

available, though not in tRNA^{Phe}. This is in agreement with the melting behavior.

A more detailed analysis has been done with tRNA^{Phe}. From this analysis it was shown that the oxidizable adenosine residues are 35, 36 (anticodon), 38 (anticodon loop), and 76 (3' terminus). From these data a general three-dimensional model for tRNA has been proposed by folding together stem, dihydrouridine loop, and T Ψ loop of the cloverleaf structure. This is depicted for tRNA^{Phe} in Figure 8 and is compatible with all chem-

ical, physicochemical, and biochemical evidence so far available.^{51,54}

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Water Structure in Organic Hydrates

GEORGE A. JEFFREY

Crystallography Laboratory, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

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Determinations of crystal structures of organic compounds have been concerned mainly with the stereochemistry of the isolated molecule. The results provide numerical information relating to the chemistry of the compound, in the form of bond lengths, valence angles, and conformation angles. The equally detailed information provided by these structures concerning interatomic vectors between molecules has not been so extensively correlated. The organic chemist is not much concerned with it. Most of his experiments are conducted in the liquid or gaseous phases to which the arrangement of the molecules in the solid has little relevance. Consequently, these intermolecular data have attracted the attention of only the comparatively few solid-state chemists or crystallographers who are curious as to how the shape and electron distribution in molecules affects the way they can cohere to form a regular lattice.¹

In recent years, progress in the use of computers has made it possible to use these intermolecular data more quantitatively. In particular it has been possible to derive numerical parameters for potential energy functions for hydrocarbons by least-squares methods and, conversely, correct crystal structures have been successfully predicted by minimizing the lattice repulsive energies calculated from these functions.^{2,3}

Since the ubiquitous water molecule occurs in more crystals than any other single molecule, it is tempting to enquire whether the data available from the crystal structure determination of hydrates can be used to obtain a better comprehension of the cohesive forces between water molecules and other molecular or ionic species.

Up to 1963, about 350 inorganic hydrate and 90 or-

ganic hydrate crystal structures had been determined,^{4,5} and the numbers now probably exceed 1000 and 300, respectively. Attempts to use these data have revealed some general principles in the case of inorganic hydrates,^{6,7} but the organic hydrates have scarcely been considered. An important deterrent is the elusive understanding of the electronic nature of the hydrogen bond, which is the principal cohesive force exercised by water molecules in organic hydrates. The absence of a generally accepted expression for the potential energy function of the hydrogen bond is a severe disadvantage, and the pronounced directional character of these forces is an added complication in any attempt to rationalize the intermolecular distances observed in crystalline hydrates. Another difficulty is uncertainty in the location of the hydrogen atoms, which must be known for complete description of a hydrogen bond. Neutron diffraction studies which could provide this information are, for economic reasons, much less numerous than X-ray crystal structure determinations. Hydrogen bonds cannot be recognized with certainty from interoxygen distances alone, in the absence of an observed electron (or proton) density peak for the hydrogen, because oxygen-to-oxygen nonbonding equilibrium distances vary over approximately the same range as do hydrogen bond distances (*i.e.*, 2.5 to 3.0 Å).⁸ A hydrogen bond can be described as a directional cohesive force resulting from a redistribution of the electron density which permits the insertion of a proton between two nonbonded oxygens without increasing their

(4) R. W. G. Wyckoff, "Crystal Structures," Vol. 3, 2nd ed, Interscience Publishers, New York, N. Y., 1965.

(5) J. R. Clark, *Rev. Pure Appl. Chem.*, **13**, 50 (1963).

(6) R. Chidambaram, *J. Chem. Phys.*, **36**, 2361 (1962).

(7) W. H. Baur, *Acta Cryst.*, **19**, 909 (1965).

(8) Interesting examples where it is difficult to distinguish nonbonded and hydrogen-bonded O...O interactions in the absence of neutron diffraction work are as follows: 5-nitrobarbituric acid trihydrate (B. M. Craven, S. Martinez-Carrera, and G. A. Jeffrey, *ibid.*, **17**, 891 (1964)); 5-hydroxyiminobarbituric acid monohydrate (B. M. Craven and W. J. Takei, *ibid.*, **17**, 415 (1964)); nitranilic acid hexahydrate (E. K. Anderson, *ibid.*, **22**, 204 (1967)).

(1) A. I. Kitaigorodskii, "Organic Chemical Crystallography," Consultants Bureau, New York, N. Y., 1961.

(2) D. P. Craig, R. Mason, P. Pauling, and D. P. Santry, *Proc. Roy. Soc. (London)*, **A286**, 98 (1965).

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Table I
Classification of Organic Hydrates^a

Structural characteristics

Ices	Infinite three-dimensional hydrogen-bonded framework structures
Hexagonal, cubic, high-pressure ices, II-VII ^b	
Clathrate hydrates	Nonbonded guest molecules stabilize clathrate voids in polyhedral host structures of hydrogen-bonded water molecules
gas hydrates	Water and anions form closely related hydrogen-bonded host structures and the cations occupy the voids
peralkylammonium salt hydrates	Water host structure has definite polyhedral clathrate voids occupied by hydrogen-bonded alkylamine molecules
Semiclathrate hydrates	
Water framework structures	
Three-dimensional	Water molecules form hydrogen-bonded nets, sheets, columns, ribbons, or chains. There are no recognizable clathrate voids, and the functional groups of the molecules strongly influence the structure.
Two-dimensional	
One-dimensional	
Hydrates with isolated water molecules	Structure determined principally by the ionic coordination or hydrogen-bonding function of the solute species

^a Hydrates ordered in the degree to which $(\text{OH}_2)_n$ is structure determining. ^b B. Kamb, *Science*, **150**, 205 (1965).

separation. To the X-ray crystallographer, the electron density peaks of water hydrogens appear to be more difficult to locate than those of hydrogens attached to carbon atoms, and this is not unexpected because of the greater electronegativity of oxygen relative to carbon.

In the inorganic hydrates the water molecules generally complete the coordination shell of the cations and hydrogen bond to the anions. The structures therefore tend to represent the stereochemical requirements of the ions rather than those of the water. The same is true for organic hydrates with one or two waters of crystallization per molecule. From the known crystal structures of this type, it is difficult to perceive more than some general statement concerning the water structure, such as "that the environment of water molecules is most commonly tetrahedral with three or four hydrogen-bonded neighbors, but an approximately planar threefold coordination is not uncommon."⁶ What is most striking in these structures is the versatility with which water can become involved in a crystal lattice of organic molecules. Since most organic hydrated crystal structure determinations were done for reasons other than curiosity about the water, there is variety but little systematics in the data available. The review of water molecules in hydrated organic crystals,⁶ which surveyed the results obtained between 1950 and 1963, gives a better impression of the type of organic molecules which interested crystallographers during that period than it reflects any tendencies toward hydrate formation. In fact, as is pointed out, the total environment of the water molecule is seldom fully described in the published work.

A less complex problem seems to be presented by the study of the high hydrates of organic molecules. If the hydration number is large enough, the water molecules can form infinite three-dimensional frameworks similar to those observed in the ices, but modified in response to the presence of other molecules. The structure of these organic hydrates, where the water molecules are in the majority, is of particular interest in molecular biology for the clues which might be given to the be-

havior of water in biological systems, where the content of the bound water is high, but the direct observation of structure is especially difficult.^{9,10}

One of the characteristics of the high hydrates is that, in the absence of a knowledge of the water structure, it is frequently impossible to predict accurately their stoichiometry. Many crystals of high hydrates are in fact nonstoichiometric, and the structure determination gives an ideal formula which may or may not be realized in any particular preparation of crystals. This is reminiscent of silicate chemistry prior to the determination of the structure of the silicates. It suggests that there may develop in the future a well-defined field of hydration chemistry that requires for its understanding the same kind of basic structural rationale as did silicate chemistry prior to the X-ray structure determination of the silicates.

A scheme for classifying organic hydrates is given in Table I as a basis for the ensuing discussion. This classification is arranged according to the extent to which the hydrogen-bonded water molecules appear to be the primary structure-determining component of the hydrate crystal.

The Ices and the Gas Hydrates

The ices¹¹ reveal the atomic structural patterns for the regular cohesion of water molecules in the absence of perturbations from other molecules or ionic species. With the possible exception of ice VII, all the ices of known structure have four-connecting networks with hydrogen bonds linking tetrahedral or nearly tetrahedral coordinated oxygens.¹² The ices VI, VII, and VIII have been described as self-clathrates because their structures consist of two unconnected, but inter-

(9) For example, I. M. Klotz, *Science*, **128**, 815 (1958); G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3382, 3401 (1962); O. Hechter, *Fed. Proc.*, **24**, 591 (1965); I. M. Klotz, *ibid.*, **24**, 524 (1965); H. J. C. Berendsen, *ibid.*, **25**, 971 (1965).

(10) Cf. "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman Co., San Francisco, Calif., 1968, pp 343-355.

(11) B. Kamb, in ref 10, pp 507-541.

(12) B. Kamb, A. Prakash, and C. Krobler, *Acta Cryst.*, **22**, 706 (1967).

penetrating, lattices.¹³ The analogy between the hydrogen bonds linking oxygens in hexagonal and cubic ices and the oxygen bonds linking silicons in β -tridymite and β -cristobalite is well known. Recently, Kamb,¹⁴ in describing the mineral melanophlogite, which is structurally analogous to the clathrate gas hydrate, $6X \cdot 46H_2O$, has pointed out the similarities between the structures of the high-pressure ices II, III, V, VII and the polymorphs of silica, α -quartz, silica K, coesite, and stishovite, respectively. These relationships arise because both $(OH_2)_n$ and $(SiO_2)_n$ form (4:2) framework structures with tetrahedral and linear, or almost linear, coordination. It is not surprising therefore that there are analogies between the discussions of structural models for short-range order in liquid water and aqueous solutions and in amorphous silica and the glasses.¹⁵⁻¹⁷

Most resembling the ices are the water structures found in the gas hydrates.¹⁸⁻²⁰ These are clathrates²¹ in which hydrogen-bonded water molecules form host lattices with characteristic polyhedral voids,²² the most common of which is that with twelve regular pentagonal faces, *i.e.*, the pentagonal dodecahedron. In these water host structures each oxygen atom is hydrogen-bonded to four neighbors with coordination angles that differ from tetrahedral by only a few degrees. Were it not for the formation of voids leading to a low density relative to ice, the water structure in the gas hydrates would be energetically competitive with ice. The role of the guests in these clathrates is to fill the voids and thereby stabilize these "icelike" structures. The size and shape of the guest species are important, for they must fit into the voids, but their chemical function is not, providing that they do not interact chemically with the water molecules. The stoichiometry of these hydrates is determined by the physical dimensions of the guests in relation to those of the voids. Thus a small molecule such as CH_4 can fill both small and large voids to form a hydrate with the ideal formula $8CH_4 \cdot 46H_2O$. Larger guests form a hydrate with larger voids as in $C_3H_8 \cdot 17H_2O$. Benzene is also reported to form a gas hydrate, with the assistance of a help-gas,²³ but

larger molecules do not.²⁰ The majority of compounds which form gas hydrates are hydrocarbons, halogens, and halogenated hydrocarbons.²⁰ They are hydrophobic and comparatively insoluble in water, and hydrate formation takes place from a two-phase system. It corresponds to an order of magnitude higher solubility in the solid than in liquid water. It is not surprising, therefore, that there is no functional interaction with the water molecules and, apart from the physical size effect, the guest species have little or no influence on determining the structure of the water-host lattice.

Among the gas hydrate formers there are, however, a group of polar substances such as the cyclic ethers²⁴ and acetone.²⁵ The structures of the hydrates of tetrahydrofuran and ethylene oxide have been examined in detail,^{26,27} and it has been established that these are true clathrates with no hydrogen-bonding interaction between the host and guest. At the time these structures were determined, it was assumed that all cyclic ethers and ketones, which did not exceed the size limitations of the voids of gas hydrate structures, would as a class behave similarly, but later work on the amine hydrates suggests that this presumption needs to be further tested. The dioxane hydrate,²⁴ for example, should be examined because its size may be close enough to the limit that the oxygens could be forced into hydrogen bonding with the water structure for steric reasons. It is clear, however, that if the molecule is not too large, clathrate hydration will take precedence over hydrogen bonding in the solid state and will suppress this property of the functional group, which is usually associated with solubility in the liquid state. It is not known to what extent, if any, the clathration persists on melting a hydrate such as that of tetrahydrofuran. This is an extremely difficult problem to explore by diffraction or spectroscopic methods because of the marked similarity in the short-range order of the hydrate and ice lattices, which is the most that one can expect to persist on melting.

Structurally, there seems to be no distinction between the clathrate hydrate formation of a cyclic ether and a hydrocarbon of comparable size. Ethylene oxide appears to be small enough to enter both types of voids, since hydration numbers have been reported between 6.76 and the eutectic composition at 7.21.²⁸ Cyclopropane, which is a slightly larger molecule, forms both the 12- and 17-Å cubic hydrates,²⁹ as does trimethylene oxide.³⁰ Tetrahydrofuran, like propane, forms only the 17-Å hydrate and can be stabilized by a "help-gas." The crystal structure actually studied²⁶ had a stoichiometry with full occupancy of the large voids and less

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(17) F. Ordway, "A Study of Random Network Models," Report No. 6353.00100, Melpar, Inc., Arlington, Va., 1966.

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(20) M. von Stackelberg, *et al.*, *Z. Elektrochem.*, **58**, 25, 40, 99, 104, 162 (1954).

(21) H. M. Powell, "Non-Stoichiometric Compounds," L. Mandelkern, Ed., Academic Press, New York, N. Y., 1964, Chapter 7.

(22) G. A. Jeffrey and R. K. McMullan, *Progr. Inorg. Chem.*, **8**, 43 (1967).

(23) Where the dimensions of the guest molecules are such that they can only occupy the large voids, the decomposition temperature of the hydrate is raised by a few degrees if a smaller gas molecule is present which can occupy the pentagonal dodecahedra. This was called the "hilfegase" effect by M. von Stackelberg and W. Meinhold, *Z. Elektrochem.*, **58**, 40 (1954). The effect can be demonstrated very simply by passing H_2S into a mixture of carbon tetrachloride and water at 5° to give a white precipitate which, when stoichiometric, has the formula $CCl_4 \cdot 2H_2S \cdot 17H_2O$.

(24) M. von Stackelberg and B. Meuthen, *Z. Elektrochem.*, **62**, 130 (1958).

(25) A. S. Quist and H. S. Frank, *J. Phys. Chem.*, **65**, 560 (1961).

(26) T. C. W. Mak and R. K. McMullan, *J. Chem. Phys.*, **42**, 2732 (1965).

(27) R. K. McMullan and G. A. Jeffrey, *ibid.*, **42**, 2725 (1965).

(28) D. N. Glew and N. S. Rath, *ibid.*, **44**, 1710 (1966).

(29) D. R. Hafemann and S. L. Miller, to be published.

(30) D. F. Sargent and L. D. Calvert, *J. Phys. Chem.*, **70**, 2689 (1966).

than half-occupancy of the pentagonal dodecahedra by the "help-gas," H_2S , giving $8.0\text{C}_4\text{H}_8\text{O} \cdot 6.4\text{H}_2\text{S} \cdot 136\text{H}_2\text{O}$. Physically the systems are very different because with the cyclic ethers crystallization occurs from a single liquid phase rather than at a gas-liquid or liquid-liquid interface as with the hydrocarbons and halogenated hydrocarbons.

The Peralkylammonium Salt Hydrates

The tetra-*n*-butyl- and tetraisoamylammonium salt hydrates first discovered by Kraus and coworkers³¹ belong to this same class of clathrate hydrates. The large polyhedra necessary to accommodate (*n*- C_4H_9)₄ N^+ , (*i*- C_5H_4)₄ N^+ , their phosphonium analogs, or (*n*- C_4H_9)₃ S^+ ions have a close geometrical relationship to those which hold the guest molecules in the gas hydrates,²² so much so that there are isostructural relationships between the two series of crystal structures. For example, (*n*- C_4H_9)₃ $\text{SF} \cdot 20\text{H}_2\text{O}$ ³² is isostructural with $6\text{Cl}_2 \cdot 46\text{H}_2\text{O}$.¹⁹ The principal difference in the structures is that with the alkylammonium salts it is the water and the anions which form the hydrogen-bonded host framework lattice. These are, therefore, not true clathrates in the sense that the term was originally defined by Powell,³³ since the cations must be subjected to the ionic crystal field of the surrounding negatively charged water-anion cage. However, this difference is not perceptible in the structural environment of the cations compared with a hydrocarbon molecule in a similar water environment. In (*n*- C_4H_9) $\text{N}^+ \cdot \text{C}_6\text{H}_5\text{COO}^- \cdot 39.5\text{H}_2\text{O}$, for example,³⁴ there are 30 alkyl carbon to water oxygen distances at normal van der Waals separations between 3.6 and 4.0 Å, and the N^+ atom is 4.18 Å from the oxygen of the benzoate ion.

In some structures the anion is localized in the water framework, while in others it is disordered. This accounts for the remarkable similarity in the X-ray diffraction patterns of the hydrates of the tetra-*n*-butylammonium fluoride, chloride, bromide, acetate, chromate, tungstate, oxalate, bicarbonate, and hydrogen phosphate.³⁵ In the benzoate, referred to above, the anion also acts to stabilize a void. The carboxylate oxygens form part of the water framework while the benzyl group occupies a 14-hedral cage in an especially compact manner. There are 36 distances between 3.2 and 4.0 Å between the six benzyl carbons and the water oxygens of the surrounding cage. Similar anionic function as part host-part guest is expected in the structures of the isomorphous *m*-chlorobenzoate, *p*-fluorobenzoate, butyrate, valerate, isocaproate, and picolinate.³⁶ This

versatility in the anions does not extend to the cations. Both tetra-*n*-butyl- and tetraisoamylammonium ions fit very very elegantly into the water cages, with as many as 40 van der Waals separations of 3.5 to 4.0 Å between the alkyl carbon atoms and the water oxygens. This appears to be a necessary condition for crystallization, since attempts to obtain hydrates of tetra-*n*-propyl- and tetraallylammonium salts were unsuccessful, as were those with tetra-*n*-butylammonium tetraphenylboron and ammonium tetraphenylboron.³⁶ In all cases, however, these solutions became characteristically viscous, and the inability to crystallize these hydrates may be due to the absence of appropriate nucleation. In one experiment, tri-*n*-butylsulfonium fluoride gave a monoclinic form instead of the common cubic structure. In this structure,³⁷ a single large water-anion cage composed of 96 waters enclosed two sulfonium ions, "back to back," with a $\text{S} \cdots \text{S}$ separation of 4 Å, thus providing an interesting example of cationic pairing in the solid state. Attempts to grow other batches of these crystals always resulted in the more stable cubic modification.

Other examples where water molecules and ions form a hydrogen-bonded clathrate lattice to enclose an ion of opposite charge are found in tetramethylammonium hydroxide pentahydrate³⁸ and hexafluorophosphoric acid hexahydrate.³⁹ In both structures the geometry of the clathrate cage is based on cuboctahedra rather than pentagonal dodecahedra, *i.e.*, the polyhedral cages are formed from squares and hexagons rather than pentagons and hexagons. In $(\text{CH}_3)_4\text{N}^+ \cdot \text{OH}^- \cdot 5\text{H}_2\text{O}$, the anion and water molecules clathrate the cations, whereas in $\text{PF}_6^- \cdot \text{H}^+ \cdot 6\text{H}_2\text{O}$ the anion is a guest inside a cuboctahedron of hydrogen-bonded water molecules. It is inferred that the acidic proton is associated with the water structure, but this has not yet been verified experimentally.

In these high hydrate structures, questions of stoichiometry, the nature of the chemical bonding, and particularly the recognition of the geometrical relationships between the extended water lattices have depended heavily on crystal structure investigations. Here, as with silicate chemistry, the structure determinations have provided the recognition of relationships which could not be readily inferred from the chemical formulas of the compounds. The need for a general structural basis for understanding the formation of these hydrates becomes even more acute in the next class of structures which we have called "semiclathrates" in Table I. These are also structures in which the water molecules form hydrogen-bonded lattices with recognizable cages of well-defined geometry. The guest molecules occupy these voids as in a true clathrate, but also enter into a specific hydrogen-bonding relationship with the surrounding water structure through their functional groups.

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(38) R. K. McMullan, T. C. W. Mak, and G. A. Jeffrey, *ibid.*, **44**, 2338 (1966).

(39) H. Bode and G. Teufer, *Acta Cryst.*, **8**, 611 (1955).

Table II
The Alkylamine Hydrates

	Hydration no. reported from phase studies by Pickering ^a					Hydration no. (mp, °C) from crystal structure studies
Methyl		3.0, ^b 3.5			10 ^c	
Dimethyl	1			7		7.8 ^d (-16.9)
Trimethyl	2			7 ^c	10, ^b 11	20 ^c 10.25 (5.0)
Ethyl	0.5		5.5			7.6 ^d (-7.5)
Diethyl	0.5 ^b	3.0 ^b	5.5 ^c	8	11 ^c	36 ^c 7.0, ^d 8.67 (-6.0)
Triethyl		2		8 ^c		31 ^c
Propyl	0.5	3.5 ^c		8		6.5, 10.0 ^d (-13.5)
Isopropyl		3.5 ^c		8		8.0 (-4.0)
Dipropyl	0.5		5.5 ^c			
Isobutyl				7	14 ^c	36 ^c
sec-Butyl		2 ^c			11 ^c	34 ^c
t-Butyl						9.67 (-1.0)
Amyl			5.5 ^c			37 ^c
Octyl ^e		1.5	6.0			
Dodecyl ^e	0.7	2.0		4		
Octadecyl ^e	0.7	2.0				

^a Reference 40. ^b W. C. Somerville, *J. Phys. Chem.*, **35**, 2412 (1931). ^c Hydrate formation uncertain, indicated only by breaks in freezing point curves. ^d Hydration number derived from crystal data, not complete structure determination. ^e A. W. Ralston, C. W. Hoerr, and E. J. Hoffman, *J. Amer. Chem. Soc.*, **64**, 1516 (1942).

Table III
Structural Characteristics of the Alkylamine Hydrates

Name, mp, °C, and formula per unit cell	Amine-water relationship	Hydrogen-bonded <i>n</i> -hedra (H ₂ O) _{<i>n</i>} ^a
<i>t</i> -Butylamine hydrate, -1, 16(CH ₃) ₃ ·CNH ₂ ·156H ₂ O	Nonbonded within 17-hedra	17-Hedra (7 ³ ·6 ² ·5 ⁹ ·4 ³) 8-Hedra (4 ⁴ ·5 ⁴)
Diethylamine hydrate, -6, 12(CH ₂ CH ₂) ₂ NH·104H ₂ O	Hydrogen bonded in distorted 18-hedra and in an irregular cage	18-Hedra (5 ¹² ·6 ⁶) Irregular cage (6 ⁶ ·5 ⁸ ·4 ³)
Trimethylamine hydrate, 5, 4(CH ₃) ₃ N·41H ₂ O	Hydrogen-bonded in very distorted 15-, 26-polyhedra	12-Hedra (5 ¹²) ^b 15-Hedra (5 ¹² ·6 ³) 26-Hedra (5 ²⁴ ·6 ²) ^c
Isopropylamine hydrate, -4, 10(CH ₂) ₂ CH·NH ₂ ·80H ₂ O	Hydrogen-bonded in very distorted 14- and 16-hedra	8-Hedra (6 ² ·4 ⁹) 12-Hedra (5 ¹²) ^b 14-Hedra (4 ² ·5 ⁸ ·6 ⁴) 16-Hedra (5 ¹² ·6 ⁴)
<i>n</i> -Propylamine (stable, -35°), 16CH ₂ CH ₂ CH ₂ NH ₂ ·104H ₂ O ^d	Hydrogen bonded in very distorted 14-hedra and 16-hedra	11-Hedra (4 ² ·5 ⁸ ·6 ⁴) ^e 14-Hedra (5 ¹² ·6 ²) 16-Hedra (5 ¹² ·6 ⁴)

^a *m*ⁿ refers to *n m*-sided faces, *i.e.*, the 17-hedra have three heptagons, two hexagons, nine pentagons, and three squares. The notation used is that described by A. F. Wells, "The Third Dimension in Chemistry," Oxford University Press, London, 1962. ^b The pentagonal dodecahedra, where occurring, are very regular. ^c These are derived from two 14-hedra (5¹²·6²) sharing a common hexagonal face. ^d C. A. Shelton and D. Panke, *Acta Cryst.*, **A25**, S147 (1969). ^e This polyhedron is empty.

The Alkylamine Hydrates

Examples of the semiclathrates have so far been found in the alkylamine hydrates, some 35 of which were reported from phase studies carried out at the end of the past century by Pickering.⁴⁰ This series of compounds appears to display an extraordinary variety of hydrogen-bonded water structures, all representing different compromises between the clathrate hydration of the hydrocarbon groups and hydrogen bonding with the functional group. Pickering's results are summarized in Table II, together with some more recent results on higher analogs and some crystal data. The alkylamines generally form two types of hydrates, low hydrates with one-half, one, or two waters of crystallization and the high hydrates with hydration numbers between six and eleven. The significance of the discontinuities in the freezing-point curves at very high hy-

dration numbers around 35 has not yet been explored. The high homologs have the interesting feature that the hydrates form a stable liquid-crystal phase between the crystalline solid and the melt.

The preliminary crystal data have been reported on nine of the high hydrates,⁴¹ and five have been studied in detail. There are no crystal data on the low hydrates. The most striking contrast between the amine hydrates and the gas hydrates is in the variety of the structures observed. In the gas hydrates, two basic structures serve a wide variety of hydrate-forming molecules; in the amines each structure so far studied represents a different compromise between the requirements of hydrogen bonding and clathration.

The results on the five structure determinations as they relate to the water environment of the amine molecules are summarized in Table III. Only the

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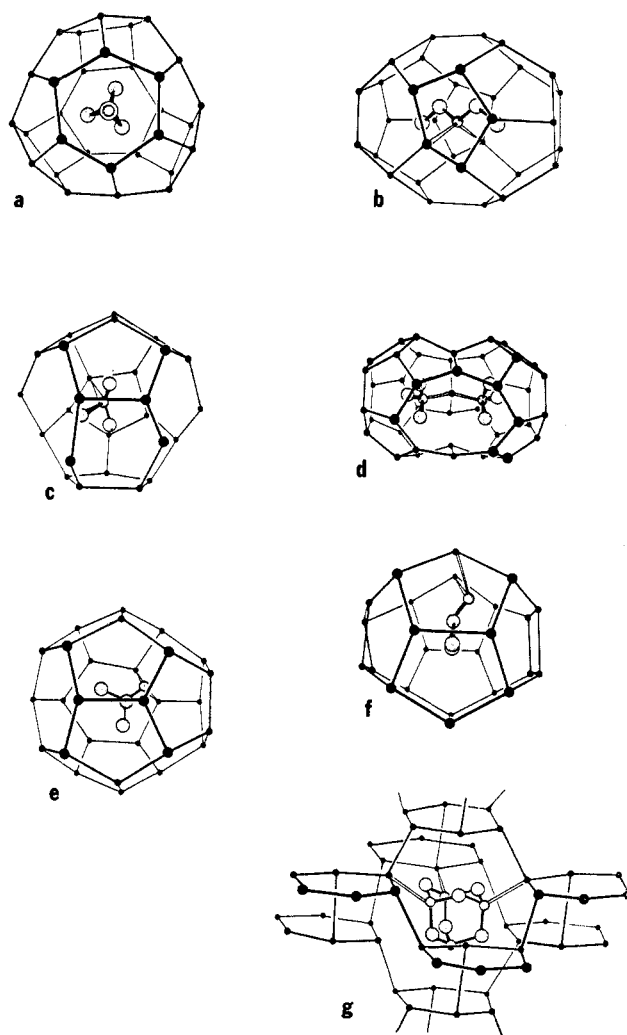
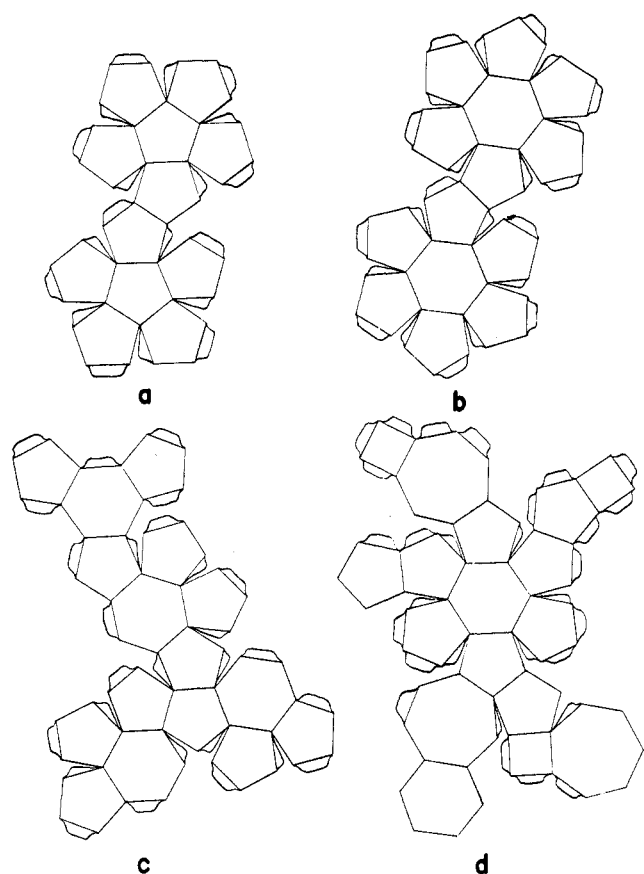


Figure 1. Diagrams for constructing the 12-, 14-, 16-, and 17-hedra found in the clathrate hydrates. The edges which are not peripheral should be scored with a sharp knife prior to folding. A convenient scale model in which the vertices represent oxygen positions and the edges hydrogen bonds is obtained if these are drawn on cards with the edge lengths 3.5 cm; *i.e.*, 1.25 cm = 1 Å, which is the same scale as the Corey-Pauling-Koltum packing models. Alternately, approximate "free space" models can be made on the same scale with edge lengths of 2.1 cm (assuming a van der Waals radius of 1.4 Å for oxygen). (a) The pentagonal dodecahedron (5^{12}); (b) the 14-hedron ($6^2 \cdot 5^{12}$); (c) the 16-hedron ($6^4 \cdot 15^{12}$) [these polyhedra enclose the guest species in the gas hydrates of the type $2X \cdot 6Y \cdot 46H_2O$ and $2X \cdot Y \cdot 17H_2O$ and occur in distorted form in many of the other clathrate and semiclathrate hydrates]; (d) the 17-hedron ($7^3 \cdot 6^2 \cdot 5^9 \cdot 4^3$) [this polyhedron encloses the amine molecule in $(CH_3)_3 \cdot CNH_2 \cdot 9.75 H_2O$].

t-butylamine hydrate,⁴² $(CH_3)_3CNH_2 \cdot 9.75H_2O$, is a true clathrate, where the amine occupies the voids in the water host structure, with $(CH_3) \cdots O$ and $(NH_2) \cdots O$ van der Waals separations which are somewhat longer than is generally observed in the gas hydrates (*i.e.*, 3.8–4.2 Å). The 17-hedra cage, which is occupied by the amine, is larger than the 16-hedra found in the gas hydrate series, as can be demonstrated by constructing paper models based on the paper folding diagrams given in Figure 1. The host lattice in this structure could accommodate hydrocarbon guest species which are larger than those which occur in the 17-Å gas hydrate structure. The reason that this has not been observed, with butane, for example, may be due to an additional component in the lattice energy of the amine hydrate

Figure 2. Environment of amine molecules in water clathrate cages: (a) *t*-butylamine molecule nonbonded within 17-hedron, in $(CH_3)_3CNH_2 \cdot 9.75H_2O$; (b) diethylamine molecule bonded within 18-hedron, in $(C_2H_5)_2NH \cdot 8.66H_2O$; (c) trimethylamine molecule bonded within distorted 15-hedron, in $(CH_3)_3N \cdot 10.25H_2O$; (d) two trimethylamine molecules and additional water molecule bonded within 26-hedron, in $(CH_3)_3N \cdot 10.25H_2O$; (e) isopropylamine molecule bonded within 16-hedron, in $(CH_3)_2CHNH_2 \cdot 10H_2O$; (f) isopropylamine molecule bonded within 14-hedron, in $(CH_3)_2CHNH_2 \cdot 10H_2O$; (g) structure of hexamethylenetetramine hexahydrate. The carbon and nitrogen atoms of the amine molecules are shaded; the water oxygen atoms are the solid vertices and the solid edges are hydrogen bonds. The $N \cdots (H) \cdots O$ hydrogen bonds are open. The hydrogen atom positions are not shown.

arising from dipole interactions. The 17-hedral water cages are polar and the amine guest molecules are aligned with their C–N bonds along the polar threefold axes of these cages, as shown in Figure 2.

In the three other amines so far studied, there are specific hydrogen-bonding interactions between the primary, secondary, and tertiary amine groups and the water structure, which nevertheless forms recognizable polyhedral cages around the molecules (see Table III and Figure 2). Together with the larger occupied cages, there are also smaller vacant polyhedra formed by the hydrogen-bonded water molecules, as in the gas hydrates and the peralkylammonium salt hydrates.

(42) R. K. McMullan, G. A. Jeffrey, and T. H. Jordan, *J. Chem. Phys.*, **47**, 1229 (1967).

Three of these have only been observed in the amine hydrates. Two are octahedra with four square and four pentagonal faces and with six square and two hexagonal faces. These polyhedra are smaller than the familiar pentagonal dodecahedron, which also appears in two of these amine hydrates. They are comparable in size with the voids in the hexagonal ice structures. The third is an 11-hedron, which is only slightly smaller than the pentagonal dodecahedron.

In each of these semiclathrate structures, the compromise between hydrogen bonding of the functional group and the clathration of the hydrocarbon residue is achieved by a different structural mechanism as illustrated in Figure 2. In the diethylamine hydrate,⁴³ the NH groups donate a hydrogen bond to and accept a hydrogen bond from two water molecules on opposite sides of cavities, which resemble spheroids approximately $13 \times 8 \times 8 \text{ \AA}$; this divides the cavities into two halves, each of which accommodates an ethyl group. The water structure in $(\text{CH}_3\text{CH}_2)_2\text{NH} \cdot 8.66\text{H}_2\text{O}$ has two types of voids. One of these cavities is recognizable as a distorted 18-hedron with twelve pentagons and six hexagons (*i.e.*, $5^{12} \cdot 6^6$); the other is too irregular to encourage a rational description and is difficult to depict except by means of a three-dimensional atomic model.

In the trimethylamine hydrate,⁴⁴ $(\text{CH}_3)_3\text{N} \cdot 10.25\text{H}_2\text{O}$, each functional group accepts one hydrogen bond from an adjacent water molecule. This occurs in two ways. In the 15-hedra ($5^{12} \cdot 6^3$), one of the water molecules per polyhedron directs a hydrogen bond inward toward the nitrogen atom of the enclosed "guest," as shown in Figure 2. The other mode is more complex. A pair of amine molecules are hydrogen bonded to an additional water molecule, which in turn is hydrogen bonded to a large cage formed by two 14-hedra, sharing a common hexagonal face. Despite the complexity introduced by the amine molecules which distort the faces of the polyhedra, this structure can be recognized as belonging to a general class in which the 12-hedra share faces to form an extended layer in two dimensions.²² The cavities which accommodate the "guest" species are then formed by linking vertices through additional water molecules in the third direction. Other examples of this type of structure are the orthorhombic tetraisoamylammonium fluoride hydrate (*i*- C_5H_{11})₄- $\text{NF} \cdot 38\text{H}_2\text{O}$ ⁴⁵ and the monoclinic tri-*n*-butylsulfonium hydrate (*n*- C_4H_9)₃ $\text{SF} \cdot 23\text{H}_2\text{O}$.³⁷ The corresponding gas hydrate structure, which would be a decahydrate, has not been found.

The isopropylamine hydrate structure, $(\text{CH}_3)_2\text{CHNH}_2 \cdot 8.0\text{H}_2\text{O}$, contains 12-hedra and 16-hedra and can be related geometrically to the well-known cubic 17- \AA gas hydrate structure.⁴⁶ The 12-hedra are unoccupied and undistorted. The 16-hedra are occupied by an

amine molecule with the functional group hydrogen bonding to form a $\text{O} \cdots \text{H}-\text{N}-\text{H} \cdots \text{O}$ bridge across two oxygens in place of the edge of the undistorted polyhedra (Figure 2). The other mode of accommodating the amines is by expanding a 12-hedron into irregular 14-hedra which possess two square and four hexagonal faces. This leaves small unoccupied voids in the hydrate framework which are the octahedra with two hexagonal and six square faces. In the *n*-propylamine hydrate, the nitrogens replace a vertex of the polyhedral water framework in one mode of bonding; in the other a hydrogen-bonded dimer of two amines forms a bridge across a void.

In summary, then, the amine molecules have been observed to interact with the surrounding water framework in the following ways: (1) forming no hydrogen bonds with the water structure, as in $16(\text{CH}_3)_3\text{CNH}_2 \cdot 156\text{H}_2\text{O}$; (2) forming one donor and one acceptor hydrogen bond which bridges across the water oxygen vertices at opposite sides of a void, as in $12(\text{CH}_3\text{CH}_2)_2\text{NH} \cdot 104\text{H}_2\text{O}$; (3) forming two donor hydrogen bonds bridging across two adjacent oxygens which would form an edge in a regular gas hydrate type of polyhedron, as in $10(\text{CH}_3)_2\text{CHNH}_2 \cdot 80\text{H}_2\text{O}$; (4) forming two acceptor hydrogen bonds from a bridging water oxygen, as in $4(\text{CH}_3)_3\text{N} \cdot 41\text{H}_2\text{O}$; (5) replacing a water oxygen vertex and bridging across a void by a hydrogen-bonded dimer of two amine molecules, as in $16\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 \cdot 104\text{H}_2\text{O}$.

There is good reason to believe that further studies of the remaining hydrates reported by Pickering will each reveal a new water framework suitably "engineered" to fit the particular stereochemistry of the alkylamine. It is impossible, however, to predict which, if any, will be clathrates with a nonbonded amine guest, nor can one anticipate the precise stoichiometry.

Belonging to this same general classification as a semiclathrate is the well-known hexamethylenetetramine hexahydrate.⁴⁷ Since three of the four tertiary amine nitrogens are hydrogen bonded to the water structure, shown in Figure 2, the geometry of the cyclic amine plays a more dominant role in determining the structure of the hydrate. The water structure is a well-defined framework, but it is not polyhedral, *i.e.*, it cannot be described in terms of polyhedra with planar or distorted planar faces. However, it bears a close topological relationship to the β -quinol clathrate host lattice in the first clathrate structure to be discovered and must therefore be considered in this context.⁴⁸ No other examples of this type of water structure have been found. Indeed it is an interesting observation that, with this exception, all the water structures in clathrate and semiclathrate hydrates are polyhedral. In the presence of nonpolar or partially nonpolar molecules, water undoubtedly prefers to form lattices which contain a predominance of planar or nearly planar pentagons, hexagons, and squares. This is in contrast to the framework structures of the ices, where puckered pen-

(43) T. H. Jordan and T. C. W. Mak, *J. Chem. Phys.*, **47**, 1222 (1967).

(44) D. Panke, *ibid.*, **48**, 2990 (1968).

(45) D. Feilke and G. A. Jeffrey, *ibid.*, **35**, 1863 (1961).

(46) D. Panke and R. K. McMullan, Abstracts of American Crystallographic Association Meeting, Tucson, Ariz., Feb., 1968, No. K7.

(47) T. C. W. Mak, *J. Chem. Phys.*, **43**, 2799 (1965).

(48) D. E. Palin and H. M. Powell, *J. Chem. Soc.*, 571 (1948).

tagons or hexagons occur which do not form obvious polyhedra.

The only other cyclic amine hydrate which has been studied in detail is that of piperazine,⁴⁹ $C_4H_8(NH)_2 \cdot 6H_2O$. This is not a clathrate hydrate. The water molecules form hydrogen-bonded frameworks which extend two dimensionally and are linked in the third direction by hydrogen bonding through the secondary amine groups. Nevertheless, it is still a recognizable cousin to the clathrate hydrates because it has a two-dimensionally extended water structure consisting entirely of face-sharing pentagons.

Classification of Organic Hydrates

The hydrate structures observed with the cyclic ethers and amines are in marked contrast to those formed by organic molecules with a multiplicity of polar functional groups. Comparatively few hydrates are reported for the carbohydrates and polyols, despite their high solubility. Where water molecules are incorporated in the crystal lattice, their structure-determining role is secondary to the hydrogen-bonding system formed by the hydroxyl groups. These systems generally consist of extended chains or spirals and form very compact molecular packing arrangements with comparatively high densities. Even in the rare cases where there is a high water component in the crystal, as in raffinose pentahydrate,⁵⁰ there is no hint of formation of a partial clathrate hydrate structure such as found in the piperazine hexahydrate. Rather the water molecules seem to have a space-filling function in channels formed by hydrogen-bonded helices of the trisaccharide molecules. Other classes of water-soluble organic compounds which have been extensively studied by crystal structure determination are the amino acids, peptides, pyrimidines, and organometallic salts. Like the carbohydrates, the amino acids do not form many hydrates, and the inclusion of water molecules in the crystal lattice is the exception rather than the rule. Of the 15 known amino acid structures (including polymorphs, but excluding salts), only in proline and arginine were the mono- and dihydrates, respectively studied. Monohydrates are also found in some of the peptide crystal structures, but there is no evidence of the type of hydration which occurs with the alkylamines.⁵¹ The pyrimidines tend to form more hydrates, unless they are substituted by alkyl groups, as in the barbiturates, but again there is no hint of clathration. The structures are dominated by the intermolecular hydrogen bonding of the functional groups, which frequently align the planar molecules in ribbons. Where water molecules are present, they also form extended chains or ribbons. Of the organometallic complexes, hydrates are most common in the carboxylate compounds, with the isolated water molecules or chains

Table IV
Hydration Properties of Organic Molecules in the Crystalline State

Hydrogen bonding	carbohydrates, polyols, amino acids, peptides, pyrimidines, purines, urea, ureides, acids and salts, amides, nitriles, aldehydes, phenols, quaternary methylammonium ion, glycols, polyoxymethylenes, alcohols, ketones, cyclic amines, aliphatic amines, cyclic ethers, quaternary <i>n</i> -butyl- and isoamylammonium ions, mercaptans, alkanes, alkyl halides (rare gases, halogens, ClO_2 , SO_2 , H_2S , N_2O , CO_2 , CS_2 , COS).	Low hydrates
↑		↑
↓		↓
Hydrophobic clathration		High hydrates

of hydrogen-bonded water molecules having a very secondary role in determining the structure.

Of the 2000 organic crystal structures determined in the period 1960–1966,⁵² about 200 were hydrates. Inspection of these, together with earlier data,³ suggests a classification such as shown in Table IV. The quaternary methylammonium ion is placed in the middle of the classification not so much because it is unique but because it provides three known examples of differing hydration behavior depending upon the anions. $(CH_3)_4NOH \cdot 5H_2O$ is a polyhedral clathrate hydrate³⁸ with the cation as guest and a water-anionic host lattice. In $(CH_3)_4NF \cdot 4H_2O$ the cations also lie within a framework of hydrogen-bonded water molecules and anions,⁵³ but there is no topological relationship to the polyhedral clathrate hydrates. In $[(CH_3)_4N]_2SO_4 \cdot 4H_2O$, a saltlike assembly of ions is interspersed with extended chains of water molecules⁵⁴ and the tendency to form a framework water-anion structure has completely disappeared. The tetramethylammonium salts form other hydrates which are difficult to crystallize and identify. More intensive detailed study of these would probably reveal more samples ranging from structures dominated by clathrate hydration to those where the theme is primarily a saltlike arrangement of the ions.

Above the midline of Table IV are placed classes of water-soluble organic compounds where framework or clathrate hydrates are not anticipated. Below the midline are the possible hydrate formers in order of certainty that semiclathrate or clathrate hydrates will be or have been found, taking into account the limitations on molecular dimensions that have been discussed earlier in this article. Near the midline both low and high hydrates may be found, as with the alkylamines.

Acetone is the only known ketone to form a clathrate hydrate; it is the gas hydrate type with ideal stoichiometry $6(CH_3)_2CO \cdot 46H_2O$.^{22,55} Ethanol forms two hydrates at about -80° with approximately the same

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(53) W. J. McLean and G. A. Jeffrey, *J. Chem. Phys.*, **47**, 414 (1967).

(54) W. J. McLean and G. A. Jeffrey, *ibid.*, **49**, 4556 (1968).

(55) D. W. Davidson and G. J. Wilson, *Can. J. Chem.*, **41**, 1424 (1963).

(49) D. Schwarzenbach, *J. Chem. Phys.*, **48**, 4134 (1968).

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composition as those of cyclopropane and trimethylene oxide. These are either clathrate hydrates or closely related semiclathrates.⁶⁶ Methanol also forms a hydrate, but it is a hemihydrate.⁵⁷ Hydrates have been reported for other alcohols and for the glycols, but mostly with low content.⁵⁸ The interesting exceptions are the hexahydrates of *meso*-2,3-butanediol, 2-methyl-2,3-butanediol, pinacol, and 2,5-dimethyl-2,5-hexanediol. These hydrates might be clathrates of the corresponding cyclic ether in the solid state. This would be the antithesis of the alloxan mono- and tetrahydrates which were found to be a dihydroxy derivative and its trihydrate in the crystalline state.^{59,60}

Hydration in Solution

The concept of structural persistence from the crystalline solid to the liquid near the melting point has strong support.⁶¹ The question therefore arises as to whether the tendency of water molecules to form clathrate cages around certain organic molecules or ions is limited to the solid crystalline state. Since Pauling proposed his clathrate hydrate model for liquid water,⁶² clathrate hydration has been a useful model to assist in the interpretation of the behavior of aqueous solutions. It is clearly consistent with the hypothesis that there is a stabilization of water structure by nonelectrolytic solutes, which occupy "voids" and thereby hinder the thermal motion of neighboring solvent molecules. However, it is difficult to establish whether these "voids" have any real structural relationship to those observed in the clathrate hydrates. This is perhaps not surprising for solutions of hydrocarbons in water since the most striking feature of the gas hydrate formation is that it corresponds to a solubility in the solid which is orders of magnitude greater than that in the liquid. The systems which pass from crystalline solid to homogeneous aqueous solution without change in composition on melting may be more amenable to both theory and experiment.

To some physical chemists it seems clear that in cold aqueous solutions of nonelectrolytes there must exist some "liquid analogy" to clathrate hydration as distinct from "normal" ionic hydration, whereas to others there appears to be no evidence of any short-range order that can be related to the crystalline structure of the clathrate hydrates. The solution properties of tetraalkylammonium ions have been well studied and described as due to "hydration of the second kind,"⁶³ and as " β structure,"⁶⁴ as distinct from the hydration of

normal ions and the "flickering icebergs" of Frank.⁶⁵⁻⁶⁷ The cationic pairing observed in the crystal structure of $(C_4H_9)_3SF \cdot 23H_2O$ appears to have its counterpart in the cation association⁶⁸ postulated to account for the partial molar volume changes⁶⁹ and heats of dilution⁷⁰ of large tetraalkylammonium salt hydrates. The near-infrared spectra of aqueous solutions of $(C_4H_9)_4NBr$ show changes which can be interpreted as a reduction in the structure-enhancing ability of the cations above 1.9 *m*, which is approximately the concentration of the solid hydrate.⁷¹ On the other hand, the X-ray diffraction data on solutions of $(C_4H_9)_4NF$ can be better fitted with a model based on the occupancy of voids in the ice I structure than with a gas hydrate model.⁷²

The solution properties of organic molecules generally have received less systematic quantitative attention than those of the alkylammonium salts. In consequence, the evidence which might link or disprove a connection between water structure in the liquid and in a crystalline hydrate is even more circumstantial. The structural properties of alcohol-water mixtures have been well reviewed and discussed,⁷³ but unfortunately there have been no comparable crystal structure studies of either the alcohols or their hydrates. On the other hand, the alkylamine hydrates are now comparatively well explored in the crystalline state, but the physical chemistry of the solutions has only been studied for a few isolated examples.⁷⁴ There are two interesting analogies. One is between the discussion of the competing hydrophobic and hydrophilic interactions leading to the existence of a lower consolute temperature⁷⁵ and those leading to the formation of a semiclathrate hydrate. The second is that the basicity of the substituted methylalkylamines in water is not that predicted by organic theory for the isolated molecules or that observed from mass spectroscopic data.^{76,77} Similarly in the semiclathrate hydrates, one would not predict from electronic theory that a primary amine would be a non-bonded guest, as in $16(CH_3)_3CNH_2 \cdot 156H_2O$, whereas a tertiary amine would be a hydrogen-bonded guest, as in $4(CH_3)_3N \cdot 41H_2O$.

It is indeed conceivable that between 15 and -100° there exists a world of structural hydrate chemistry, concealed, like the major part of the iceberg, from usual observation.

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