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## INCLUSION COMPOUNDS

Inclusion compounds are combinations of two or more compounds one of which is contained within the crystalline framework of the other. The components of an inclusion compound are each capable of existing separately, and they have no obvious way of uniting chemically. They are held together by secondary valence forces and by hydrogen bonds. Inclusion compounds differ from conventional hydrogen-bonded systems, however, in that the size and shape of the "host" and "guest" molecules are critically important in the former, whereas in the latter such considerations may play little or no part.

Inclusion compounds are frequently called adducts or complexes because of the noncovalent nature of the bonds connecting the components and the variation in composition possible with some of them. It is preferable as well as convenient to refer to them as compounds because they are often indistinguishable from ordinary crystalline compounds; they are isolated and characterized in a similar way, and their properties differ from those of the components from which they are made.

Inclusion compounds have been known for over one hundred years, although they were not recognized as such until comparatively recently (41,44,47). The great interest in them stems largely from their utility in the separation of organic compounds, but they have numerous other interesting applications, some of which will be discussed. The elucidation and understanding of their structure is also a recent development and is a result of the application of modern physical and chemical tools.

Inclusion compounds can be divided into three main classes, depending on the shape of the framework structure. It may be a *channel (canal)*, a *cage (clathrate)*, or *layers (sandwich)*. In naming inclusion compounds, the substance whose name is stated is the framework-forming substance. For example, in urea or cyclodextrin inclusion compounds, urea or cyclodextrin, respectively, is the framework or including substance. Table I lists numerous inclusion compounds. The preparation, properties, and uses of the more important ones are described in this article.

TABLE I. Main Classes of Inclusion Compounds.<sup>a</sup>

<u>Channel (Canal)</u>	<u>Layer (Sandwich)</u>
Urea	Clays
Thiourea	
Choleic acids	<u>Miscellaneous</u>
Zeolites	4,4'-Dinitrodiphenyl
Cyclodextrins	Horse methemoglobin
	Acetylene
<u>Cage (Clathrate)</u>	Lipoproteins
Hydroquinone	Cellulose
Water (gas hydrates)	Starch
Ammonia-nickel cyanide	Graphite
	Phenols
	Zinc salts of acid dyes

<sup>a</sup> The compound named is the framework-forming component.

Other types of inclusion compounds have been described in the literature. Some of them are named in Table I, but information on them is relatively sparse or there is still dispute regarding their structure. The extensive reviews should be consulted for details (41,42,47,49).

Before discussing specific inclusion compounds, six factors which are of general applicability should be stated (43):

1. As a rule the framework structure is not that of the framework-forming component when it crystallizes alone. Examination of the components gives no indication of the crystal structure of the inclusion compound nor of substances likely to form inclusion compounds.

2. The dimensions and shape of the framework of the compound doing the including are subject to minor variations only, thus restricting compounds being included to those molecules whose shape and size permit them to fit into the space available. Thus, normal paraffin hydrocarbons fit into the urea channels in urea inclusion compounds, whereas highly branched isomers are too large.

Not only must molecules capable of inclusion have the size and shape to fit into the available space, but they must be sufficiently large so as not to escape through the openings in the framework. For instance, methanol can be included in hydro-

quinone, ethanol is too large and water is too small. Argon can be included in hydroquinone but helium is too small.

3. The stability of an inclusion compound and the tenacity with which a compound is held in molecular association are not always explainable by the mutual attraction of the components. The crystalline argon-hydroquinone inclusion compound has a negligible vapor pressure and is stable for long times, yet no interaction between the components is likely. This phenomenon is attributed to the imprisoning action of the molecular cage of hydroquinone which encloses the argon. Each atom of argon is surrounded by hydroquinone molecules which are held together tightly by numerous strong hydrogen bonds.

4. Any process which destroys the framework structure or supplies sufficient energy will set free the included components. Solution or heating are the best ways to destroy inclusion compounds. Thus, the stable argon-hydroquinone inclusion compound is readily decomposed with liberation of argon by solution of the inclusion compound in any solvent for hydroquinone. Zeolite inclusion compounds are best destroyed by heating under vacuum, although in this case the framework (zeolite) is not appreciably altered.

5. Inclusion compound formation is restricted to particular molecules by geometrical rather than by chemical characteristics. Thus, resorcinol (1,3-dihydroxybenzene) does not form cage inclusion compounds with argon and methanol, yet its closely similar isomer, hydroquinone, with the hydroxyl groups in the 1,4- position, will. One of the best examples of the importance of molecular geometry is the failure of highly branched hydrocarbons to form inclusion compounds with urea, whereas isomeric straight-chain hydrocarbons do so readily.

6. With some inclusion compounds, various compositions up to a limiting one may exist; in others only the limiting composition is formed. Crystallization of hydroquinone from methanol gives a cage inclusion compound with all the cavities filled, and the limiting composition, 3 hydroquinones to 1 methanol, is obtained. When an inert solvent is used to bring the components together, a considerable portion of the available spaces in the hydroquinone cages are empty. Urea inclusion compounds, on the other hand, always have the limiting composition regardless of the method of preparation.

### Channel Inclusion Compounds

**Urea Inclusion Compounds.** These form the most important and most thoroughly investigated class of inclusion compounds. Numerous reviews on the subject have been written (41,45,47,48). In 1940, F. Bengen (4) discovered that urea forms beautifully crystalline inclusion compounds with straight-chain compounds containing about six or more carbon atoms, but not with branch-chain or cyclic compounds. He prepared inclusion compounds from straight-chain hydrocarbons, acids, esters, alcohols, aldehydes, and ketones. Subsequently, other investigators, notably W. Schlenk (46), showed that these and many other classes of straight-chain compounds also form urea inclusion compounds.

Urea inclusion compounds are most conveniently prepared by bringing together urea and the compound to be included, preferably in a mutual solvent such as methanol. The inclusion compound precipitates and is easily separated and handled. Numerous preparative methods are available depending on the solubility and vapor pressure of

the compounds being studied, whether a high yield or high purity of inclusion compound is desired, and, if mixtures are being studied, what degree of separation is desired. Preparative methods have recently been reviewed (48).

In general, ease of formation and stability of urea inclusion compounds increase with increasing chain length. The maximum chain length reported to form a urea inclusion compound with straight-chain hydrocarbons is C<sub>60</sub>; with esters, C<sub>46</sub>. These chain lengths are not necessarily upper limits.

In no case studied is any urea inclusion compound stable above 133°C., the melting point of urea. Table II shows how the room temperature stability of urea inclusion compounds of aliphatic ketones, as measured by half-life times, increases with chain length (46). At a chain length of 7 or fewer carbon atoms, the inclusion compound will not endure very long. The rate of increase of half-life with increasing chain length, however, suggests that, at a chain length of 8 or more carbon atoms, the stability of the inclusion compound will be high, and this is found to be the case. In urea inclusion compounds of other homologous series of *n*-aliphatic compounds, about 8 carbon atoms represent the shortest chain length which yields an inclusion compound stable at room temperature for long periods of time. In general, the stability varies in some inverse way with the vapor pressure of the included compound, although vapor pressure is not the sole criterion for stability.

TABLE II. Half-Life Times at Room Temperature of Urea-Ketone Inclusion Compounds.

Compound included	Number of carbon atoms	B.p., °C.	Vapor pressure, mm., 25°C.	Half-life time, min.
Acetone	3	56.5	230	4
Methyl ethyl ketone	4	79.6	100	10
Diethyl ketone	5	102.7	18	140
Di- <i>n</i> -propyl ketone	7	143.7	1.1	1500

Certain branched-chain or cyclic compounds will also form urea inclusion compounds provided that there is a sufficiently long straight chain in the molecule and the branch or cycle is not too large (17,25,30,31,35,46). Thus, 1-phenyloctadecane and 1-cyclohexyleicosane, in which the rings are at the end of long, straight chains, form urea inclusion compounds, whereas benzene and cyclohexane do not. Phenyl hexanoate does not form a urea inclusion compound because the straight-chain part of the molecule is too short, but phenyl dodecanoate does.

Urea inclusion compounds crystallize almost exclusively in hexagonal prisms, whereas urea itself is tetragonal (27). In forming the inclusion compound, the urea molecules build up the framework structure in a helical way (46). The unit cell (Fig. 1) contains six molecules of urea (solid circles) which occupy the edges of a prism spiralling over a length of 11.1 Å.

A cross-sectional view of the hexagonal urea is shown in Figure 2A. The included compound (not shown) is attached to the ureas by van der Waals' forces, London dispersion forces, or induced electrostatic attractions. The urea channel is about 6 Å at its widest part and almost 5 Å at its narrowest. Straight-chain hydrocarbons (Figure 2B) have a cross section of about 4.1 Å and form inclusion compounds readily. Hydrocarbons with a single methyl branch (Fig. 2D) require a channel diameter of about 5.5 Å. When the straight-chain portion of such compounds is relatively short, as in 3-methylheptane, the compound does not form a urea inclusion

compound, but it forms one readily when admixed with a straight-chain compound that does. Compounds with a double branch on one carbon atom, such as 2,2,4-trimethylpentane (Fig. 2E) require a channel diameter of about 6 Å in all directions, and no urea inclusion compound has yet been obtained with such materials. Benzene (Fig. 2C) requires a channel diameter of 5.9 Å and does not form a urea inclusion compound.

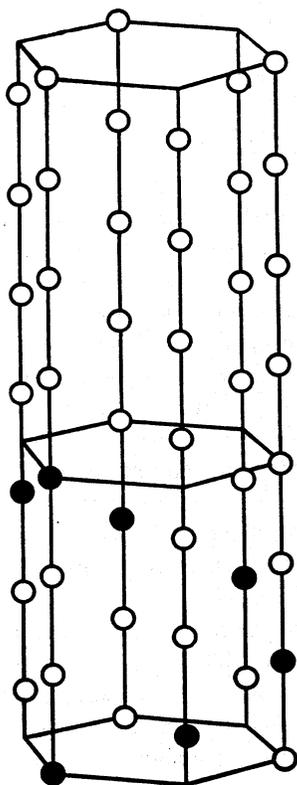


Fig. 1. Structure of hexagonal urea in inclusion compounds.

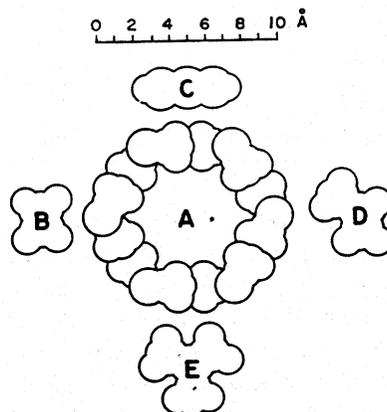


Fig. 2. Cross section of hexagonal urea (A); *n*-octane (B); benzene (C); 3-methylheptane (D); and 2,2,4-trimethylpentane (E).

Table III shows some typical results obtained in preparing urea inclusion compounds from methyl esters of straight-chain fatty acids containing 8–18 carbon atoms (16). The yields of all the inclusion compounds shown can be brought above 85% by the use of large excesses of urea during the preparation. Urea inclusion compound formation is an equilibrium reaction and, by the mass action effect, large quantities of urea give more complete conversion to inclusion compound (23).

The molar ratio of urea to included compound is not a whole number and increases linearly with increase in chain length of included compound. On the other hand, the weight ratio of urea to included compound is reasonably constant at 3:1. This conclusion is based on results obtained with numerous straight-chain compounds, such as methyl esters of fatty acids, fatty acids, hydrocarbons, halides, mercaptans, and ketones. Only the limiting composition of urea to included compound is obtained (45,46,48).

The composition of urea inclusion compounds can be determined by a variety of chemical and physical methods. Among the chemical methods, functional group

TABLE III. Urea Inclusion Compounds of Methyl Esters of C<sub>8</sub> to C<sub>18</sub> Fatty Acids.

Methyl ester	Inclusion compound		
	Yield, %	Ratio of urea to ester	
		Molar	Weight
Octanoate	59	8.7	3.3
Decanoate	69	9.6	3.1
Dodecanoate	73	11.0	3.1
Tetradecanoate	72	12.2	3.0
Hexadecanoate	66	13.4	3.0
Octadecanoate	100	14.5	2.9
<i>cis</i> -9-Octadecenoate	51	14.4	2.9
<i>trans</i> -9-Octadecenoate	60	13.9	2.8

analysis is usually the best. Determination of acid or saponification number of an inclusion compound permits calculation of the composition of acid or ester inclusion compounds, respectively. Urea has a slight saponification number for which a correction must be made. Inclusion compounds of unsaturated compounds can also be analyzed directly by the usual halogen absorption methods. Ultimate analysis (carbon, hydrogen, nitrogen, sulfur, halogen) is employed when functional group methods are inapplicable. When both methods are used the results usually check well. If desired, the inclusion compound can be decomposed by addition of hot water to dissolve the urea, or by addition of a hot organic solvent, in which urea is insoluble, to dissolve the included compound(s). Urea or the included compound(s) can be determined by chemical or optical methods (refractive index, optical rotation, ultraviolet, and infrared adsorption) or by evaporation and weighing the residue. Refractometric and calorimetric methods have also been reported.

Various methods have been reported for the decomposition of urea inclusion compounds and reisolation of the included compound(s). The most satisfactory method is addition of water to dissolve the urea, leaving the included compound(s) as an oil or solid for easy separation. Conversely, the inclusion compound can be heated with a nonincluding solvent, such as benzene, isooctane, or carbon tetrachloride, in which urea is insoluble. The included compound(s) will be extracted from the inclusion compound. With volatile compounds, quantitative recovery can often be obtained by atmospheric, vacuum, or steam distillation. By distilling through a fractionating column, simultaneous decomposition and fractionation of mixed inclusion compounds can be effected.

Numerous applications of urea inclusion compounds have been described, mainly in the petroleum and fat fields (45,48). Separation of straight-chain hydrocarbons from crude petroleum fractions is readily accomplished by the use of urea. Mixed *n*-paraffins from about C<sub>7</sub> to C<sub>50</sub>, depending on the starting stock, can be obtained uncontaminated by branched and cyclic compounds. Fractional distillation of the mixed *n*-paraffins yields substantially pure individual compounds. The fraction that does not form an inclusion compound has an extremely low pour point. Reductions in pour point of over 100°F. have been accomplished.

This technique has been used in the preparation of dewaxed lubricating oils without use of refrigeration, low pour-point kerosine stocks for use as low-vapor-pressure jet fuel or for blending with gasoline to be used as high-vapor-pressure jet fuel, and low pour-point distillate fuels from light and heavy stove oils. These

separations are more efficient than distillation in lowering the pour point. Increase in the octane number of gasoline by 11 to 12 units has also been accomplished by removal of straight-chain components as urea inclusion compounds. The mixed straight-chain hydrocarbons separated in these processes can be used in wax formulations and to raise the cetane number of diesel fuel. Another interesting application is the analysis of petroleum hydrocarbon mixtures for straight-chain components. *n*-Paraffins containing 14 or more carbon atoms can be precipitated from mixtures substantially quantitatively. For qualitative identification only, the urea inclusion compound precipitation procedure can be used with *n*-paraffins containing as few as 7 carbon atoms.

In the field of fats, the most obvious application is the separation of free fatty acids, which readily form urea inclusion compounds, from fats, tall oil, polymerized fatty acids, and other substances which do not. Also, urea can be used to fractionate mixtures of fatty acids, esters, alcohols, and other derivatives. There are three main types of separation, namely, separations based on differences in chain length, degree of unsaturation, and branching. In separations based on differences in chain length, advantage is taken of the fact that the longer chain compounds form urea inclusion compounds preferentially. Therefore, if insufficient urea is employed to combine with all the components of a mixture, the longer chain components will combine with the urea and precipitate. For best results, the components to be separated should differ in chain length by at least 4 carbon atoms and preferably by 6. Obviously, when the chain length difference is 6 or more carbon atoms, other separation methods, such as distillation or crystallization, can be used. If the substances are heat labile or if crystallization, temperatures required are extremely low,  $-90^{\circ}\text{C}$ . for example, the urea method, which is operative at room temperature to  $0^{\circ}\text{C}$ ., may be preferable.

In separations based on differences in unsaturation, advantage is taken of the fact that as a long chain compound becomes more unsaturated it shows greater deviation from the normal straight-chain structure. Therefore, at a given chain length, saturated components of a mixture would be expected to form urea inclusion compounds preferentially to monounsaturated, monounsaturated preferentially to diunsaturated, and so on. Taking advantage of this difference in ability to form inclusion compounds, purified saturated, oleic, linoleic, linolenic, and more highly unsaturated fatty acids, as well as their methyl esters, have been isolated from natural sources. The method has also been applied to alcohols and nitriles. No temperature below about  $0^{\circ}\text{C}$ . is required in these separations, whereas the usual fatty acid or ester solvent purification techniques may require crystallization temperatures in the range of  $-50^{\circ}$  to  $-90^{\circ}\text{C}$ .

In studies on wool wax and other alcohols as well as on other classes of compounds, separation of straight chain or only slightly branched compounds from the more highly branched has been accomplished by preferential urea inclusion compound formation. In the further fractionation of alcohols, acetylation of the alcohols isolated from the inclusion compound followed by reformation of the inclusion compound, precipitates the acetates of primary alcohols leaving the acetates of secondary alcohols unincluded and in the filtrate. The purpose of acetylation is to increase the length of the straight chain in the primary alcohols while enlarging the size of the branched group in the secondary alcohols, thereby permitting a separation of primary from secondary alcohols. On the other hand, certain branched-chain compounds which do not form urea inclusion compounds can be caused to form them readily by

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TABLE IV. Dissociation Temperatures of Urea Complexes.

Acids	Dissociation temp., °C.	Methyl esters	Dissociation temp., °C.	Alcohols	Dissociation temp., °C.	Miscellaneous	Dissociation temp., °C.
Caproic (C <sub>6</sub> )	64						
Caprylic (C <sub>8</sub> )	73	Caprylate	55	Nonanol	57	Vinyl pelargonate	52
Pelargonic (C <sub>9</sub> )	80.5			Decanol	68		
Capric (C <sub>10</sub> )	85	Caprate	67	Dodecanol	80		79
Lauric (C <sub>12</sub> )	92.5	Laurate	77.5				
Tridecyclic (C <sub>13</sub> )	96						
Myristic (C <sub>14</sub> )	103	Myristate	96	Tetradecanol	91		
Palmitic (C <sub>16</sub> )	114	Palmitate	118	Hexadecanol	107	Vinyl palmitate	113
Stearic (C <sub>18</sub> )	126	Stearate	132	Octadecanol	124	Vinyl octadecyl ether	125.5
Oleic (C <sub>18</sub> , <i>cis</i> )	110	Oleate ( <i>cis</i> )	110	Oleyl ( <i>cis</i> )	98		
Elaidic (C <sub>18</sub> , <i>trans</i> )	116	Elaidate ( <i>trans</i> )	125	Elaidyl ( <i>trans</i> )	118		
10-Hendecenoic (C <sub>11</sub> )	90						
9,10-Epoxy stearic ( <i>cis</i> ), m.p. 59°C.	118						
9,10-Epoxy stearic ( <i>trans</i> ), m.p. 55°C.	125						
9,10-Dihydroxystearic m.p. 95°C.	107	9,10-Dihydroxystearate m.p. 70°C.	120				
12-Hydroxystearic, m.p. 81°C.	125	9,10-Dihydroxystearate m.p. 103°C.	114				
12-Ketostearic, m.p. 82°C.	115						

lengthening the straight chain. For example, although the methyl- and ethylbutanols and -hexanols do not form inclusion compounds, their esters with long-chain fatty acids, such as 3-methylbutyl hexanoate, 2-methylbutyl decanoate, 2-ethylhexyl octanoate, and 2-ethylbutyl decanoate, do. The corresponding esters with straight-chain acids containing fewer carbon atoms do not form inclusion compounds.

Polyunsaturated fatty materials cannot be stored for long periods because they are readily autoxidized. Urea inclusion compounds of unsaturated fatty materials, however, do not autoxidize when exposed to air, and this is a convenient way to store labile fatty materials. From the structure of the inclusion compound it can be seen that the fatty molecules occupy a restricted space in the crystal lattice of the urea. The crystal lattice probably offers a barrier against the free penetration of oxygen, and the restricted space in the lattice is too small to permit the formation of peroxides if oxygen were to penetrate. Furthermore, autoxidation is known to be a chain reaction, and it is unlikely that such a mechanism could operate between the strictly separated fatty molecules in the crystal lattice.

Urea can be used in the concentration of long-chain fatty peroxides. These substances are branched in the sense that they contain a bulky group along the straight chain. The clean-cut separation of unoxidized (straight chain) from peroxidic material can be accomplished by urea precipitation of the former. The nonincluded (filtrate) fraction consists of peroxide concentrates (70-90% peroxide in the case of methyl oleate peroxides), and yields are usually high.

All urea inclusion compounds have been reported to have the melting point of urea. Therefore, there must be some temperature at which the inclusion compound decomposes into its components, which presumably are immiscible, and the urea melting point is observed. This initial temperature of decomposition, which has been defined as the dissociation temperature, can be readily observed by slowly heating several crystals of transparent inclusion compound on a Kofler hot stage attached to a low- or medium-power microscope. When decomposition ensues, the transparent crystals become milky. Repetition on a fresh sample permits duplication of the dissociation temperature of any particular inclusion compound to  $\pm 1.5^\circ\text{C}$ . Table IV lists the dissociation temperatures of urea inclusion compounds of approximately 40 fatty compounds (16). In each homologous series, the dissociation temperatures of inclusion compounds of adjacent or closely adjacent members are sufficiently far apart to permit identification. This is in contrast to the melting points of the common derivatives of long-chain compounds. If the dissociation temperatures for each of the four homologous series in Table IV are plotted against number of carbon atoms, straight lines are obtained which converge near the melting point of urea. For a given number of carbon atoms, the most stable inclusion compounds are obtained with the acids, then the alcohols, the methyl esters, and the vinyl esters.

The sensitivity of dissociation temperatures and their use in structure work are best illustrated by comparing the dissociation temperatures of several *cis-trans* pairs (oleic-elaidic acid, *cis* and *trans*-9,10-epoxystearic acids, methyl oleate-elaidate, and oleyl-elaidyl alcohols). In each pair the vapor pressure and number of carbon atoms is the same, but the dissociation temperature of the *trans* isomer is significantly higher than that of the *cis* isomer. The inclusion compound of the *trans* isomer is more stable, even though the secondary valence forces involved in the formation of inclusion compounds from *cis-trans* pairs are identical. Examination of molecular models of *cis-trans* isomers shows that the *trans* isomers have little or no additional spatial require-

ments in the urea channel over those of the corresponding saturated compounds (cross section, about 4.1 Å). In contrast, the cis compounds have slightly greater spatial requirements, and slight distortion of the normal shape of the long-chain molecule must occur for it to be accommodated in the urea channel. Thus, with cis compounds some strain is present, thereby yielding a less stable inclusion compound, which is reflected in the dissociation temperature.

A novel application of urea inclusion compounds has been described by Schlenk (26), and only a limited amount of information is available on it. If a urea inclusion compound is prepared from any substance, either the crystals will all have a right hand helix or they will all have a left hand helix. This is determined solely by chance, the first crystals to be formed acting as a seed for all the others. If an inclusion compound is prepared from a racemic mixture, crystals will be obtained which can be symbolically represented, assuming that a right hand helix forms, as D-form-right hand helix and L-form-right hand helix. These, of course, are no longer mirror images and should have slightly different solubilities. Therefore, if a racemic mixture is treated with insufficient urea to precipitate the compound completely as inclusion compound, the isomer which preferentially precipitates will be the one whose inclusion compound has the lower solubility, and a slight concentration of it will be accomplished. A few crystals of this are reserved; the remaining crystals are decomposed, and the regenerated compounds are again treated with insufficient urea to precipitate all the material. The solution, however, is first seeded with the crystals which have been reserved for this purpose. This ensures that the same direction of helix will form as in the first case, and an additional concentration of the same isomer will be achieved. This process, repeated many times, will ultimately separate optical isomers. Separation of optically isomeric chlorooctanes has been accomplished, and it has been mentioned, with no details given, that the absolute configuration of amino acids can be determined.

**Thiourea Inclusion Compounds.** Thiourea inclusion compounds with organic compounds were discovered independently by Fetterly (37,38,39) and by Angla (40) in the middle 1940's. In substantially every other respect, thiourea is similar to urea, but the types of compounds with which it forms inclusion compounds are quite different. Thiourea forms them with many branched-chain and cyclo-aliphatic compounds, but generally not with straight-chain compounds, aromatics, and terpenes. Thus, urea and thiourea separation techniques complement each other. Originally it was thought that thiourea did not form inclusion compounds with any straight-chain compounds, but it was recently reported that *n*-paraffins with 16 or more carbon atoms will form them with thiourea at 0°C. or even at as high a temperature as 25°C.; *n*-tetradecane will form one at 0°C. but not at 25°C., and paraffins with 12 or fewer carbon atoms do not form them even at 0°C. Thiourea inclusion compounds with *n*-paraffins have low stability (18).

Table V lists some compounds reported to form inclusion compounds with thiourea. None of these forms urea inclusion compounds. Although aromatic compounds generally do not form thiourea inclusion compounds, specific ones will in which a predominating part of the molecule is highly branched, *e.g.*, *p*-methylphenyl *tert*-butyl ketone. The molar ratio of thiourea to hydrocarbon is somewhat lower than the molar ratio of urea to straight-chain hydrocarbons.

X-ray data on thiourea inclusion compounds have been published (27). The unit cell of thiourea in the inclusion compound is rhombohedral, and the arrangement

TABLE V. Compounds Forming Thiourea Inclusion Compounds.

<u>Hydrocarbons</u>	<u>Halogen Compounds</u>
2,2-Dimethylbutane	Chloroform
2,3-Dimethylbutane	Bromoform
2,2,3-Trimethylbutane	Iodoform
2,2,4-Trimethylpentane	Carbon tetrachloride
Hexamethylethane	Tetrachloroethane
2,2,3,4-Tetramethylpentane	Hexachloroethane
Decahydronaphthalene	Isopropyl iodide
Cyclopentane	<i>tert</i> -Butyl chloride
Methylcyclopentane	<i>tert</i> -Butyl bromide
Ethylcyclopentane	<i>tert</i> -Butyl iodide
Cyclohexane	Bornyl chloride
Methylcyclohexane	Chlorocyclohexane
Alkylcyclohexanes	
Cyclohexene	<u>Alcohols</u>
3-Ethyltetracosane	Cyclohexanol
1,1-Dimethylcyclopentane	Pinacol
1,1,2-Trimethylcyclopentane	Borneol
1-Methyl-1-ethylcyclopentane	Trichlorotrimethylcarbinol
<i>cis</i> -1-Methyl-3-ethylcyclopentane	
<i>trans</i> -1-Methyl-3-ethylcyclopentane	<u>Ketones</u>
1-Cyclohexyloctane	Methyl isobutyl ketone
1-Cyclohexyleicosane	Pinacolone
1,4-Di- <i>n</i> -decylcyclohexane	Cyclohexanone
<i>exo</i> -Perhydro-4,7-methanoindene	Alkylcyclohexanones
2-Cyclohexyleicosane	Cyclopentanone
1,2-Dicyclohexylethane	Menthone
1-Cyclohexyl-3-cyclopentylpropane	Pulegone
1-Phenyl-2-cyclohexylethane	Camphor
1-Cyclopentylheneicosane	Cyclohexenone
Dicyclopentyl	Thujone
<i>cis</i> (0,3,3) Dicyclooctane	<i>p</i> -Methylphenyl <i>tert</i> -butyl ketone
1,3-Dicyclopentylcyclopentane	
Menthane	
Pinane	
Camphane	

of the thiourea molecules is similar to that of urea molecules in urea inclusion compounds. The larger size of the sulfur atoms, however, results in a larger channel, about 8 Å in diameter, in which branched or cyclic compounds fit.

Methods of preparation, isolation, analysis, and decomposition of thiourea inclusion compounds are essentially the same as for urea inclusion compounds. The lower stability of the thiourea compounds requires that more precautions be taken in their handling and storage.

**Choleic Acids.** Inclusion compounds in which desoxycholic acid and apocholic acid, collectively known as choleic acids, are the framework-forming substances have been known since 1916. Wieland and Sorge (33) were apparently the first to appreciate that the combinations of bile acids with fatty acids, which are so difficult to separate, are actually molecular adducts of some kind. Go and Kratky (14) showed by x-ray studies that desoxycholic acid crystallizes with an open structure containing free channels in the center capable of including a variety of other organic compounds.

Table VI lists the classes of organic compounds known to form choleic acid inclusion compounds. The size and shape of the included compound do not appear to be critical since branched, unbranched, large, and small molecules can be included. The usefulness of choleic acid inclusion compounds in separations is limited because of the nonspecificity of separation and also because of the high cost of the framework-forming components.

**TABLE VI. Compounds Forming Choleic Acid Inclusion Compounds.**

Alcohols	Fatty Acids
Aliphatic	Hydrocarbons
Cholesterol	Aromatics
Aldehydes	Olefins
Benzaldehyde	Paraffins
Alkaloids	Polynuclear
Dibasic acids	Ketones
Esters	Camphor
Fatty acid esters	Phenols
Phenyl salicylate	

Choleic acid inclusion compounds are best prepared by mixing solutions of the components. In general, these inclusion compounds are exceedingly stable even in solution, and they may have melting points higher than those of the components. Some, however, are completely dissociated in solution (sebacic acid-desoxycholic acid).

X-ray powder patterns of choleic acid inclusion compounds are essentially identical. Single crystal studies show the presence of a channel about 8 Å wide. The molar ratio of components is generally the limiting value and, as distinguished from urea inclusion compounds, is a whole number. Table VII lists the composition of desoxycholic acid-fatty acid inclusion compounds. Note that the number of moles of desoxycholic acid in the inclusion compound does not exceed 8 even though calculations of channel length indicate that more are required. This suggests that the larger chain fatty acids are not fully extended in the inclusion compound so that more of the chain than expected will pack into the channel.

**TABLE VII. Fatty Acid-Desoxycholic Acid (DCA) Inclusion Compounds.**

C atoms in acid	Molar ratio of DCA to acid	
	Calculated	Found
2	—	1
3	4	3
4-8	4	4
9-14	6	6
15-20	8	8
21-25	10	8
26	12	8

Formic acid does not form an inclusion compound.

On the other hand, with certain long-chain esters, such as ethyl arachidate and ethyl cerotate, the number of moles of desoxycholic acid found in the inclusion com-

pound per mole of ester is as high as 12 and in one instance (octyl stearate) the number of moles of desoxycholic acid found, 10, is less than that calculated, 12.

Choleic acid inclusion compounds of water-insoluble substances, such as fats and hydrocarbons, are soluble in dilute alkali, thereby permitting these materials to be handled in aqueous media.

Choleic acid inclusion compounds can also be used in the separation of racemic mixtures. Since the framework-forming compounds are optically active, they can be used to effect partial separations of racemic mixtures of optically active substances, such as camphor and dipentene, because the inclusion compounds formed from the *d*- and *l*-isomers of the racemate are no longer mirror images.

An interesting point bearing on the structure of choleic acids is that in inclusion compounds of ketones, such as benzoylacetone, acetylacetone, and ethyl acetoacetate, the ketones are in the completely enolized form.

**Zeolites.** Zeolites are also inclusion compounds of the channel type. See Vol. 12, pp. 295, 328. They are sometimes called molecular sieves, because of their mode of action, or Barrer minerals, after the name of the man who has been most active in the field (1,2,36).

Certain natural hydrated silicates, such as analcite and chabazite, as well as some synthetic aluminosilicates, have a channel-like structure with channels 5-6 Å in diameter. These may be filled with cations, such as sodium or potassium, or water. By heating these minerals with water, the ions can be displaced completely, filling the interstitial spaces with water. Heating the minerals to 300-360°C. for about 24 hr. removes the water but causes little or no alteration in the framework of the mineral. The channels can then be filled with many kinds of neutral molecules whose cross section does not exceed about 4 Å.

Table VIII lists some substances which are capable of inclusion. Highly branched aliphatic and aromatic hydrocarbons are not included, and the longer straight chain aliphatic hydrocarbons are included at a low rate. Quantitative separation of certain mixtures is, therefore, possible.

TABLE VIII. Substances Included in Zeolites.

Hydrocarbons	Miscellaneous	Gases
Methane	Methylene dichloride	Argon
Ethane		Krypton
<i>n</i> -Propane		Xenon
<i>n</i> -Butane		Neon
<i>n</i> -Pentane		Hydrogen
<i>n</i> -Hexane		Oxygen
Isobutane		Ammonia
Ethylene		
Acetylene		

These minerals show a greater selectivity than charcoal, and separation of neon from helium can be effected at -195°C. since 35 times as much neon is included as helium. Some molecules are included at temperatures as high as 300°C., but the rare gases are included and separated best at -15 to -195°C. Relatively large quantities of substances can be included in these minerals. Table IX shows the capacity of chabazite and analcite in milliliters of included compound per gram.

Zeolites and urea are similar in preferring to include straight-chain molecules rather than branched compounds. Two important differences, however, are: (a) the compositions of a urea inclusion compound made from a given substance is always the same (the limiting value) regardless of the conditions of preparation, whereas in the zeolites the composition will vary up to the limiting value depending on how much

TABLE IX. Including Capacity of Zeolites (ml./g.).<sup>a</sup>

	Chabazite	Analcite
Water	266	97
Ammonia	193	72
Hydrogen	186	69
Oxygen	181	67
Nitrogen	170	63
Methane	173	64
Ethane	125	46
<i>n</i> -Heptane	59	22

<sup>a</sup> Volumes calculated at 760 mm. and 0°C.

compound is available for inclusion and, (b) the stability of urea inclusion compounds increases with increasing chain length of included compound, but in zeolites the reverse is true.

Recently it was shown that silver analcite can be used in the quantitative separation of sodium and potassium ions from cesium. This separation has been termed an ion-sieve separation as distinguished from molecular sieve (3).

**Cyclodextrins (Schardinger Dextrins).** Cyclodextrins are formed by the enzymic degradation of amylose by the amylase of *Bacillus macerans* (24). The cyclodextrins are cyclic oligosaccharides having chains of 6, 7, or 8 glucose units connected head-to-tail to form large rings. They are usually designated  $\alpha$ ,  $\beta$ , or  $\gamma$ , and they have channel diameters of 6, 8, or 10–11 Å, respectively (9,10,11,12). Owing to the way the glucose molecules are packed, the cyclodextrins have pre-formed channels, even before an inclusion compound is formed, as distinguished from urea inclusion compounds, but similar to the zeolites.

$\alpha$ -Cyclodextrin forms inclusion compounds with relatively small molecules such as chlorine, bromine, and iodine, paraffin and chlorinated hydrocarbons, fatty acids and alcohols, and benzene derivatives with small substituents.  $\beta$ -Cyclodextrin also forms inclusion compounds with bromine and iodine but not with chlorine which is too small. Bromobenzene is too large for the  $\alpha$ - but fits into the channel of  $\beta$ - or  $\gamma$ -cyclodextrin.  $\gamma$ -Cyclodextrin forms only a loose inclusion compound with iodine (channel too large), but forms stable inclusion compounds with large organic molecules. As in the cases previously discussed, the inclusion compounds are formed by intimately mixing the components.

Cyclodextrin inclusion compounds are often stable up to 100°C., even under vacuum, but usually dissociate in aqueous suspension at 60–70°C. Steam distillation is a convenient way to isolate a volatile, bound component. The composition of these inclusion compounds depends on the amount of compound available for inclusion and may be as high as 30%. The x-ray pattern of a cyclodextrin and the inclusion compounds obtained from it are the same, thus demonstrating that the included compound is in the empty space and the lattices are the same.

The blue color which develops with starch and iodine has been known since about 1800, but it was only recently that it was shown to be caused by the formation of an inclusion compound. A blue color is formed because iodine is present in the channel in a polymeric, blue modification. This inclusion compound is stable in dilute aqueous solution.

### Cage (Clathrate) Inclusion Compounds

**Hydroquinone Inclusion Compounds.** An important class of cage inclusion compounds are those in which hydroquinone is the framework-forming component. In 1886 Mylius studied the interaction of hydroquinone with formic acid and concluded that he had not obtained a true chemical compound but that the molecules of hydroquinone were enclosing those of formic acid. It was not until 1947, with the thorough investigations of Powell and co-workers (19,20,21), that the structures and properties of this class of inclusion compounds were understood.

If hydroquinone is recrystallized from a solvent with which it is capable of forming an inclusion compound, the hydroquinone will crystallize in the form of a cage in which the limiting quantity of solvent molecules are included, that is, all cavities are occupied. The composition of these inclusion compounds is 3 hydroquinones to 1 solvent molecule. Typical solvents are methanol, acetonitrile, and formic acid.

A variety of gases also form inclusion compounds with hydroquinone. These are prepared by crystallizing hydroquinone under pressure of the particular gas from a solvent with which it does not form an inclusion compound. Such diverse gases as hydrogen chloride, hydrogen bromide, hydrogen sulfide, carbon dioxide, sulfur dioxide, nitrogen, acetylene, oxygen, nitric oxide, cyanogen chloride, hydrogen cyanide, and the rare gases, argon, krypton, and xenon, form inclusion compounds. In these cases, all of the available cavities in the cage will not be filled; the number of vacant spaces is variable and depends on the molecules available for enclosure when the cage is formed. Molecules which are too large, such as ethanol, and molecules which are too small, such as helium, do not form hydroquinone inclusion compounds.

The hydroquinone-gas compounds are generally stable at room temperature and atmospheric pressure, but evolve the gas when the hydroquinone is dissolved. These inclusion compounds are convenient for handling certain gases at atmospheric pressure, particularly the rare gases.

The structure of the hydroquinone cage is shown in Figure 3. The circles are oxygen atoms forming hexagons, the solid lines are hydrogen bonds between hydroquinone molecules, and the broken lines are the axes between the para oxygen atoms of the individual hydroquinone molecules. The carbon atoms of each benzene ring have been omitted for simplification. The stability of the structure stems from intermolecular hydrogen bonds. The cage structure can undergo some distortion to accommodate nonspherical molecules, but in no case can the molecule to be included exceed 4 A in diameter.

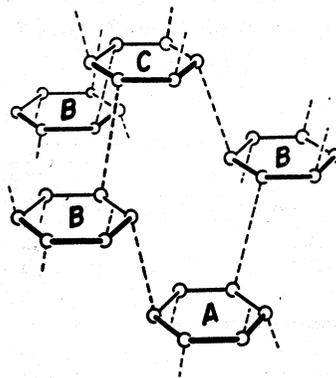


Fig. 3. Hydroquinone cage structure.

The clathrates of hydroquinone with oxygen and nitric oxide show magnetic susceptibility (8). The inclusion compounds with most of the polar liquids described earlier show dielectric absorption at ultrahigh radio frequencies, but in that with methanol the dielectric absorption occurs at audio frequencies (6).

A detailed thermodynamical and statistical interpretation of hydroquinone inclusion compounds was recently given (32,34).

**Water (Gas Hydrates).** For many years it has been known that natural gas lines occasionally plug up and then rupture during cold weather. Examination of the break reveals a white crystalline mass which for a long time was assumed to be ice. Detailed study, however, showed that these crystals consist of a combination of methane (predominant) and other gases with water. It is now known definitely that these crystals are cage inclusion compounds with ice as the framework-forming component and the gas as the included substance. The melting points of these hydrocarbon inclusion compounds vary with pressure and have been reported to be as high as 77° F. at 4000 p.s.i.

TABLE X. Gas Hydrates.

Included compound (b.p., °C.)	Decomposition temperature, atmospheric pressure, °C.	Dissociation pressure at 0°C.	Critical decomposition temp., °C.	Mole ratio of water to included compound
Argon (-190)	-43	105 atm.	—	6
Methane (-161)	-29	26 atm.	21.5	6
Krypton (-152)	-28	14.5 atm.	13	6
Carbon tetrafluoride (-130)	—	—	20.4	—
Xenon (-107)	-3.4	1.5 atm.	24	6
Ethylene (-102)	-13.4	5.5 atm.	18.7	6
Ethane (-93)	-15.8	5.5 atm.	14.5	6
Nitrous oxide (-89)	-19.3	10.0 atm.	12	6
Phosphine (-87)	-6.4	1.6 atm.	28	6
Acetylene (-84)	-15.4	5.7 atm.	16	6
Carbon dioxide (-79)	-24	12.3 atm.	10 (45 atm.)	6
Methyl fluoride (-78)	—	2.1 atm.	18	6
Hydrogen sulfide (-60)	0.35	731 mm.	29.5 (23 atm.)	6
Arsine (-55)	1.8	613 mm.	28.3	6
Propane (-42)	0	760 mm.	8.5	6
Hydrogen selenide (-42)	8.0	346 mm.	30	6
Chlorine (-34)	9.6	252 mm.	28.7 (6 atm.)	6
Ethyl fluoride (-32)	3.7	530 mm.	22.8	6
Tetrafluoroethylene (-32)	—	—	—	—
Methyl chloride (-24)	7.5	311 mm.	21	6
Stibine (-17)	—	—	—	—
Sulfur dioxide (-10)	7.0	297 mm.	12.1 (2.3 atm.)	6
Methyl bromide (4)	11.1	187 mm.	14.5 (1.5 atm.)	8
Methyl mercaptan (6)	6	—	—	—
Chlorine dioxide (10)	15	160 mm.	18.2	6
Ethyl chloride (13)	—	201 mm.	4.8 (590 mm.)	15
Ethyl bromide (38)	—	155 mm.	1.4 (166 mm.)	15
Methylene dichloride (42)	—	116 mm.	1.7 (160 mm.)	15
Methyl iodide (43)	—	74 mm.	4.3 (175 mm.)	15
Dichloroethane (57)	—	56 mm.	1.5 (170 mm.)	15
Bromine (59)	—	45 mm.	6.2 (93 mm.)	8-15
Chloroform (61)	—	45 mm.	1.6	15
Sulfuryl chloride (69)	—	—	—	15

Solid combinations of gases with water have been known since about 1810 when Davy reported the hydrate of chlorine,  $\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ . Work on hydrates of other gases, as well as of low-boiling liquids, was conducted intermittently during the next century and additional examples and many of the physical characteristics were described. Their actual structure, however, was developed only within the past decade, largely by von Stackelberg and co-workers from x-ray investigations (5,28,29).

Table X lists the compounds reported to form water inclusion compounds and also gives some of their characteristics. The included compound is always a gas or low-boiling liquid. The highest boiling liquid reported to form an inclusion compound is sulfuryl chloride, b.p.  $69^\circ\text{C}$ . At atmospheric pressure, the inclusion compounds are stable only at relatively low temperatures. In most cases the stability roughly parallels the boiling point of the included compound, that is, the higher the boiling point the higher the stability. It is noteworthy that most of the compounds listed in Table X are hydrophobic and they do not form hydrogen bonds nor exist as hydrogen bonded molecules. The molar ratio of water to included compound is a whole number. Most of the inclusion compounds have a ratio of 6 moles of water per mole of included compound, but ratios as high as 16:1 and 17:1 have also been reported. The composition appears to be invariant (the limiting value).

Gas hydrates crystallize in the cubic system. Two cubic systems have been described, one for small and one for large included molecules. The length of molecules which can be included ranges from about 4–7 Å, although all molecules within this range are not necessarily included. Molecules of proper size which are not included are carbon tetrachloride, benzene, carbon disulfide, and ethyl iodide. Also, molecules which are too small do not form gas hydrates.

Examples are helium, neon, nitrogen, hydrogen, carbon monoxide, and nitric oxide.

**Ammonia-Nickel Cyanide.** Many years ago K. A. Hofmann showed that benzene, thiophene, furan, pyrrole, aniline, and phenol, but not their homologs, formed compounds with ammoniacal nickel cyanide. Only recently, however, it was shown that this organic-inorganic combination was an inclusion compound of the cage type (22).

Figure 4 shows the structure of the best known ammonia-nickel cyanide inclusion compound, namely, that with benzene. The unit cell is tetragonal and contains one molecule of benzene. The inclusion compound is a beautifully crystalline solid prepared by intimately mixing benzene with the aqueous solution of the nickel-ammonia complex ion at  $0^\circ\text{C}$ . Since homologs of benzene are not included, it is possible to prepare benzene of 99.992 mole % purity, in high yield from ordinary thiophene-free benzene with a minimum of effort (7).

#### Layer (Sandwich) Inclusion Compounds

**Clays.** For about twenty years, largely as a result of the work of Gieseking (13) and of Hendricks (15), it has been known that certain hydrated clays, such as halloysite

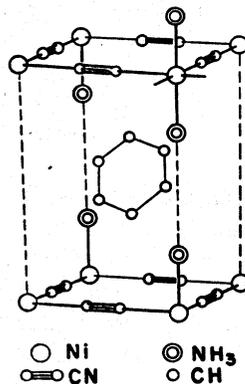


Fig. 4. Ammoniacal nickel cyanide-benzene inclusion compound,  $\text{Ni}(\text{CN})_2 \cdot \text{NH}_3 \cdot \text{C}_6\text{H}_6$ .

and montmorillonite (see Vol. 4, pp. 26, 28; Vol. 12, pp. 291-92) form layer or sandwich inclusion compounds with polar organic molecules which take the place of water loosely bound in the clays. The water can be displaced by heating the clay under vacuum at 100°C. or by mixing it with the organic compound to be included, thus

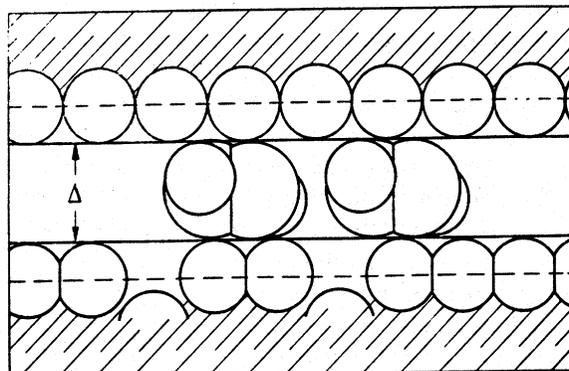


Fig. 5. Halloysite-ethylene glycol inclusion compound.

leaving room for inclusion of foreign molecules. With halloysite only the latter technique is used, since removal of water by heating results in a clay which does not include organic molecules; with montmorillonite both techniques are used.

Figure 5 shows a schematic cross section of the halloysite-ethylene glycol inclusion compound. The layer width,  $\Delta$ , may vary from 3-12 Å depending on the compound included, and in the case illustrated is about 3.7 Å. Table XI lists compounds re-

TABLE XI. Organic Compounds Forming Layer (Sandwich) Inclusion Compounds with Clays.

Methanol	Benzene
Ethanol	Naphthalene
1-Propanol	Tetrahydronaphthalene
1-Butanol	
1-Pentanol	2-Chloroethanol
1-Hexanol	Ethylenediamine
1-Heptanol	Acetone
1-Hexadecanol	Acetaldehyde
	Acetonitrile
4-Heptanol	Nitromethane
2-Octanol	Nitrobenzene
2-Ethyl-1-butanol	
2-Methyl-2-butanol	
Cyclohexanol	
Ethylene glycol	
1,3-Propanediol	
Butanediol	
Glycerol	
1,4-Dioxane	
Ethylene glycol monomethyl ether	
Ethylene glycol monoethyl ether	
Ethylene glycol monobutyl ether	
Diethylene glycol	
Triethylene glycol	

ported to form layer inclusion compounds with one or both of these clays. With the exception of the hydrocarbons, all the compounds are highly polar. Generally, montmorillonite includes larger molecules than will halloysite. Even such large molecules as brucine, codeine, adenosine, and guanosine are reported to form sandwich inclusion compounds.

Both ionic and van der Waals' attractions account for the attachments between host and guest molecules in these inclusion compounds. Van der Waals' forces alone are not sufficient to permit a stable inclusion compound to form, thus accounting for the failure of saturated hydrocarbons (hexane, decahydronaphthalene) to form them. Strong polarity or polarizability is a requisite for the formation of clay inclusion compounds. In this respect they differ markedly from the gas hydrates.

**Miscellaneous.** Other types of inclusion compounds have been described in the literature. Some of them are named in Table I, but information on them is relatively sparse or there is still dispute regarding their structure, thus accounting for their omission in the body of this article. The extensive reviews should be consulted for details (41,42,47,49).

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