *Atti R. Accad. Lincei*, 1938, **27**, 101; *Gazzetta*, 1939, **69**, 790.
[4] Rapson, Saunder, and Stewart, *J.*, 1946, 1110.
[5] Schlenk, *Annalen*, 1949, **565**, 204.
[6] Smith, *Acta Cryst.*, 1952, **5**, 224.
[7] Schlenk, *Annalen*, 1951, **573**, 142.
[8] Palin and Powell, *J.*, 1948, 815.
[9] Powell, *J.*, 1950, 468.
[10] Rayner and Powell, *J.*, 1952, 319.
[11] von Stackelberg, *Naturwiss.*, 1949, **36**, 327.
[12] Clausen, *J. Chem. Phys.*, 1951, **19**, 259, 662.
[13] Pauling and Marsh, *Proc. Nat. Acad. Sci.*, 1952, **38**, 112.
[14] Evans and Richards, *Nature*, 1952, **170**, 246.
[15] *Idem*, personal communication.

Attraction between particular parts of the two molecules will require their proximity in the crystal structure. Each atom of one molecule will be intricately bound up with its surroundings, and as with some other complex structures, the ratio of A to B molecules will be simple. Whatever the nature of the intermolecular attraction, this may require a simple molecular ratio which in itself is not evidence for the integral combining power associated with chemical-bond formation. Among the molecular compounds in which special attractions between the component molecules are operative may be numbered some, though not necessarily all, of those formed between aromatic polynitro-compounds and other aromatic molecules. Various categories of interacting pairs have been considered recently by Mulliken.[16] The intermolecular compounds considered in this Lecture are those in which special interactions are not of such importance. Their crystal structures are of a different kind; frequently one component forms a framework of some sort which encloses spaces, either open or closed in which the second component is held. The first component forms an open structure, but the two together are more closely packed.

Spaces of this kind may arise in several ways. Intermolecular spaces are left when globular molecules are in closest packed array. The dimensions of the holes are proportional to those of the molecules, and for large molecules would be of a size capable of containing smaller molecules of a second component.

The molecule itself may have a cavity. This is the case in the large ring systems of α-, β-, and γ-dextrin.[17]

Molecules of one component may be subject to strong mutual attractions and these may be directed in space in such a way as to produce an open structure, just as hydrogen bonding causes the open crystalline structures of resorcinol or ice. An open structure, formed by such a substance may have vacant spaces large enough to contain molecules of a second component if these are available. β-Quinol which may be obtained in suitable conditions may be so regarded although the normal form, α-quinol, has a different crystal structure. In other cases the framework structure has no separate existence, but is formed only in the presence of the second component. For example, urea under the influence of strong attractions between NH_2 groups and the oxygen atoms of neighbouring molecules normally forms a structure which is not closely packed. In presence of straight-chain hydrocarbons, and a little methanol as solvent, it forms a much more open structure which clearly could not exist on its own. The urea molecules are tightly bound to each other—perhaps more so than in urea itself—and stability arises from the enclosure of the long paraffin in the channels. Similarly in gas hydrates, water molecules are linked to form cages not found in ordinary ice.

In the examples mentioned there is a type of linkage between molecules of the one component, *viz.*, hydrogen bonding which may be reckoned as a chemical interaction. But any type of intermolecular attraction, if it is strong enough, may have a similar effect. Van der Waals forces may be sufficient.

The open structure thus formed is often common to a series of compounds. The second component may be varied in character much more than the first, provided it meets the structural requirements imposed by the almost constant pattern of its partner.

Examples include those in which molecules of one component are located in channels or closed cavities in the structures formed by the other component. These are convenient categories but there is no precise dividing line; a set of adjoining cavities differs only in degree from a channel. Further, whether a space is to be considered as closed depends on what is being enclosed.

Part of the question concerning which pairs of molecules will form intermolecular compounds of this kind is answerable. Which molecules will form enclosing structures is not obvious, but, when such a structure is known, the nature and number of enclosable molecules can be understood and in part predicted. In all cases the enclosed molecule must not be too large for the available space. Some possibilities will now be considered.

A Three-dimensional Framework encloses Cavities of Limited Size.—There are strict limitations on the shape and size of the enclosed molecule. Of two chemically related molecules, *e.g.*, two members of a homologous series, one may be enclosed but the other excluded by its great dimensions. Too small a dimension may also result in no compound. Examples are provided by the clathrate compounds of quinol which have cavities capable of containing molecules chemically as diverse as sulphur dioxide, formic acid, methanol, hydrogen chloride, nitrogen, cyanogen chloride, and xenon. Homologues such as ethanol and other large molecules do not form similar compounds. The helium atom is too small to do so. In this case there is a definite numerical ratio of cavities to molecules of the enclosing structure. Since each cavity can hold no more than one

[16] Mulliken, *J. Phys. Chem.*, 1952, **56**, 801.

[17] Freudenberg and Cramer, *Chem. Ber.*, 1950, **83**, 296.

molecule there is a limiting composition with a maximum ratio of enclosed to enclosing molecules. Although this cannot be exceeded there may be lower values when some of the cavities are unoccupied. Molecular compounds of this kind may therefore obey a law of definite proportions or they may not. For the quinol clathrates all the spaces are filled when the substance to be included, *e.g.*, methanol or methyl cyanide, is used as the solvent for crystallisation, and a ratio such as 3Quinol : MeOH results. When, as in the case of argon and other substances, an indifferent solvent for quinol and the enclosed substance has to be used, and a sufficient concentration of gas perhaps achieved only by raising the pressure, a number of holes may be left vacant. The number of vacant spaces is variable and depends on the molecules available for enclosure when the cage is formed. The ratio of the two components in this case is not simple.

A similar maximum ratio of enclosed to enclosing molecule and a size limitation for the enclosed component are found in the gas hydrates. There have been modifications of detail in the structural interpretation but as a general concept it is agreed that the hydrating molecules are packed into spaces in ice-like lattices. The " ice " forms, unlike ordinary ice, are cubic, and whole groups of hydrates have a common type and size of unit cell. The voids are of various sizes and co-ordination numbers. A cubic cell of side $a = 12$ Å and hydrating numbers about 5—8, are found for a group of small-molecule hydrates, and another group of larger molecules has hydrating numbers 16—18 and a unit cell of 17 Å. For the 12-Å type Clausen[12] makes the basic void an undeformed pentagonal dodecahedron of water molecules, co-ordination number 20 (for small molecules); and a medium void for somewhat larger molecules has 12 pentagonal and 2 hexagonal faces, co-ordination number 24. A unit cell has 46 water molecules. There are 6 small voids and 2 medium voids. Hence the ratios of molecules may be $46 : 6 = 7\frac{2}{3} : 1$ (medium) or $46 : 8 = 5\frac{3}{4} : 1$ (small). The size of the hydrating molecule determines which voids are filled. Table 2 gives hydrating numbers for two groups of molecules.

TABLE 2. *Ratios for gas hydrates.*

Small molecules		Medium molecules (some smaller voids not filled)	
Gas	H_2O	Gas	H_2O
A	4·5	C_2H_6	7
CH_4	6·3	C_2H_4	7·4
C_2H_2	5·7	C_2H_5F	8·27
PH_3	5·9	SO_2	8
H_2S	5·7	CH_3Cl	7·2
CO_2	6	Cl_2	6·91
N_2O	6	Br_2	10
H_2Se	5·87		

Some points in the chemistry of intermolecular compounds are illustrated by the clathrates and the gas hydrates. Thus no great attraction exists between the molecules of the two components. Indeed, for the formation of this kind of compound, not only is small intermolecular action possible but it seems to be essential. Those molecules which form gas hydrates are as a rule hydrophobic. A hydrophilic molecule, *e.g.*, HCl, will combine with water to make a hydrate of a different sort. Aldehydes, alcohols, acids, amines, amides, and various other molecules which are capable of hydrogen-bond formation do not form gas hydrates and, in general, substances easily soluble in water do not form them even if their molecular size is favourable.

Since the form of attraction between the components is thus mainly of the general van der Waals type, it acts in a very indiscriminate way and mixed compounds may be formed, some cavities containing one enclosed molecule, some another.

The comparatively slight attraction between cage and occupant is manifest in another way. The enclosed molecule may be capable of rotation or other movement in its cavity or may occupy statistically different fixed positions in its cavity. This has been found directly by Fourier analysis, which shows sulphur dioxide to be in rotation about one axis in its quinol cage. The dielectric properties of some other clathrates lead to similar conclusions concerning the motion of imprisoned molecules.[18] The poor *X*-ray scattering by the gas hydrates indicates similar freedom of motion for them in their " ice " cavities.

Channels in a Three-dimensional Structure.—If the channels can be regarded as cylinders or other spaces which are uniform along their lengths the enclosable molecules must be of suitable, restricted cross section but their length is not limited. Thus members of homologous series may behave similarly. Examples are found in the urea–*n*-hydrocarbon adducts and related compounds.

[18] Dryden and Meakins, *Nature*, 1952, **169**, 324.

In this case the composition may be definite although the molecular ratio is not simple. The number of enclosing molecules necessary to surround a given molecule of *n*-paraffin can be calculated from the known dimensions of the cell, the number of urea molecules it contains, and the dimensions of a paraffin together with the intermolecular spacing between two paraffin ends. Thus Smith [6] gives the length of hydrocarbon chains as [1·256(*n* – 1) + 4] Å (for *n* odd and nearly so for *n* even). Since $c = 11{\cdot}01$ Å and corresponds to 12 ureas and 2 channels, U/H, the molecular ratio urea : hydrocarbon, is given by

$$\frac{U}{H} = \frac{12[1{\cdot}256(n-1)+4]}{2 \times 11{\cdot}01} = 0{\cdot}6848(n-1) + 2{\cdot}181$$

If the channels are not uniform we may expect departures from this type of equation. This is the case for the thiourea adducts [7] with ωω′-di*cyclo*hexylalkanes. Thiourea adducts differ structurally from those of urea but there is a general resemblance between the two series. The channels are, as might be expected, larger. To fill them it is necessary to have molecules thicker than the normal paraffins. That the principle of good space filling, under the influence of van der Waals attraction, is of basic importance in these compounds is made clear by the non-existence of *n*-paraffin–thiourea compounds. Branched paraffins form adducts, and a similar rule for composition in relation to molecular length applies. But the thiourea channels are less uniform in character than those in urea and there are marked periodic variations in attractive forces. Accordingly the adducts with ωω′-di*cyclo*hexylalkanes do not show a continuous variation of molecular ratio with increase in length of the paraffin chain.

Chemical Purification by Means of Inclusion Compounds.—The dimensional limitations of the spaces in inclusion compounds suggest chemical uses in separation and purification processes. The principles are simple. The space of fixed shape and size will contain only certain molecules. From mixtures, therefore, one molecule may be taken in and another not. In clathrates there are severe limitations, and homologues are separable. In channel structures homologues are not separable, but branched and straight forms may be separated. *cis*- and *trans*-Isomers may be separated. The possible variations are endless but need individual study.

In practice the matter may not be quite so simple. A molecule which does not normally enter the urea or thiourea channels may do so when accompanied by another substance which normally goes in. Conversely a compound that normally forms a complex may be prevented from doing so by the presence of one that does not.[19]

The complex $Ni(CN)_2NH_3,C_6H_6$ has been used to obtain benzene of 99·992% purity in large yield.[20]

Tri-o-thymotide.—The substance tri-*o*-thymotide recently discovered by Wilson Baker, Gilbert, and Ollis,[21] illustrates many of the points which have been mentioned. Tri-*o*-thymotide crystallises with one-half of a molecule of *n*-hexane, chloroform, or several other substances. An *X*-ray investigation [22] showed that tri-*o*-thymotide, which has a molecule of rather awkward shape, will crystallise by itself from some solvents, but that from many others it crystallises in a solvated form. For some of these compounds the solvent, which may ordinarily be very volatile, is removed only on heating at 180° in a good vacuum. Examples are the compounds with benzene, chloroform, and *n*-hexane.

The crystal structures of these compounds are not all the same but they fit into several groups. A large number of small molecules give trigonal crystals with an almost constant form of unit cell. Molecules in this class are *n*-alcohols up to pentanol, and a number of other short molecules such as *n*-propyl iodide, acetone, *sec.*-butyl bromide and iodide, active amyl alcohol, carbon disulphide, chloroform, ethylene dibromide, and benzene. There is little doubt that hundreds of other substances of suitable molecular dimensions could be similarly included. The detailed crystal structure is not known but certain inferences can be drawn. The general behaviour is similar to that of clathrates or urea adducts. The chemical nature of the included molecule seems of little importance. Its size is. The spaces in which the included component lies seem to be of limited length. Thus *n*-hexane, *n*-hexanol, *n*-heptanol, *sec.*-octyl and cetyl bromide, all of which have longer molecules than those previously mentioned, give molecular addition compounds, but these have a different symmetry. They are, however, rather similar in unit-cell dimensions and, like the trigonal compounds, contain six molecules of the main tri-*o*-thymotide component, related to each other by three-fold screw-axes of symmetry. Thus it

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[19] Linstead and Whalley, *J.*, 1950, 2987.

[20] Evans, Ormrod, Goalby, and Staveley, *J.*, 1950, 3346.

[21] Baker, Gilbert, and Ollis, *J.*, 1952, 1443.

[22] Newman and Powell, *J.*, 1952, 3747.

appears that tri-*o*-thymotide molecules adjust themselves to the longer partners by forming an alternative, though related, structure. Perhaps the cavities give place to channels, or one type of channel to another. Similarly the cavities of the trigonal variety which contain the smaller molecules must be limited in breadth. Bromoform, clearly not too long a molecule, does not form the trigonal structure. Its greater width, compared with that of chloroform, must be the determining factor. This is confirmed by experiments with other selected molecules. A single side-chain substituent such as the bromine atom of *sec.*-butyl bromide, does not broaden the molecule too much for its inclusion. However, *iso*butene dibromide and acetylene tetrabromide were found, as expected, not to enter the trigonal structure. Nor do these broad, but on the whole, short molecules enter the cavities of the hexagonal form which will accommodate molecules as long as cetyl bromide and as broad at least as *sec.*-octyl bromide. Instead, they form molecular compounds with tri-*o*-thymotide which have special structures of their own. The composition is in each case one tri-*o*-thymotide to one other component molecule, and so far each of them is the only member of its structure type. It may be expected that other substances of molecular shapes which it is possible to some extent to select and predict will form related structures.

Structures with Dissymmetric Cages or Channels.—The tri-*o*-thymotide molecule is not identical with its mirror image but may have a form resembling a three-bladed propeller. It can be converted into its mirror image by rotations about the single bonds of the central ring system. The interconversion is sterically hindered. It has been shown from *X*-ray examination and symmetry considerations that pure orthorhombic tri-*o*-thymotide contains equal numbers of *dextro-* and *lævo*-molecules, but molecular compounds of tri-*o*-thymotide with benzene or with *n*-hexane contain molecules of one hand only. The crystals themselves do not reveal this by means of enantiomorphous faces, but the *X*-ray diffraction pattern proves that the space-group is enantiomorphous. These findings have been exploited in chemical operations which lead to separations of *dextro-* and *lævo*-molecules.[23] The tri-*o*-thymotide–benzene adduct has been grown in large crystals. When a single crystal is dissolved in chloroform the solution rotates the plane of polarisation of light. Thus the normally racemic tri-*o*-thymotide has been induced to resolve spontaneously. In solution the rotation disappears rapidly through racemisation of the tri-*o*-thymotide according to a first-order reaction which has a half-life period of about 3½ minutes at 20°. As a result of this rapid racemisation the whole of the tri-*o*-thymotide may be obtained in the *dextro*-form. A single crystal may be grown in a time long compared to the half-life, so that equilibrium of *dextro-* and *lævo*-forms is maintained in solution while the *dextro*-form alone is removed from it. If a nucleus of the opposite hand is used all the tri-*o*-thymotide may be removed in the *lævo*-form. By suitably seeding a cooling solution the whole of the crystalline adduct may be obtained in either the *lævo-* or the *dextro*-form without growing large crystals.

Since the tri-*o*-thymotide framework in the crystal is enantiomorphous the spaces that it encloses in the two kinds of crystals must also be mirror images of each other. When, therefore, an adduct is formed by crystals of the substance from a solvent which is itself a racemic mixture, it would be expected that any one crystal will take in preferentially the *dextro-* or the *lævo*-form of a solvent molecule according to the shape of its cavities. The volume available for the excluded molecule is sufficient but its configuration is wrong. When the experiment is carried out with *sec.*-butyl bromide it is found that crystals of a homogeneous crop, prepared by growth from a single nucleus, will rotate the plane of polarisation of light when dissolved in chloroform. The large rotation due mainly to the tri-*o*-thymotide decays rapidly throughout racemisation and leaves a much smaller permanent rotation due to the *sec.*-butyl bromide. The rotation of the resolved butyl bromide is found to be of the same sense as that of the tri-*o*-thymotide which it accompanies.

By these methods substances have been obtained in optically active form without the use of any optically active starting material in its resolved form. Schlenk [24] has reported similar resolutions by means of urea adducts. They belong to an enantiomorphous space-group but in this case the molecules which form the framework are not dissymmetric. Cramer [25] finds partial optical resolutions in the dextrin adducts. Here the dextrin molecules themselves already exist in optically active form.

[23] Powell, *Nature*, 1952, **170**, 155.
[24] Schlenk, *Experientia*, 1952, **8**, 337.
[25] Cramer, *Angew. Chem.*, 1952, 136.