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Separation & Purification Reviews

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597294>

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To cite this Article Makin, E. C.(1973) 'Clathrates in Separation Processes', Separation & Purification Reviews, 1: 1, 371 — 407

To link to this Article: DOI: 10.1080/03602547308068944

URL: <http://dx.doi.org/10.1080/03602547308068944>

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CLATHRATES IN SEPARATION PROCESSES

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I. Introduction

In the field of separations and purification, clathrate chemistry has been neglected. This may be attributed, at least in part, to the lack of development of adequate analytical techniques. With X-ray diffraction developed, perfected to a high degree of sophistication and this tool now available in many laboratories, the way is clear.

Inclusion compounds are now known in several different forms ranging from spherical cavities, canal-like structures, layer complexes, crystals with interconnecting chambers and tubular structures. Thus, a wide choice is available to accommodate a specific need or problem.

Since, in certain conditions, very little attraction is necessary for intermolecular compound formation, many of the $1/2 n^2$ possible compounds may exist. As Powell noted,¹⁸ combining pairs such as urea and straight chain paraffins are most unlikely partners from the ordinary chemical viewpoint and may never have been brought together with intent.

A similar viewpoint may be taken with complex clathrates or gas hydrates. However, once the initial reaction is discovered by design or accident, logical extrapolation takes over and the ramifications are defined. Failure to form a compound may be due to unsuitable conditions. For example, methanol or other mutual sol-

vent for hydrocarbon and salt is necessary to effect the reaction of urea with normal paraffins.

While hydrogen bonding may be associated with some clathrates, acting as organic molecular sieves, van der Waals' forces may be sufficient to induce compound formation. Clathrates are considered here as inclusion or cage-like compounds acting as molecular sieves but not exhibiting any strong chemical bonding. To reduce the scope of such a broad field, this presentation will be restricted to more recent advances in the chemistry of clathrates that can be formed and dissociated at will.

Methods of predicting clathration capabilities have not been too successful due to the fact that clathrate hosts often assume a new lattice structure in this capacity and clathrates are extremely sensitive to molecular geometry of their guest components.

Many compounds remain to be found - some with capabilities of separating materials difficult or impossible to resolve by any other means. It is the writer's hope that this brief discussion will stimulate further advances in a fascinating field.

II. Scope

In the present discussion, emphasis is placed on four areas of clathrate chemistry:

- a. Urea and thiourea adducts
- b. Quinol structures
- c. Hydrates
- d. Werner complexes

with particular attention directed to hydrates.

Molecular interactions in comparison with other condensed phases and the physical and thermodynamic properties of clathrates have been considered in several excellent texts and reviews.^{8,12,15} These reviews serve well as a base from which one can develop the most recent advances in appropriate detail.

III. Properties of the Clathrates

It is possible for two chemical compounds, having no obvious means of chemical bonding, to form a new stable crystalline molecular compound. This type of crystalline compound includes the urea and thiourea complexes of hydrocarbons, fatty acids, alcohols and esters, molecular compounds of quinol with the rare gases, hydrocarbon hydrates and hydrates of halides, nitrogen compounds and oxygen containing organic species^{12,15}.

Clathrates have been referred to as organic molecular sieves. Organic molecular sieves are probably a misnomer. The phenomenon associated with clathrate or cage compounds is not limited to organic species. However, emphasis is directed to clathrates of organic compounds in this discussion.

Clathrates differ from other complex compounds, as previously noted, in that the molecules of their components are associated without ordinary chemical bonding. In these, as well as less generalized examples than those cited, the stable crystalline molecular compound may usually be formed and dissociated by controlling the pressure - temperature relationship of the reaction environment. Of even greater interest, is the fact that relatively small differences in temperature and pressure provide a means of sieving molecular species differing in molecular geometry as well as reactivity.

The well known inorganic molecular sieves - zeolites - are similar to clathrates in that they derive their compound separating ability from a precisely tailored molecular geometry that provides channels of specific molecular dimensions. These channels are highly restrictive in their separating ability. Further, they are amenable to numerous absorption - desorption cycles but require considerable thermal or other energy to complete a cycle.

Organic clathrates, being crystalline compounds that possess regular geometric structures capable of trapping other molecules in

their cavities, may also be considered as molecular sieves. Table I compares the geometry of inorganic and organic cage structures. While by no means complete, the examples cited display a remarkable similarity of molecular geometry.

They can be channel type spaces such as the urea or thiourea adducts, cholic acids, dextrin adducts and dinitrodiphenyl adducts. Sheet or layered inclusion compounds are exemplified by clay absorbates and cage inclusion compounds include the water cage hydrates, hydroquinone clathrates and cyano amines of certain metals.^{19,26}

Molecular associations of cage systems represent extremes in bond strengths varying from bonding energies in the low van der Waals' range to those sufficiently strong to be considered covalent.

TABLE I
Spatial Properties of Some Cage Systems

<u>System</u>	<u>Free Diameter of Cage in Å</u>	<u>Free Diameter of Cage Openings, Å</u>
Hydroquinone-SO ₂ Clathrate	5.2	small
Hydroquinone-Ar Clathrate	4.2	small
Urea-n-Alkane Adducts	5.2	5.2
Thiourea-Hydrocarbon Adducts	6.1	6.1
Water Clathrate, Type I, Cage 1	5.2	small
Cage 2	5.9	
Water Clathrate, Type II, Cage 1	4.8	small
Cage 2	6.9	small
Zeolite 4A, Cage 1	7	3.2
Cage 2	11.8	4.9

Ref. R. M. Barrer, Nature 178, 1410 [1956]

This discussion will be restrictive but not entirely limited to cage-like structures that can be formed and dissociated with modest energy changes. These compounds provide a potentially new frontier for tailoring a cage-like structure to sort molecules on the basis of molecular geometry. They may be essentially non-reactive in the classical chemical sense but are easily prepared with simple equipment. Thus, while most are now laboratory curiosities, many known compounds offer a challenge to the biochemist, chemist and chemical engineer in their potential use in separation processes.

IV. Structural Types and Relationships

Inclusion compounds exist in several forms depending on the molecular architecture of the host compound and the geometry of the cavities produced.

The tube-like structures of urea and thiourea complexes are well known. X-ray investigations of the urea-n-paraffin hydrocarbon complexes show that the urea molecules form a hollow channel just large enough to accommodate the planar zigzag of the hydrocarbon molecule²⁸. Their ability to sort molecular species on the basis of small differences in molecular geometry has been well defined. In the formation of cages around a molecule, structural relationships dictate the kind of molecules that will be enclosed. Molecules small enough to escape through a given lattice or framework will not form inclusion compounds with it. A guest molecule must be properly oriented at the moment of enclosure or it will not fit and hence be excluded.

In general, molecules of different shapes tend to orient themselves in such a way that they fit together and large void spaces are seldom found. There are no interatomic distances between adjacent molecules of dimensions less than or greatly in excess of the van der Waals' radii sum.

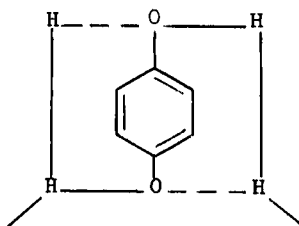
This normal form of crystal formation may be altered in structures where several kinds of interatomic forces are in operation. When the forces are stronger than van der Waals' forces as in the case of water, the more open structure of the water aggregate is the result of strong interaction through hydrogen bonding between one oxygen atom and its neighbors.

Hydroquinone and water clathrates represent cage-like structures having variable void spaces with very small interconnecting apertures or channels. In other words, they do have the capability of lattice flexibility within limits.

Catechol or hydroquinone can enclose small molecules such as oxygen, xenon, sulfur dioxide, methanol, nitrous oxide or oxygen. Clathrate formation depends on molecular form rather than on chemical bonding indicated by the fact that the inert gases are capable of forming stable quinol complexes. Molecules thus enclosed can be stored for a long time frequently at ambient temperature and pressure. When desired, the crystal framework can be destroyed by either melting or dissolving in a suitable solvent. The trapped compound is thus released.

Hydroquinone complexes are linked together by hydrogen bonds between oxygen atoms with the cavities bounded by hydroxyl groups and the benzene rings of the quinol molecules. This system is depicted below:

Six repeating units of the type shown below form a quinol cage about 4 \AA in diameter.



John F. Brown, Jr., Scientific American Vol. 207 No. 1, 84 [1962]

CLATHRATES IN SEPARATION PROCESSES

Many water-soluble substances contain water of crystallization when they crystallize out of solution. Most of these substances are not clathrates. Water molecules are attached by the usual chemical bonds.

True hydrates of gases and low boiling liquids fall into two groups with properties summarized in Table II.

TABLE II
Gas Hydrate Structures

	<u>Structure I</u>	<u>Structure II</u>
Crystal System	Cubic	Cubic
Unit Cell Edge Å	12.1 ± 0.2	17.2 ± 0.2
Water Molecules/Unit Cell	46	136
Cages/Unit Cell	8	24
Dia., Å, Large Cages	5.9	6.9
Number of Large Cages in Cell	6	8
Dia., Å, Small Cages	5.2	4.8
Number of Small Cages in Cell	2	16
Hypothetical Formula	S·3L·23 H ₂ O	2 S·L·17 H ₂ O

Where S and L indicate small and
large cavities respectively.

Gas hydrate structures apply to low molecular weight hydrocarbons, halohydrocarbons as well as certain cyclic ethers.

X-ray crystallographic studies have shown that in these clathrates the water molecules are linked together, through hydrogen bonds, mostly in rings of five molecules rather than the rings of six typical of ordinary ice. These five molecule rings are joined together forming dodecahedrons. Interstitial space results since dodecahedrons cannot be placed in any arrangement to completely fill a specific void.

Trialkylsulfonium salts and tetra-alkylammonium salts form hydrates similar in structure to the gas hydrates. The compound

$2[nC_4H_9]_3 S^+F^- \cdot 40 \cdot H_2O$ has a crystal lattice similar to that of the 'gas hydrate containing 46 water molecules. Another example, $2[i-C_5H_{11}]_4 N^+F^- \cdot 76 H_2O$ contains 68 per cent water yet remains an ice or hydrate form until heated to 88°F.

The crystalline inclusion compounds formed by urea and thio-urea are a honeycomb-like structure of about 5Å and 7Å respectively. The larger cage of thiourea is due to the greater size of the sulfur atom compared to oxygen linking the nitrogen-hydrogen bonds to form the helix around the guest compound.

Other compounds forming canal-like structures include desoxycholic acid, starch and cyclodextrin derivatives. Proteins also form highly hydrated crystals containing as much as 90% water.³¹

Desoxycholic acid forms unusual combinations with fatty acids. Their composition depends upon the number of carbon atoms of the fatty acid involved.

<u>Fatty Acid</u>	<u>Molecules Desoxycholic Acid Required for Adduct</u>
Up to C ₈	4
C ₉ to C ₁₄	6
C ₁₅ and higher	8

In addition to fatty acids, acenaphthene, cholesterol, xylene, naphthalene, hexaldehyde and camphor form complexes with desoxycholic acids⁷.

The starch iodine reaction apparently involves iodine atoms joined together to form a long, straight polyiodide chain and the starch molecule comprised of glucose units in a polymeric chain wraps around the iodine.

On the other hand, cyclodextrins are rigid, doughnut shaped molecules formed by joining glucose units together in rings. Three cyclodextrins, containing six, seven or eight glucose units, have internal diameters of about six, eight and ten Ångströms respectively.

Thus, these variations in the void spaces of the structure provide sufficient differences to accommodate one specie and exclude another.

V. Preparative Methods

A. Urea Adduction

Laboratory methods and scale-up procedures will be considered. In the case of urea or thiourea adduction, the solution-slurry systems have been adequately described in the literature.⁹

A typical laboratory preparation follows:

A 5-10 ml sample of a hydrocarbon and 100 ml of a saturated solution of urea in methanol are reacted by stirring or by agitation in a shaker. In a typical case, decane is reacted at 20 to 25°C for from twenty minutes to an hour or more depending upon the efficiency of the mixing system.

The solid hydrocarbon urea complex is collected on a sintered glass funnel and is washed with a urea-methanol solution and then with cyclopentane or cyclohexane to remove any adhering unreacted hydrocarbon. The urea complex may be dried, preferably at about 0°C, in a stream of nitrogen and the hydrocarbon is recovered by dissociating the complex in a few ml of 70-90°C water.

An aqueous solution of urea may also be used but frequently has the disadvantage of forming emulsions or thick, syrupy reaction products with high molecular weight hydrocarbons, alcohols, fatty acids and the like.

In some cases an aqueous solution system may be satisfactorily employed by adding a low boiling inert solvent for unreactive species present in the sample being processed. Halogenated solvents such as methylene chloride, ethylene dichloride, chloroform and carbon tetrachloride are particularly useful in this regard with hydrocarbon systems being separated.

The halogenated solvent extracts unreacted material from the reaction mass and forms a discrete lower layer.

However, a solid urea or thiourea slurry may also be of value particularly where large samples of separated product are desired.

For example, 500 gms of crystalline urea are thoroughly wetted with 100 gms of dry methanol and thoroughly mixed. To this is added adductable hydrocarbon, fatty acid, etc. in an inert solvent such as a naphthene or low molecular weight isoparaffin. In separating normal paraffins from a mixed stream such as gas oil, diesel fuel or kerosene the unreactive species in the mixed stream suffice as a diluent.

Adductable material in the reaction mixture is adjusted to the following mole ratio of urea to hydrocarbon chain:

$$m = 0.65n + 1.5$$

where m = moles of urea in the adduct

n = number of carbon atoms in the n -alkane.

Adduction takes place immediately as evidenced by a 3 to 5°C temperature rise in a reaction of this type. A C_6 to C_8 isoparaffin is added to facilitate removal of unreacted species. After ten to thirty minutes reaction at 20-25°C, the slurry is vacuum filtered on a Buchner funnel. It is reslurried in isoparaffin, filtered, washed with 100 cc of 20-25°C isoparaffin and filtered dry. The adduct is dissociated by heating in 1 liter of water to 50°C. Yields are 90 to 98% of the theoretically adductable material in 95+% purity in a single stage. At C_{12} and higher, isoparaffins of corresponding molecular weight co-adduct.

The use of regeneratable fixed beds, on the other hand, has not received the attention it deserves. Since urea crystals expand in their accommodation of encapsulated species, provision must be made for this phenomena in the development of a fixed urea bed in order to be useful. Solid tetragonal urea has a density of 1.33 compared to a density of 1.20 for the hexagonal n -alkane urea adduct.

The writer and his associates developed a fixed bed urea process using crystalline urea dispersed on an inert fibrous support.¹⁴

"Fibre-Frax" [aluminum silicate fibers] and fiber glass or glass wool are preferred. Rolls or mats of insulating fiber glass have been successfully employed by installing in the prerequisite tubular reactor of glass or metal and leaching the glass mat free of commercial binder with a hot aromatic solvent. Fibrous asbestos is less desirable due to its linear symmetry of fiber compared to random structures of the commercial materials.

Microphotographs of these two type supports at 120X are shown in Figures 1 and 2. Urea dispersed in the randomly distributed fibrous carriers does not migrate appreciably in spite of the fact that the urea tends to develop a smaller crystal as it undergoes successive adduction - decomposition cycles.

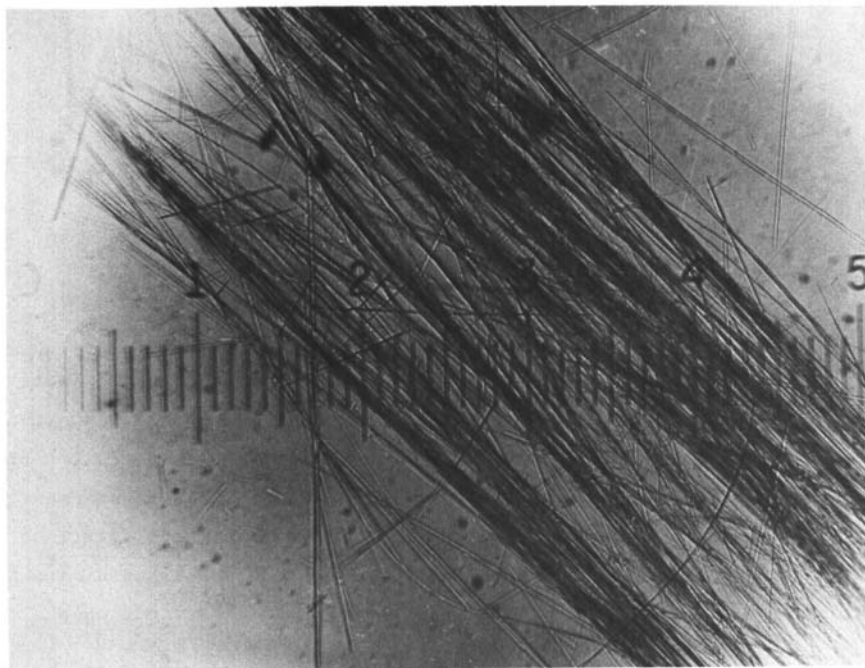


FIGURE 1.

Fibrous Asbestos 120X



FIGURE 2.

"Fibre-Frax" 120X

Urea is precipitated in place by percolating a 70-90°C almost saturated aqueous solution through the fiber glass bed. The wetted support is cooled to 25-30°C thereby crystallizing out a portion of the available urea but still containing a cooled saturate aqueous solution. The bed is then flushed with isopropanol to precipitate out additional urea, distributed through the support by washing out the aqueous phase. The urea bed is finally dried by a nitrogen flow or other inert gas.

Typically a urea bed thus prepared will consist of 85% urea and 15% fiber glass by weight and will contain about 13.3 lbs of urea per cubic foot. [213 gms per liter]

In a typical case, a hydrocarbon stream containing the desired n-alkane was percolated through the bed maintained at 20-25°C. Usually 1 to 3 wt. % methanol is included in the hydrocarbon feed stream as a mutual solvent serving as an activator.

Dry 99+ % isopropanol is also effective particularly at 2 to 5 wt. % of the mixed hydrocarbon charge to the urea bed.

Unadducted hydrocarbon is washed out of the bed using 5 to 10 volumes of wash liquor per volume of adductable feed. Here too, low molecular weight naphthenes or isoparaffins are preferred having a boiling point at least 40 to 50°C lower than the desired product to facilitate separation of the unreacted species from the wash liquor.

Finally, adducted material is recovered by passing hot toluene, methyl cyclohexane or other non-adductable material through the bed at 80 to 100°C. The percolate is recovered and the desired species is separated by distillation.

In a typical example, a reactor was prepared by packing a 2" diameter by 12" length of pyrex pipe with a rolled batt of fiber glass [50 gms]. A 70-90°C almost saturated aqueous solution of urea was percolated through the fiber glass packing and the bed was allowed to cool to room temperature. This was followed by an isopropanol wash which removed water and precipitated out additional urea to yield approximately 200 gms of urea dispersed quite uniformly throughout the fiber glass bed.

Mixtures containing adductable material to be separated are percolated through the bed at 20 to 30°C followed by a suitable wash liquid to remove occluded unreacted material. The desired adducted species is recovered by the addition of a hot [90 to 100°C] wash such as toluene to dissociate the complex. A vacuum may be applied instead of the hot wash with adducted material recovered in a suitable low temperature trap.

While the porous fixed bed process was developed primarily for n-alkane recovery from mixed hydrocarbon systems, any urea adductable species could be separated.

Modifications of this technique may be employed as an analytical tool and as a preparative separation column. Thus, separation of complex mixtures involving species capable of forming urea or thiourea clathrates are performed in simple equipment with 90% and better recovery of unreactive compounds.

Urea may also be dispersed satisfactorily by adding the appropriate amount of solid urea to a sample of Fibre-Frax or glass wool broken down in a Waring blender. Using cold pentane as a suspending medium the slurried urea - inert fibrous carrier - is transferred to a suitable column for use. Chromatographic separations could be made in this fashion using one of several available techniques for slicing the column and recovering the adducted material. Urea utilization is usually 40 to 50% of the theoretical in the case of C_{10} - C_{15} n-alkanes.

In all cases, due to the fact that solid systems of urea or thiourea dispersions involve reaction at the crystal surface, a relatively high mole ratio of 5 to 10:1 of the theoretical urea requirement is recommended in analytical type separations. Washing with an inert hydrocarbon such as isopentane, neohexane and similar hydrocarbons is preferred. When handling adductable species with a carbon chain of C_{10} or less, higher resolution may be achieved by cooling the wash liquid to 5 or 10°C.

B. Hydrate Clathration

Hydrates are easily prepared in pressure cells equipped with a suitable agitator and appropriate apertures for the introduction of reagents and inert gases to pressurize the reaction system.

A 500 ml capacity stainless steel cell designed and built in this laboratory is shown in Figure 3. An exploded view is shown in Figure 4, as well as a schematic diagram depicted in Figure 5. Attention is directed to the sight-glass of the cell. This is a 4-1/2" by 1-5/16" Macbeth Al glass, 11/16 of an inch thick. Pressures of 200 to 300 psig are easily and safely accommodated by the apparatus.

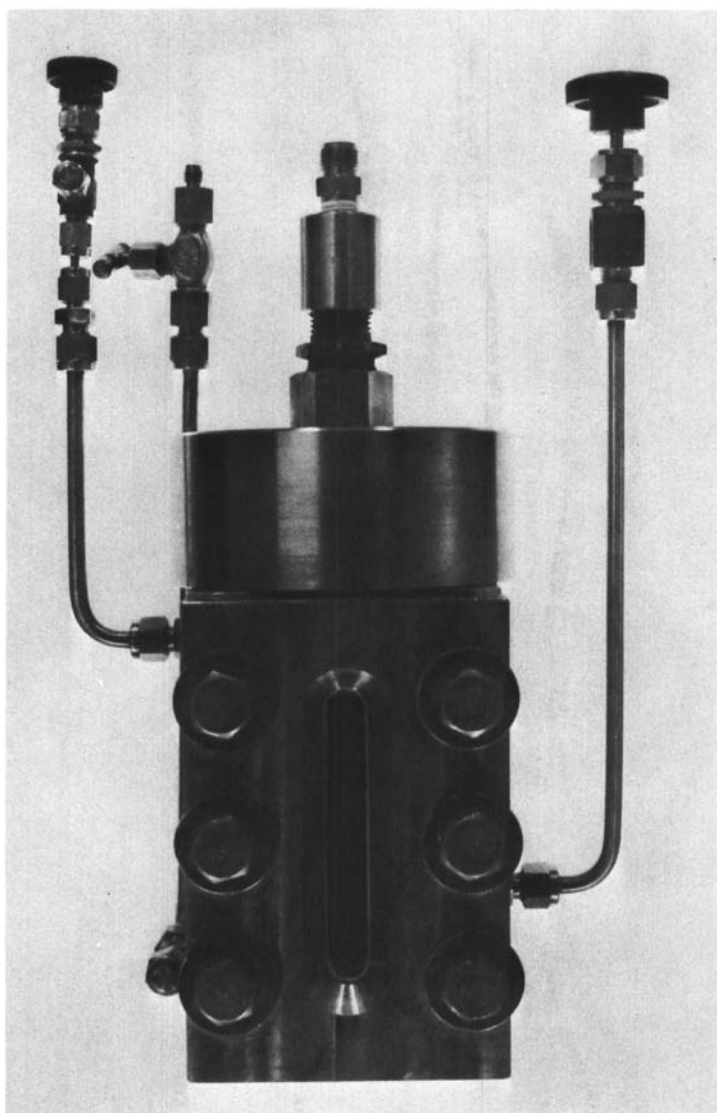


FIGURE 3.

Cell for Clathrate Preparation and Equilibria Studies

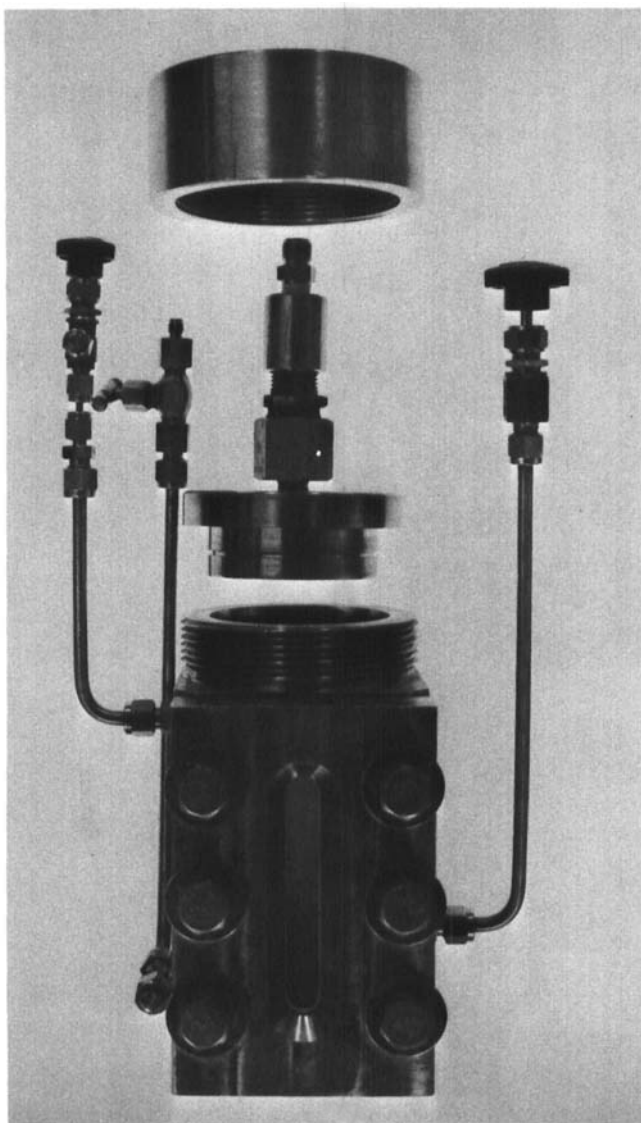


FIGURE 4.

Exploded View of Cell Used for Clathrate Studies

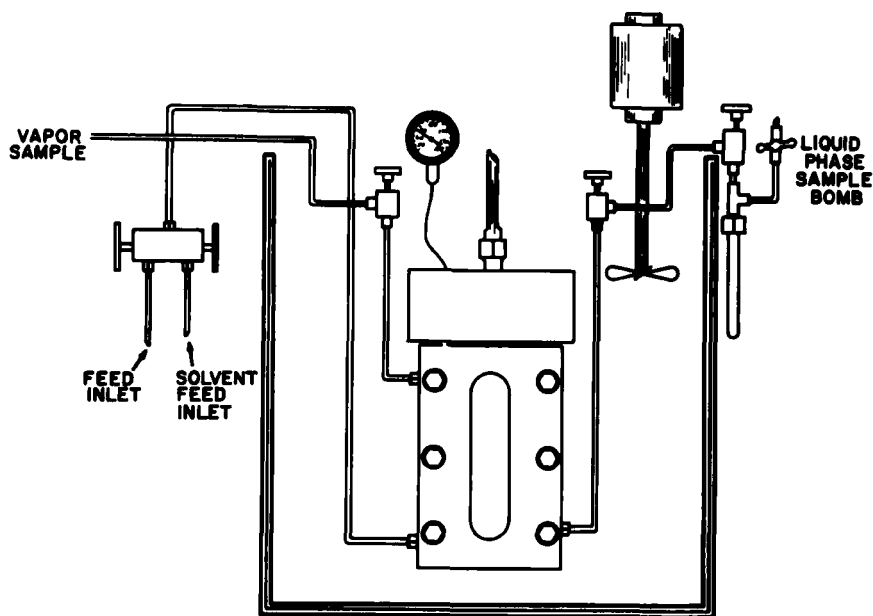


FIGURE 5.

Apparatus for Equilibria Studies of Clathrates


Two methods for preparing hydrates have been developed in this laboratory, the choice being dependent on the aqueous solubility of the hydrating agent in question.

Method I.

Hydrates of various Freons and other alkyl halides are prepared by adding wet-ice to the pressure cell in a constant temperature bath maintained at about 4°C below the critical formation temperature of the specific hydrate involved.

Table III summarizes several typical reagents and properties of their hydrates. These hydrates are relatively easy to prepare and use in the laboratory.

TABLE III
Properties of Typical Hydrating Agents

<u>Name</u>	<u>Structure</u>	<u>b. p., °C</u>	<u>Critical Hydrate Prop.</u>	
			<u>T., °C</u>	<u>Press., mm Hg.</u>
Freon, F-11	CCl_3F	25	6.5	410
Freon, F-21	CHCl_2F	8.9	8.7	760
Freon, F-1426	$\text{CH}_3\text{CFC1}_2$	9.6	13.1	1743
Methyl Bromide	CH_3Br	3.56	14.7	1141
Tetrahydrofuran		64-66		

The pressure cell is evacuated as completely as possible at this predetermined temperature [usually less than 6 mm absolute] and the primary hydrating agent is added. In the case of compounds having a boiling point above the reactor temperature, the compound was charged via a small stainless steel cylinder and needle valves to control the flow of the reagent to the cell. Nitrogen was preferably employed as a pressurizing gas for the charging tube. Where normally gaseous compounds were used as the hydrating reagent they were added as a gas from a small cylinder containing the prerequisite amount of hydrate former.

The compounds to be separated are added and the resultant system was usually between 0 and 10 psig. By adjusting the pressure via nitrogen addition to a pressure of up to 50 psig and/or lowering the temperature 2 to 5°C near the critical for the hydrate induced effective separations of low molecular weight hydrocarbons such as C_4 and C_5 compounds.

Cold filtration of the hydrates using a refrigerated jacketed Buchner funnel or sintered glass funnel was found to be the most efficient technique for handling the encapsulated species.

With systems normally gases at ambient temperature and pressure, the unreacted material may be recovered by lowering the pres-

sure to atmospheric. The clathrated material may then be recovered by raising the temperature about 5 or 10°C to dissociate the hydrate.

Method II.

Hydrate forming agents completely miscible in water or nearly so exhibit a melting point change varying continuously with composition. Palmer has studied such systems.¹⁶

Solutions of this type tend to subcool and seeding with the hydrate will frequently reduce subcooling from an 8 or 10°C range down to a manageable 1 or 2°C.

Seed hydrate is obtained in the classical manner. A few cc of the reaction mixture, such as a 77.5/22.5 volume ratio of water to tetrahydrofuran is added to a test tube, cooled below the crystallization point of the hydrate and then a glass stirring rod is rubbed gently on the inside walls of the container.

A predetermined amount of water and the water soluble hydrating agent is cooled to wet ice temperature [0 to +3°C] and the system is seeded if necessary. Tetrahydrofuran hydrate, as an example is easily prepared by maintaining a 77.5/22.5 volume ratio of water to the organic component.

In both methods of hydrate preparation, nitrogen or helium has been used to stabilize the hydrate formed by merely increasing the absolute pressure on the system with these inert gases. Usually only one or two atmospheres pressure suffices. Neither gas forms a hydrate and is of such size that it is not trapped by a hydrate former.

A very compact and efficient apparatus for fractionating pairs of inert gases with gas hydrates has also been described by Barrer and Edge.³

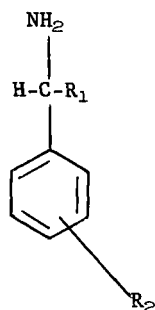
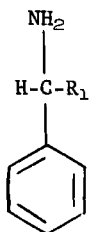
Their work indicated high separation factors were attainable at low temperatures with chloroform hydrates.

Residual Gas Vol. % Composition	Clathrated Gas Vol. % Composition	T, °C	Fractionation Factor
92.3% Ar	54.5% Ar	-78	10.0
7.6% Kr	45.4% Kr		
94.0% Ar	43.4% Ar	-30	21
5.9% Xe	56.5% Xe		

A number of other separations are cited in the reference paper.

C. Werner Complex Clathrates

Werner complexes have been found to form clathrates with various aromatic species. Tailored structures are possible to separate aromatic isomers of mono - and poly-substituted benzenes and naphthalenes. DeRadzitsky and Hanotier⁸ have summarized a broad spectrum of aromatic structures amenable to separation using nickel thiocyanate complexed with primary benzyl amine compounds of the following types:



R_1 = primary alkyl group

R_1 = H or a primary alkyl group

R_2 = Various substituents

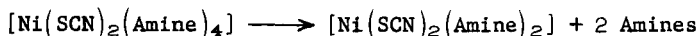
R_2 may be polar or non-polar in any position on the ring. Strongly acidic or basic groups for R_2 such as $-SO_3H$, $-NH_2$ and some reactive groups such as $\begin{array}{c} \text{O} \\ \parallel \\ -C-H \end{array}$ should be avoided.

Complex Preparation

A typical preparation as recommended by DeRadzitsky and Hanotier⁸ follows:

"A solution of 0.2 mole of $\text{Ni}(\text{SCN})_2$ is formed by double decomposition of 47.5 grams of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ [0.2 mole] and 38.9 grams of KSCN [0.4 mole] in 100 ml of distilled water - 100 ml of heptane is added to this aqueous solution. To this two-phase mixture is added, with stirring, 114.8 ml of α -methyl benzylamine [0.9 mole - that is, a 12% excess over the stoichiometric quantity] dissolved in 100 ml of heptane. After stirring for 15 minutes, the resulting blue precipitate is separated by filtration, washed with a mixture of 200 ml of heptane and 100 ml of water and dried under vacuum at room temperature."

The same preparative procedure can be used for a variety of complexes. Separation of a compound by clathration is conveniently accomplished by heating the tetramine complex in suspension in the mixture to be clathrated. Cooling to form the clathrate, followed by washing, drying and low pressure steam stripping yields the clathrated species. Controlling the stripping temperature avoids destruction of the tetramine complex and provides for a cyclic process as shown below:



Complexes of metal salts and substituted pyridines have been thoroughly discussed by Schaeffer and Dorsey.²³

For example, $\text{Ni}(\text{SCN})_2$ is formed by double decomposition of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and KSCN . An equal volume of heptane is added to a 2 molar aqueous solution of the nickel salt. A 10% molar excess of α -methyl benzylamine is added to the heptane solution. After stirring a few minutes a precipitate of the amine salt is formed which is separated by filtration, washed with heptane and dried.

The complex is easily used for separating aromatic hydrocarbons and halogen derivatives of benzene. The tetramine complex is suspended in the mixture to be clathrated, warmed to induce solution and cooled to form the clathrate which may be washed with an inert solvent such as pentane, hexane and the like. Clathrated species may be recovered by decomposition with aqueous HCl and extracting the organic phase with pentane, hexane, etc. If sufficiently large samples of clathrate are involved the clathrated material may be recovered as a discrete phase.

VI. Application and Uses

The wide variety of clathrating materials capable of functioning as organic molecular sieves and readily available to the research investigator or the process design engineer suggests a broad spectrum of potential application.

Clathrate and channel-forming compounds exhibit a high degree of selective encapsulation and, in some cases, quantitative separation of a particular component or class of material passed over them or contacted in a specific manner.

For example, Kr_{85} may be occluded in a hydroquinone clathrate while SF_6 may be stored in the clathrate structure of Dianin's compound and released later under controlled conditions.

Low molecular weight aliphatic hydrocarbons may be transported and stored in a water hydrate form.

The use of urea adducts to separate optical isomers has been studied rather thoroughly. This interesting application is described in some detail below.

A. Urea and Thiourea Adducts

In addition to classic separations of straight chain compounds with urea, this interesting salt has been used to study configurative relationships of steric series.²⁷

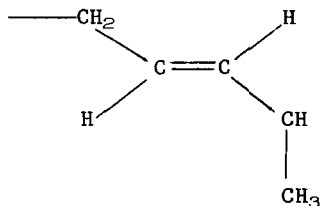
The hexagonal urea lattice can occur in two stereo-isomeric forms. A left-handed or right-handed helix may form. If crystallization is left to chance, both helix forms occur together. Schlenk²⁷ has studied this phenomenon in some detail. As an interesting example, if ethyl- α -methyl butyrate is reacted with urea to form an adduct, the ethyl[+] α -methyl butyrate is preferentially adducted by the right-handed crystals. This is explained by the author²⁷ as a result of the shape of the dextrorotatory molecule fitting better into the urea helix than the levorotatory molecule.

Rodell and Brodman have studied the urea inclusion compounds of alkenoic acids and their esters.²¹ Their observations indicated that 3-n-hexenoic and 3-n-octenoic acids do not form urea inclusion compounds. They noted that all other alkenoic acids differed from these two by the presence of a double bond in the 2-position. This trend had been observed in earlier studies of alkynes.²²

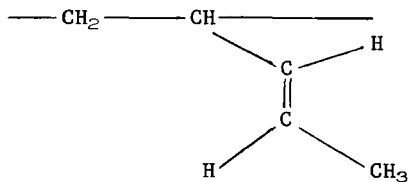
The triple bond did not prevent complex formation in 1-2- or 3-nonyne and 2- and 3-decyne but did prevent complex formation in 4-nonyne and 5-decyne. Since all the 3-alkenoic acid esters formed urea complexes, the alkyl groups of the ester apparently give added van der Waals' stabilization.

Recently Russian workers studied the radiation polymerization of piperylene in urea complexes.¹³

Infrared spectra of urea encapsulated polypiperylene indicated only the trans - [1,4 + 1,2] - units. Restrictions of the canal suggest the 1,4 trans configuration to be the most probable.



trans 1,4



trans 1,2

Although the guest molecules in a canal complex, such as urea, are inaccessible to external attack by reagents without breaking down the canal-like structure, they are capable of interaction.

Results of the irradiation experiments indicated much higher yields of polypiperylene from canal polymerization than the yield from radiation polymerization in bulk at the same temperature.

A further important observation was that the degree of unsaturation was somewhat higher in the radiation polymerization of piperylene in urea complexes [95-98%] compared to the unsaturation of bulk polymers [84-88%]. This suggests that the urea adduct molecular template minimized or excluded cyclization.

Butadiene in urea, when irradiated with a one-million-electron volt beam of electrons, also produced exclusively 1,4 trans polybutadiene.⁵

Selenourea adducts analogous to urea and thiourea inclusion compounds have been described.²⁹ Though the difference in channel diameter between thiourea and selenourea adducts is small, the latter appears to be much more selective particularly with geometric isomers.

Thiourea exhibited no preference between the cis and trans isomers of 1-t-butyl-4-neopentylcyclohexane whereas selenourea formed an adduct with the trans isomer but not the cis, thus providing a separation of the two isomers.

B. Hydrate Clathrations

While hydrate clathrates may be used to separate rare gases, aliphatic hydrocarbons, halo-alkanes and the like, they offer an intriguing challenge in other fields.

Hydrate formation has been suggested as the possible anesthetic action of certain gases such as chloroform and cyclopropane. Xenon is an effective anesthetic yet exhibits no ordinary chemical activity and enters into no combination except clathration.

It has been proposed by Pauling¹⁷ that "micro-crystals" of gas hydrate forms in the brain on certain proteins thus inhibiting their functioning. From this anesthetic and restricted application, the other extreme of the application scale involves commercial plants and processes.

Demineralization of brackish water and brine has received much attention in the past few years including purification processes involving hydrate formation. The work of Barduhn and co-workers has materially broadened the scope of potentially practical hydrating agents for this increasingly important application.¹

Krypton, xenon and argon have been fractionated by Barrer and Edge using a chloroform hydrate as the prime separating agent. Fractionation factors ranged from a low of 3.4 to as high as 93.³ Apparatus and technique are described in detail for fractionating pairs of inert gases. The separation obtained reversed normal relative volatility in favor of molecular size. Preferred encapsulated species are spherical molecules. Thus, argon may be separated, via the proper hydrate, from air, oxygen or nitrogen.

Selective hydrate formation has been patented in the separation of a propane-propylene system.¹¹ In the described process, propane hydrate is selectively formed and the olefin is enriched in the hydrocarbons separated from the hydrate phase.

The encapsulated species has a much lower vapor pressure than the parent compound. This will vary depending upon the type of hydrate formed and the influence of secondary stabilizing compounds. Here again, one finds a variety of possibilities for inducing separations difficult to achieve by more conventional means.

Hydrates, in general, are a type of clathrate similar to inorganic molecular sieves [zeolites] in structure. This was pointed out in Table I. They derive their compound separating ability from a combination of precisely tailored molecular geometry and their adsorption capacity.

Research of the writer and co-workers has shown some interesting and unexpected results working with simple aliphatic-molecules.¹⁰ Model binary hydrocarbon systems and hydrates were used in preliminary studies to define the potential capabilities of this separation tool.

Using the pressure cell illustrated in Figure 3, the vapor-hydrate equilibria data summarized in Tables IV and V were obtained. A binary hydrocarbon feed of isobutane and n-butane yielded comparable enrichment factors and hydrocarbon loading of the hydrate from two radically different hydrate forming species, Freon-11 and tetrahydrofuran.

Thus, the hydrate forming species was apparently less influential on the resultant separation than the hydrocarbon feed composition. In both cases, excellent enrichment of the more compact isobutane molecule was obtained.

TABLE IV
Freon-11 Hydrate
Isobutane, n-Butane Binary

<u>Wt. % Iso-</u> <u>butane in</u> <u>Binary Feed</u>	<u>Wt. % Iso-</u> <u>butane in</u> <u>Hydrate Phase</u>	<u>Enrichment</u> <u>Factor</u>	<u>C₄ Loading</u> <u>Wt. % of</u> <u>Hydrate</u>	<u>Pressur-</u> <u>izing</u> <u>Gas</u>
8.7	22.0	3.0	4.2	N ₂
12.2	24.1	2.3	3.6	N ₂
29.4	49.7	2.4	-	N ₂
48.5	86.5	6.8	-	N ₂
48.5	80.5	4.4	-	N ₂
48.5	86.3	6.7	-	He
48.5	81.2	4.6	-	He
48.5	80.2	4.4	-	He
91.8	95.7	2.0	5.4	N ₂
91.9	95.0	1.7	4.9	N ₂

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TABLE V
Tetrahydrofuran Hydrate
Isobutane, n-Butane Binary

<u>Wt. % Isobutane</u> <u>in Binary Feed</u>	<u>Wt. % Isobutane</u> <u>in Hydrate Phase</u>	<u>Enrichment</u> <u>Factor</u>	<u>C₄ Loading Wt. %</u> <u>of Hydrate</u>
10.9	27.4	2.4	3.1
23.8	47.2	6.7	3.8
44.3	57.5	6.5	1.7
78.1	93.0	3.7	4.7
83.1	92.4	2.5	3.5

Figures 6 and 7 depict these data in a McCabe-Thiele type diagram. Enrichment factors, referred to in the foregoing tables, are arbitrarily defined as,

$$K = \frac{X_h/Y_h}{X_f/Y_f}$$

where X and Y are the hydrocarbon binary and the subscripts h and f represent hydrate and feed.

Although olefin binaries behaved similarly, the enrichment factor for the encapsulated species was lower as shown in the comparison below for single stage experiments:

<u>Wt. % Iso-component</u> <u>in the Feed Binary</u>	<u>Wt. % Iso-component</u> <u>in Hydrate</u>	<u>Enrichment</u> <u>Factor</u>	<u>Hydrating</u> <u>Agent[*]</u>
Isobutene, 43.9	67.9	2.7	THF
Isobutene, 45.7	66.7	2.4	F-11
Isobutane, 48.5	80.5	4.4	F-11
Isobutene, 23.8	47.2	3.8	THF

^{*}THF and F-11 refer to tetrahydrofuran and Freon-11 respectively.

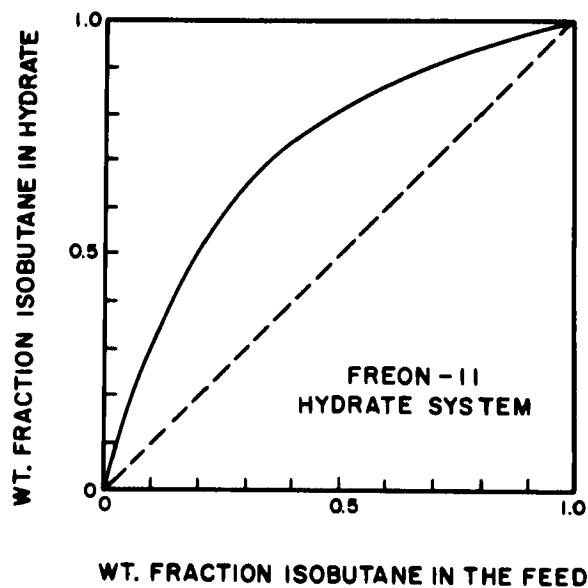


Figure 6. Liquid-Solid Equilibria Curve of Isobutane and Freon-11 Hydrate.

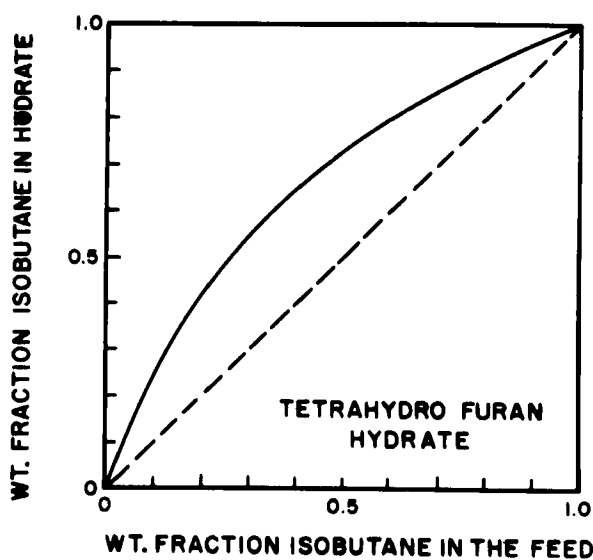


Figure 7. Liquid-Solid Equilibria Curve for Isobutane and Tetrahydrofuran Hydrate.

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In a ternary C_5 paraffin system, the neo structure [2,2 dimethyl propane] was preferentially encapsulated.

<u>Component</u>	<u>Wt. % in</u>		
	<u>Feed</u>	<u>Hydrate</u>	
		<u>F-11</u>	<u>THF</u>
Neo-pentane	33.9	58.0	84.9
Iso-pentane	31.1	24.1	8.8
n-pentane	35.0	17.9	6.3

Calculated molecular lengths for C_4 and C_5 alkanes indicate that isobutane and neopentane, as expected, are comparable at 6.72 Å.

In a situation where competition exists for the void space in the clathrate structure, molecular bulk predominates over molecular length as shown below:

<u>Component</u>	<u>Wt. % in</u>		<u>Hydrocarbon</u>
	<u>Feed</u>	<u>Hydrate</u>	<u>b. p. °C/760 mm</u>
Propane	24.7	46.4	-42.2
Isobutane	75.3	53.6	-10.2

The above separation with Freon-11 hydrate at 4°C and a system pressure of 30 psig [nitrogen] is a dramatic illustration of a reversal of relative volatility. Thus, the propane molecule having essentially the same molecular length as isobutane but with a much smaller molecular diameter than isobutane is much more readily accommodated in the available void space of the hydrate structure.

In a mixed olefin-paraffin C_4 hydrocarbon system, the characteristic behavior attributed to molecular length of the hydrocarbon in binary model studies already discussed was again evident in single stage equilibria cell tests.

<u>Component</u>	<u>Feed</u>	<u>Wt. % in</u> <u>Hydrate Phase</u>	
		<u>THF</u>	<u>F-11</u>
Isobutane	3.7	7.7	5.0
n-butane	7.1	3.7	5.5
1-butene	19.0	8.3	14.8
Isobutene	55.8	74.3	62.0
n-butene [cis + trans]	14.4	6.0	12.7

Here again, tetrahydrofuran showed significant superiority over Freon-11.

In an olefin, paraffin and diene system, the tetrahydrofuran hydrate apparently rejects butadiene. This further substantiates the apparent lack of chemical bonding in the clathrate structure. The polarity of butadiene should enhance selectivity of a THF-hydrate if the hydrating agent was capable of behaving as a solvent.

While these illustrations of the molecular sieving properties of hydrates are not comprehensive, they do furnish some insight to the potential capabilities of hydrate structures. In the capacity of molecular sieves, hydrates offer several advantages including:

- 1] The organic sieve structure is formed from an inexpensive material - water.
- 2] "Organic" sieves can be transported as a slurry through a reaction system and
- 3] Decomposition and regeneration of the sieve structure can be accomplished by small changes in temperature and pressure.

Relatively mild reaction conditions necessary to form hydrates make it possible to use organic molecular sieving applicable to thermally sensitive systems.

Werezak³² has described in some detail processing characteristics and economics of a hydrate process for aqueous solution concentration.

Coffee extracts, sucrose solutions and dilute sodium chloride solutions were studied in some detail. Ethylene oxide was preferred as a hydrate former due to its total miscibility with the aqueous solutions yielding systems that encouraged homogeneous crystallization. He notes that such systems gave large hydrate crystals and low solution viscosities.

The mild processing conditions in the use of hydrate solution concentration process suggests other areas of application such as fruit juice concentration.

C. Werner Complex

Possibilities in this area are almost as broad as imagination and ingenuity permit. Separation of C_8 aromatic isomers using nickel thiocyanate based Werner complexes has been described in patents to Union Oil.^{24,25}

Complexes of this type are not restricted to the separation of hydrocarbons nor to benzenoid compounds. Schaeffer and Dorsey²³ allude to the use of various pyridine-base complexes of nickel thiocyanate for separating isomeric nitrophenols, nitroanilines, chloronitrobenzenes and nitrotoluenes. Separations of naphthalene, 1-methyl naphthalene and diphenyl oxide from mixtures containing these compounds are also described but of even greater interest is that complexes were found for preferentially encapsulating each of the C_8 aromatic isomers.

In the patents to Union Oil, cited above, reference is made to the separation of isomeric haloalkanes, isomeric phthalic acids, alcohols, functional derivatives of hydrocarbons including oxo, carbonyl, thio or mercapto groups in addition to the other types mentioned.

While nickel salts have apparently received the most attention, manganese, copper, chromium and cobalt derivatives are also preferred cations.

DeRadzitsky and Hanotier⁸ have described the preparation of nickel thiocyanate amine complexes and their encapsulation capabilities for aromatic hydrocarbons in considerable detail.

The simplest method for evaluating the clathration capacity and selectivity for these new Werner complexes found by these authors was to form the complex by titration of the nickel thiocyanate with an amine. This was done in the presence of the compounds to be clathrated thus defining capacity and selectivity.

Clathrated compounds are recovered by decomposition of the clathrate with a mineral acid. It was noted by these authors that clathrated compounds must fit tightly in the voids of the crystalline lattice to give maximum cohesion with the aid of van der Waals' forces.

DeRadzitsky and Hanotier⁸ noted in their investigative work that one clathration stage is often as efficient as a conventional physical separation [e.g., distillation] involving hundreds of theoretical plates. Their work illustrated the fact that almost any aromatic isomer could be selectively encapsulated by the proper Werner complex.

Conversely, cyclic compounds derived from cyclohexane or decalin could not be clathrated. This was attributed to electronic as well as steric factors.

The potential use of these interesting compounds in the analytical field as well as in removing traces of an undesirable species from a laboratory sample or an industrial stream is apparent.

VII. Analytical Techniques

The rapid advance in the science of clathrates, particularly non-stoichiometric compounds, has been at least partly due to im-

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provements in X-ray crystal structure analysis. X-ray diffraction for example has differentiated the crystal lattice of urea crystallized from a solution as a loose tetragonal structure contrasted to the compact hexagonal structure of urea crystallized from a solution containing unbranched hydrocarbon chains.

This indicates that the host compound is aided by the guest component in that it forms the more compact structure.

Methods for analyzing urea complexes by X-ray diffraction are described in recent publications.^{13,20}

X-ray diffraction has been successful in defining the properties of hydrates with respect to their separating capabilities. Typical data developed in this laboratory by X-ray diffraction patterns using Cu radiation on a General Electric XRD-5 diffractometer are shown in Table VI. A Material Research Corporation low temperature attachment Model X-86G was used at 0° to minimize hydrate decomposition during analysis.¹⁰

TABLE VI

	<u>CFC1₃ - Hydrate</u>	<u>CFC1₃-iso C₄H₁₀ Hydrate</u>
Crystal lattice	Cubic	Cubic
Unit cell dimension, A ₀ =	17.260 ± 0.005 Å	17.237 ± 0.003 Å
Unit cell volume, V =	5141.9 Å ³	5121.4 Å ³
Molecules/unit cell, Z =	8	8
<u>Density</u>		
Determined	1.142	1.268
Calculated	1.145	1.300
<u>Molecular Weight</u>		
	CFC1 ₃ · 17 H ₂ O	CFC1 ₃ iso C ₄ H ₁₀ · 17 H ₂ O
Determined	442.1	488.9
Calculated	443.4	501.4

The excellent checks between the calculated and determined densities indicate a high precision in the determination of the unit cell dimensions.

Chemical composition analysis of urea or thiourea adducts is relatively simple. One merely isolates the crystalline species, washes with a low molecular weight aliphatic or alicyclic hydrocarbon and dries the sample under mild conditions to minimize dissociation.

Controlled dissociation of the urea clathrate in water followed by extraction and GLC analysis is all that is required.

Chemical analysis of hydrate systems to determine loading of the hydrate and selectivity for an encapsulated species involves low temperature filtration and GLC evaluation of volatiles recovered from a given sample.

Future of Clathrate Chemistry

There are numerous clathrating tools available today to the investigator in the field of separation and purification. Many others await discovery.

Further study is needed to better define the mechanism of clathration for improving the investigator's capability of predicting encapsulation.

While strong chemical bonding is not involved in classic clathrate structures, van der Waals' or other electronic attractive forces may frequently be associated with clathrating capabilities. Geometry of the guest molecule is generally the critical criteria for clathrate formation.

The choice of clathrating agent is frequently amenable to the thermal and chemical stability of the encapsulated species.

Inclusion compounds are now known in several different forms ranging from spherical cavities, canal-like structures, layer complexes, crystals with interconnecting chambers and tubular struc-

tures. Thus, a wide choice is available to accommodate a specific need or problem.

Application of clathrate compounds as organic molecular sieves for separating a mixture of molecules on the basis of differing geometry and for serving as chemical templates is a continuing challenge. Since there are clathrate selectivity restrictions dependent on the geometrical match of the guest molecule and the cavity in the host compound, specific tailoring for a particular need will frequently be required.

While this physical prerequisite imposes restrictions, it also serves to enhance the selectivity of a given system. Thus, the basic concept is itself the fundamental challenge. In analytical, biological and process investigations - provide the physical match or tailor one to fit your needs. The field is unlimited.

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