Computer Counting of the Number of Water Molecules in the First Layer of Crystalline Water Clathrate

Iwao TABUSHI,* Yo-ichi KIYOSUKE, and Kazuo YAMAMURA
Department of Synthetic Chemistry, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606
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Semiempirical calculation of the number of water molecules in the first layer of water clathrates in crystalline state was developed by computer aided construction of hydrogen-bonded network of water molecules. In the generalized thermodynamic considerations on four possible types of "unit clathrate," van der Waals stabilization energy, "strain" energy of the unit clathrate, and entropy term due to the motional freedom of the guest were taken into account for the calculation of free energy change for the formation of the water clathrate. The results of calculations on 37 hydrophobic organic molecules well represented the trend of the reported experimental data of X-ray studies. The present calculation also disclosed such a large unfavorable strain energy (8.72 kcal·mol^{-1})† of pentakaidecahedron that it counteracts the van der Waals stabilization. The result is in a good agreement with the fact that pentakaidecahedral cavity is rarely seen in the gas hydrates. Most importantly, these semiempirical calculations of the energetics of water clathrates afforded valuable new insights into water assembly and may be extended to give better understandings of structured water in biological system and of water clusters that develop around apolar solutions in water.

Hydrophobic interaction is assumed to be one of the most significant factors that determine protein conformation and has provided a physicochemical basis for the concept of highly specific molecular recognition that many biological macromolecules exhibit.[1] Studies on properties of an apolar solute in water are particularly relevant to water structure study for elucidation and semiempirical determination of the hydrophobic interaction.[1,2a] However, the progress of an "iceberg" theory has been retarded by contradictory results from thermodynamic and spectroscopic studies.[2b-e] Moreover, no definitive evidence for the presence of strengthened water clusters around or in proximity to the hydrophobic surface of a solute molecule was obtained from spectroscopic experiments such as NMR.[2c,f]

Assumption of a generalized hypothetical process proposed for the molecular recognition between relatively simple host and guest and application of semiempirical force field potentials were found to claim a great advantage of the first layer model of water clusters in thermodynamic considerations.[3] Thus, in our most recent theoretical treatise on chemical model of biological molecular recognition, the observed free energy change for inclusion complexing of a hydrophobic guest by α-cyclodextrin in water could be successfully reproduced by applying the above concept of water clusters. Némethy and Scheraga had shown that the work requisite to break icelike structured water (water clusters) is proportional to the number of water molecules in the first layer of the water clusters developed around an apolar solute.[4a] Their treatment of cluster model has been continuously generalized and improved by use of modified partition function, incorporating the effects of cooperative hydrogen bonding on the continuous distribution of all possible cluster size.[4a-c]

Most importantly, the breaking of the water clusters around the guest is one of the most important and crucial factors associated with the process of biological molecular recognition and, in this context, greater sophistication is necessary in non- or semi-empirical evaluation of the number of water molecules in the first layer of water clusters around a guest molecule in order to derive the thermodynamic parameters rigorously. Fortunately a lot of insight have been accumulated into crystalline water clathrates from experiments,[5] although there is no direct physicochemical evidence from experiments for the presence of water clusters in a liquid state.[2]

A variety of hydrogen-bonded networks of water molecules in the crystalline state are thus far known, whose cavity includes various types of organic molecules. The unit structure of the water clathrate varies from dodecahedron composing of 20 water molecules to hexakaidecahedron composing of 28 water molecules, yet the actual hydrates involving so-called structure I or II have composite ratios of polyhedral cavities to form the complicated structures of the hydrate lattice.[5]

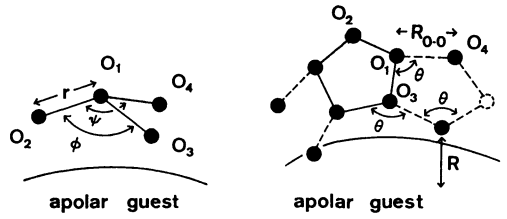
A semiempirical calculation of the number of water molecules in the first layer of water clathrate, the *unit clathrate*, was studied, by constructing and characterizing the hydrogen-bonded networks by computer method. Such the approach made a further progress in theoretical considerations of crystalline water clathrates, structured water in proteins[4d] and other molecules of biological interest, cyclodextrin[4e,f] being one of the simplest examples. In this article the authors wish to report the computer counting of the number of water molecules in the first layer for 37 hydrophobic molecules, where the predicted numbers are in good agreement with reported experimental data. In the extented procedure of the computer evaluation of the number of water molecules, we employed a fit criterion based on the thermodynamic consideration which takes van der Waals stabilization energy, "strain" energy of a polyhedron, and motional freedom of the guest into account. The present theoretical analyses have led us to the conclusions that (1) the rotational freedom of the guest is more critical than the van der Waals interaction for the stabilization of unit clathrates (2) pentakaidecahedron has too large "strain" energy to form a stable unit clathrate (3) a pentagon of hydrogen-bonded five water molecules is most appropriately used as the

† 1 cal=4.18 J.

metastable unit for the semiempirical constructions of the first layer of unit water clathrates. The energetics of water networks based on the semiempirical model was for the first time successfully developed to a simple expedient for the calculation of the number of water molecules. We are now in an advanced stage of the investigation of the water structure around apolar organic molecules in liquid water.

Method of Calculation

General Consideration of Network Construction and Computer Counting of Water Molecules. In Fig. 1a are shown fundamental parameters necessary to construct the hydrogen-bonded network of water molecules for the first layer model where r is the distance between two hydrogen-bonded oxygen atoms, and ϕ and ψ are bond angles defined by $O_2O_1O_3$ and $O_2O_1O_4$ in Fig. 1a, respectively. The fourth coordination of O_1 is neglected (first layer approximation), *viz.*, the hydrogen bond of O_1 to the water molecule in the second layer is regarded substantially the same as that in the bulk water.[6]



$R_{o-o}=2.8\pm0.1$ Å $\theta=108\pm5.8°$ $R_{vdw}\leq R\leq R_{vdw}+1.7$

Fig. 1. (a) Illustration of the distance r and the angles ψ, ϕ defined by hydrogen bond axis in the local structure of hydrogen-bonded networks of water molecules in the first layer of water clathrates. (b) Illustration of the distance R_{o-o} and the angle θ defined for the computer counting based on the method of "pentagon paving."

As preliminary trial of the network construction, we take three hydrogen bonds and van der Waals interaction between the guest and the surrounding network into consideration. Then, Cartesian coordinates (χ_j) of O_1 and O_2 are correlated by simple equations (1)—(3) to those of O_3 and O_4, of neighbored water molecules, where subscripts i and g refer to oxygen and guest,

$$\sum_{j=x,y,z}(\chi_{ji}-\chi_{j1})^2 = r^2 \quad (i=2,\ 3,\ \text{or}\ 4) \tag{1}$$

$$\sum_{j}(\chi_{j1}-\chi_{j2})(\chi_{j1}-\chi_{j2}) = r^2\cos\phi \ \text{ or } \ r^2\cos\psi \tag{2}$$

$$\sum_{j}(\chi_{ji}-\chi_{jg})^2 = R_{vdw}^2 \quad (i=1,\ 2,\ 3,\ \text{or}\ 4) \tag{3}$$

respectively, and R_{vdw} is the distance between the oxygen and the guest molecule.[7] Parameters were taken from structure I: $r=2.8$ Å, $\phi=\psi=108°$, and $R_{vdw}=3.32$ Å.[5] According to the requirements (1)—(3), consecutive determinations of coordinates of oxygen atoms were carried out for the case of argon, but the number of 12 obtained as the result of the iterative computer counting was much smaller than the X-ray results of 20 water molecules constructing a dodecahedron.[5]

Method of Pentagon Paving. Attempts to improve the disadvantage of the above somewhat complicated but still unsatisfactory treatment introduced to maximize both the vdw attractive interaction and the hydrogen bond energy, were made by introducing a pentagon which is composed of hydrogen-bonded five water molecules (Fig. 1b), since it is known that the pentagon is the important unit structure of the most stable forms of crystalline water[5] (structure I). The computer counting was executed iteratively, constructing pentagons in turn so as to satisfy geometrical relationships (4)—(6), where R_{o-o} is the distance between two

$$\sum_{j=x,y,z}(\chi_{ji}-\chi_{j1})^2 = R_{o-o}^2 \quad (i=2,\ 3,\ \text{or}\ 4) \tag{4}$$

$$\sum_{j}(\chi_{ji}-\chi_{j1})(\chi_{j2}-\chi_{j1}) = R_{o-o}^2\cos\theta \quad (i=3\ \text{or}\ 4) \tag{5}$$

$$\sum_{j}(\chi_{ji}-\chi_{j1})(\chi_{j3}-\chi_{j1}) = R_{o-o}^2\cos\theta \quad (i=2\ \text{or}\ 4) \tag{6}$$

hydrogen-bonded oxygen atoms, θ is the angle defined by three oxygen atoms (O–O$\diagdown$O), and χ are Cartesian coordinates of oxygen atom.[8]

Additional assumptions made for the present model are the followings: (1) The maximal allowancy of deformations of R_{o-o} and θ are 2.8 ± 0.1 Å and $108\pm5.8°$, respectively. Crystallographic data of water clathrate revealed that experimental values of R_{o-o} fall in the range of 2.8 ± 0.1 Å,[5p,g] and the allowancy of angle deformation ($\pm5.8°$) was, therefore, estimated on a basis of energetic equivalence to the bond deformation of 0.1 Å (0.112 kcal·mol^{-1}).

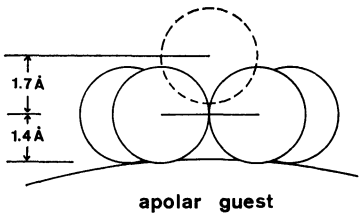


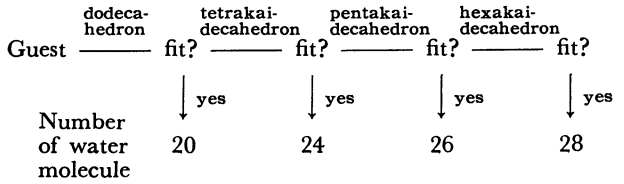
Fig. 2. A water molecule in contact with the pentagon illustrates the geometrical limit of the first layer water molecule ($R_{vdw}+1.7$ Å).

(2) A second water molecule comes into contact with the pentagon at a distance of 1.7 Å from the oxygen (Fig. 2). We, thus, assigned the distance of $R_{vdw}+1.7$ Å to the geometrical limit allowed for the first layer molecule, although the definition is a conceptual clue to the present semiempirical approach.

Fit Criterion Based on Thermodynamic Considerations. In view of the facts that hexagon appears in structure I and II which include relatively large guest molecules, four most probable polyhedra were employed as a *unit clathrate*; dodecahedron, tetrakaidecahedron, pentakaidecahedron, and hexakaidecahedron. At first the free energy change for the formation of the unit clathrate should be taken into the thermodynamic considerations.[8b] For the present purpose, all of possible free energies were introduced: van der Waals stabilization between the guest and the unit clathrate (ΔE_{vdw}),[9a] the "strain" energy of the hydrogen-bonded network of water molecules (ΔE_{strain}),[9b] and motional freedom

of the guest in the cavity (ΔS^g). The free energy change, ΔG, relevant to the formation of unit cell[9c] of crystalline water clathrate now can be calculated using Eq. 7. The number of water molecules in the first layer was calculated as shown in Scheme I, by combining the free energy calculation with the computer aided preconstruction of the network of water molecules for each postulated unit clathrate.

$$\Delta G = \Delta E_{vdw} + \Delta E_{strain} - T\Delta S^g$$
$$\Delta S^g = \Delta S^g_{rot} + \Delta S^g_{trans} + \Delta S^g_{vib} \quad (7)$$



Scheme 1.

Through the optimization of the atomic coordinates of the included guest molecule, the energy of van der Waals interaction (E_{vdw}) was maximized using Hill's potential[9d] (Eq. 8),

$$E_{vdw} = -2.25\varepsilon(r^*/r)^6 + 8.28 \times 10^5\varepsilon \exp(-r/0.0736r^*), \quad (8)$$

where r refers to the interatomic distance, r^* is the sum of the van der Waals radii of the two interacting atoms, and ε is a parameter which is defined individually for each pair of the two interacting atoms.[10]

The strain energy of the unit clathrate was calculated by use of semi-empirical force field potentials. The bond-stretching energy associated with the longitudinal deformation of the hydrogen bond is calculated by Eq. 9, where ΔR is the deviation from the equilibrium length of O···O distance (2.76 Å).[11] ΔE_θ and ΔE_α (Eqs. 10, 11) are angle strains relevant to deformations

$$\Delta E_R = \frac{1}{2}k_R(\Delta\bar{R})^2 \quad (9)$$

$$\Delta E_\theta = \frac{1}{2}k_\theta(\bar{R}-\bar{r})\bar{r}(\Delta\theta)^2 \quad (10)$$

$$\Delta E_\alpha = \frac{1}{2}k_\alpha r^{-2}(\Delta\alpha)^2 \quad (11)$$

$$\Delta E_{strain} = \Delta E_R + \Delta E_\theta + \Delta E_\alpha$$

of O–H···O angle and H–O–H angle, respectively, where R and r are the O···O and O–H bond lengths, respectively, and $\Delta\theta$ and $\Delta\alpha$ are the deformations from the equilibrium angles of O–H···O (180°) and H–O–H (109°28′), respectively. Reported parameters k_R= 22.7 kcal·mol^{-1}·Å^{-1}, k=12.7 kcal·mol^{-1}·Å^{-2}·rad^{-2}, and k_α=78.4 kcal·mol^{-1}·Å^{-2}·rad^{-2} were used.[11]

As to the motional freedom of the apolar guest,[9e] we calculated rotational freedom that makes largest contribution to the entropy term (ΔS^g). The vibrational entropy of a guest is assumed to be unchanged when the guest is sorbed within a unit clathrate of any cavity size. This assumption is supported by the following evaluation, *i.e.*, even a significant frequency change of 5 cm^{-1} for one vibration (1000 cm^{-1}) should accompany a very small entropy change of only 0.03 cal·deg^{-1}·mol^{-1}. One-dimensional, two-dimensional, and three-dimensional rotational entropies are given by Eqs. 12, 13, and 14, respectively, where N_A is Avogadro's number, κ is the Boltzman constant, h is the Planck constant, I is the moment of inertia, σ is the symmetry number, and T is the absolute temperature.

$$S^g_{rot\,(1\text{-}D)} = N_A\kappa\left\{\frac{1}{2}+\frac{1}{2}\ln\frac{8\pi^2 I\kappa T}{h^2}-\ln\sigma_1\right\} \quad (12)$$

$$S^g_{rot\,(2\text{-}D)} = N_A\kappa\left\{1+\ln\frac{8\pi^2 I\kappa T}{h^2\sigma_2}\right\} \quad (13)$$

$$S^g_{rot\,(3\text{-}D)} = N_A\kappa\left\{\frac{3}{2}+\frac{1}{2}\ln\frac{(8\pi^2\kappa T)^3 I_1 I_2 I_3}{h^6}-\ln\sigma_3\right\} \quad (14)$$

Calculations were aided by a digital computer FACOM M-190 OSIV/F4 at the Data Processing Center of Kyoto University.

Results and Discussion

The pentagon method was applied to eleven hydrophobic molecules and the counted number of water molecules in the first layer is listed in Table 1. The calculated results well reproduce experimental data. It is shown that rare gases and even methane or acetylene

Table 1. Results of counting of the number of water molecules in the first layer of unit clathrate based on the method of pentagon paving

Guest	Number of water molecules: Calcd	Exptl[5]
He	20 (dodecahedron)	
Ne	20 (dodecahedron)	
Ar	20 (dodecahedron)	20, 24
Kr	20 (dodecahedron)	20, 24
CH_4	20 (dodecahedron)	20, 24
HC≡CH	20 (dodecahedron)	20, 24
C_2H_6	unclosed 20	20, 24
Benzene	unclosed 20	28
Cl_2	20 (distorted dodecahedron)	20, 24
Br_2	unclosed 20	26
I_2	unclosed 20	

Table 2. The strain energy of unit clathrates (kcal·mol^{-1})

Unit Clathrate	ΔE_R[a]	ΔE_θ[b]	ΔE_α[c]	ΔE_{strain}
Dodecahedron	0.54	0.0	0.52	1.06
Tetrakaidecahedron	0.65	0.0	1.86	2.51
Pentakaidecahedron	3.84	0.0	4.88	8.72
Hexakaidecahedron	3.72	0.0	1.74	5.46

a) Longitudinal deformation of O···O from 2.76 Å, K_R= 22.7 kcal·mol^{-1}·Å^{-1}, Ref. 11. b) Angle deformation of O–H···O from 180°, K_θ=12.7 kcal·mol^{-1}·Å^{-2}·rad^{-2}, Ref. 11. c) Angle deformation of H–O–H from 109°28′, K_α=78.4 kcal·mol^{-1}·Å^{-2}·rad^{-2}, Ref. 11. d) Pentakaidecahedral cavity is very rare in the actual water clathrates. The extremely large strain energy (8.72 kcal·mol^{-1}) of unit pentakaidecahedron as well as the strain of ice lattice adjacent to pentakaidecahedron are reasonably attributed to the absence of pentakaidecahedral unit structure in clathrates.

TABLE 3. NUMBER OF WATER MOLECULES IN THE FIRST LAYER OF UNIT CLATHRATE AND CALCULATED VAN DER WAALS ENERGY AND STRAIN ENERGY

Guest		Calculated energies[a]				Number of water molecules	
		20	24	26	28	Calcd	Obsd[b]
He	A[b]	−0.76	−0.69	−0.76	−0.56		
	B[c]	0.30	1.82	7.96	4.90	n.s.[d]	
Ne	A	−1.66	−1.49	−1.67	−1.22		
	B	−0.60	1.02	7.04	4.24	20	
Ar	A	−4.82	−4.08	−4.40	−3.30		
	B	−3.67	−1.57	4.32	2.16	20	20, 24
Kr	A	−6.93	−5.58	−5.91	−4.46		
	B	−5.87	−3.07	2.80	1.00	20	20, 24
H_2	A	−1.67	−1.30	−1.30	−0.80		
	B	−0.61	1.21	7.42	4.66	20	
N_2	A	−3.58	−2.72	−2.68	−1.74		
	B	−2.52	−0.22	6.04	3.71	20	
O_2	A	−3.49	−2.65	−2.62	−1.69		
	B	−2.43	−0.14	6.10	3.78	20	
CO	A	−3.40	−2.90	−2.92	−2.10		
	B	−2.33	−0.40	5.80	3.36	20	
Cl_2	A	−9.20	−7.65	−7.31	−4.93		
	B	−8.14	−5.14	1.41	0.53	20	
Br_2	A	−9.05	−11.41	−11.30	−7.90		
	B	−8.00	−8.91	−2.56	−2.44	24	26
I_2	A	lp[e]	−15.01	−17.52	−13.11		
		lp	−12.50	−8.80	−7.66	24	
CH_4	A	−5.52	−4.21	−4.08	−2.62		
	B	−4.46	−1.71	4.64	2.84	20	20, 24
C_2H_6	A	−9.94	−7.17	−6.91	−4.38		
	B	−8.88	−4.66	1.88	1.08	20	20, 24
C_3H_8	A	lp	−11.48	−11.51	−9.41		
	B	lp	−8.99	−2.79	−3.96	24	28
$HC(CH_3)_3$	A	lp	−15.92	−14.75	−12.14		
	B	lp	−13.42	−6.03	−6.88	24	28
$C(CH_3)_4$	A	lp	lp	−16.52	−14.13		
	B	lp	lp	−7.81	−8.67	28	
$CH_2=CH_2$	A	−6.34	−5.27	−5.27	−4.29		
	B	−5.29	−2.77	3.45	1.17	20	20, 24
HC≡CH	A	−4.95	−4.03	−3.87	−2.66		
	B	−3.90	−1.53	4.85	2.80	20	20, 24
$CH_3CH=CH_2$	A	lp	−8.65	−8.99	−6.74		
	B	lp	−6.15	−0.28	−1.29	24	
$CH_3C\equiv CH$	A	lp	−7.64	−7.87	−5.69		
	B	lp	−5.13	0.85	−0.23	24	
$(CH_3)_2C=CH_2$	A	lp	−12.22	−11.52	−9.76		
	B	lp	−9.71	−2.80	−4.30	24	
$C_2H_5C\equiv CH$	A	lp	lp	lp	−7.38		
	B	lp	lp	lp	−1.92	28	
$CH_2=CH\cdot C\equiv CH$	A	lp	lp	lp	−5.80		
	B	lp	lp	lp	−0.35	28	
CH_3F	A	−6.23	−5.03	−4.93	−3.34		
	B	−5.18	−2.52	3.79	2.12	20	20, 24
CH_3Cl	A	−9.70	−7.69	−7.82	−5.63		
	B	−8.64	−5.18	0.90	−0.18	20	20, 24
CH_3Br	A	−10.98	−9.53	−9.29	−6.87		
	B	−9.92	−7.03	−0.57	−1.41	20	24
CCl_4	A	lp	lp	lp	−13.52		
	B	lp	lp	lp	−8.06	28	28
C_2H_3Cl	A	lp	−8.64	−8.96	−6.60		
	B	lp	−6.13	−0.24	−1.14	24	

Guest		Calculated energies[a]				Number of water molecules	
		20	24	26	28	Calcd	Obsd[5]
C_2F_4	A	−4.19	−8.22	−8.48	−6.85		
	B	−3.13	−5.72	0.24	−1.39	24	
C_3F_6	A	lp	lp	−10.52	−10.15		
	B	lp	lp	−1.79	−4.69	28	
Benzene	A	lp	−9.94	−6.76	−9.64		
	B	lp	−7.43	1.96	−4.19	24	28
Cyclopropane	A	−11.78	−9.67	−9.66	−6.93		
	B	−10.73	−7.17	−0.94	−1.47	20	
Ethylene oxide	A	−9.28	−7.17	−6.93	−4.49		
	B	−8.24	−4.66	1.79	0.97	20	24
CS_2	A	lp	−9.68	−10.34	−7.28		
	B	lp	−7.17	−1.62	−1.83	24	28

a) kcal·mol^{-1}. b) E_{vdw}. c) $E_{vdw}+E_{strain}$. d) Not stabilized. e) Largely positive.

can form a dodecahedron unit clathrate. In the case of chlorine molecule, the computer constructed network of twenty water molecules was found to have a structure of distorted dodecahedron, and each pentagons is to some extent constrained to take a puckered form. Further analyses of the results have disclosed that, incomplete constructions of water networks were seen for much larger molecules such as ethane, benzene, bromine, and iodine, and some portion of hydrophobic surfaces of those molecules are left uncovered by water molecules, four to eight more positions being open for water molecules to occupy in the region of the first layer (<1.7 Å). An advantageous clue to a priori prediction of the number of water molecules in the first layer is (a) thermodynamic consideration (*vide infra*) or (b) general modification of the paving method by incorporating the distribution of other possible diagrams than pentagon as well as with an improved concept of the first layer.

Table 3 shows the van der Waals energy and the quantitative effect of the strain energy of the polyhedron (Table 2) on the stabilization of the unit clathrate. It is apparent that the van der Waals stabilization energy decreases moderately and monotonously with the increase of the cavity size. However, since pentakaidecahedron and hexakaidecahedron have much larger strain energies (8.72 and 5.46 kcal·mol^{-1}, respectively) than the two smaller polyhedra (Table 2), the energy of the unit clathrate formation ($E_{vdw}+E_{strain}$) no longer correlates with the cavity size. For example, ethylene is most stabilized on forming the dodecahedron unit clathrate ($E=-5.29$ kcal·mol^{-1}), while the destabilization was greatest ($E=+3.45$ kcal·mol^{-1}) when it forms the pentakaidecahedron unit clathrate. Thus, the different extent of the contribution of E_{vdw} which counteracts E_{strain} resulted in a marked difference of formation energy ($E_{vdw}+E_{strain}$) of four unit clathrates (Table 3).

Remarkable van der Waals stabilizations obtained for cyclopropane ($E_{vdw}=-11.78$ kcal·mol^{-1}) and methyl bromide ($E_{vdw}=-10.98$ kcal·mol^{-1}) in dodecahedron, or isobutane ($E_{vdw}=-15.92$ kcal·mol^{-1}) and I_2 ($E_{vdw}=-15.01$ kcal·mol^{-1}) in tetrakaidecahedron, are most easily rationalized as a result of ideal fit of these molecules with the corresponding cavity size. Experimental values of ΔH for gases sorbed within preconstructed dodecahedral cavity are reported for only a few inert gases: Ar, $\Delta H=-6.1$ kcal·mol^{-1}; Kr, $\Delta H=-6.7$ kcal·mol^{-1}.[12] Therefore, the calculated values of E_{vdw}(−4.82 and −6.93 kcal·mol^{-1} for Ar and Kr, respectively) account for the most portion of the reported enthalpy changes. It is apparent from the results of Table 3 that the large portion of the net stabilization of the water clathrates originates in the large van der Waals stabilization, and the numbers of water molecules observed have been well reproduced by the present semi-empirical calculation. It has been approved, therefore, that many hydrates are stabler than ice I, those melting points being even higher than 0 °C.[1] In cases of small gas molecules (He, Ne, and H_2), however, the van der Waals attractive energy was too small to compensate the large strain energy of the unit clathrate (1.1 to 8.7 kcal·mol^{-1}). Thus the crucial magnitude of the strain energy resulted in no (or little) net stabilization of unit water clathrates of these molecules (Table 3). This result may explain why no X-ray study is thus far reported on these molecules.

In eight water clathrates (Ar, Kr, CH_4, C_2H_6, CH_2=CH_2, CH≡CH, CH_3F, and CH_3Cl), the present calculation gave the number of 20, *i.e.*, the dodecahedral unit brings more stabilization with these molecules than the tetrakaidecahedron does. Despite the above, two experimental numbers, 20 and 24, are known for those water clathrates[5] (structure I). It is most likely that the ensemble of the unit clathrate of dodecahedron alone hardly stabilizes the gross ice lattice. The enthalpy changes for the formation of structure I and structure II are reported by Child as 180 and 200 cal·mol^{-1}, respectively.[13a] This fact strongly indicates that even these actual clathrates have additional lattice energy, since the calculated energy (Table 2) predicts *ca.* one half of the observed value, *viz.*, 91 cal·mol^{-1} for 1 : 3 hybrid of dodecahedron and tetrakaidecahedron (structure I) and 110 cal·mol^{-1} for 12 : 8 hybrid of dodecahedron and hexakaidecahedron (structure II). This strongly indicates that, for the theoretical treat-

Table 4. Rotational entropy of guest molecules included by the cavity of each unit clathrate[a,b]

Guest	Dodecahedron	Tetrakaidecahedron	Pentakaidecahedron	Hexakaidecahedron
Br_2	0.0 (0)	0.0 (0)	16.03 (2)	16.03 (2)
I_2		0.0 (0)	0.0 (0)	17.57 (2)
C_3H_8		7.41 (1)	7.41 (1)	21.05 (3)
$HC(CH_3)_3$		0.0 (0)	8.68 (1)	22.12 (3)
$C(CH_3)_4$			0.0 (0)	20.52 (3)
$HC{\equiv}CH$	0.0 (0)	10.69 (2)	10.69 (2)	10.69 (2)
$CH_3C{\equiv}CH$		3.53 (1)	3.53 (1)	18.43 (3)
$(CH_3)_2C{=}CH_2$		0.0 (0)	0.0 (0)	22.68 (3)
CH_3Cl	3.52 (1)	3.52 (1)	17.56 (3)	17.56 (3)
CH_3Br	3.52 (1)	3.52 (1)	3.52 (1)	18.21 (3)
Benzene		0.0 (0)	0.0 (0)	20.47 (3)
CS_2		0.0 (0)	0.0 (0)	15.44 (2)

a) cal·mol^{-1}·deg^{-1}, 0°. b) Allowed mode of rotational freedom is given in the parenthesis.

ment of the lattice formation from unit clathrates, a semiempirical approach should be introduced to the mechanism of the strain relief over the gross crystalline lattice.

In addition, an exclusively new insight was given by the present calculations into the motional freedom of apolar molecules sorbed in water clathrates. In cases of relatively large molecules such as benzene, CS_2, and isobutane, a general trend is to be noted that the calculated number, 24, for those molecules (Table 3) is always smaller than the experimental value of 28. It is easily rationalized that in larger unit clathrates those molecules are endowed with much freedoms of restricted motions.[14] In Table 4 are listed the calculated entropies together with the rotational freedoms allowed for selected molecules. In Table 5 are given the numbers of water molecules predicted in the first layer of the water clathrate. As typically shown for propane, benzene, or CS_2, the rotational entropy drastically increases by the change of unit clathrate from pentakaidecahedron to hexakaidecahedron. As the result, the formation of hexakaidecahedral unit clathrate becomes more favorable, since the calculated ΔG value is large in the negative sign compared with those of other polyhedra (Table 5). In the case of benzene, the correct number of 28 was obtained. The results of Table 5 clearly indicate that the present calculation gives satisfactory number of water molecules in the first layer of unit clathrate, after the correction from rotational entropy term (see Table 5) is made. It is concluded, therefore, that the free energy minimization of unit clathrate can be used as the criterion for the formation of crystalline water clathrate.

The extraordinarily large strain energy of pentakaidecahedron (Table 2) rationalizes a fact that this unit structure is rare in the gas hydrates,[15] despite its appropriate cavity size for the accommodation of a relatively large guest molecule, or those large values of E_{vdw} in negative sign (Table 2) that is the intrinsically favorable factor for the formations of water clathrates.

In conclusion, it has been shown that the van der Waals interaction, the strain energy of the hydrogen-

Table 5. The free energy change (ΔG) for the formation of unit water clathrate and the calculated number of water molecules in the first layer of crystalline water clathrate

Guest	ΔG[a]				Number of water molecules	
	20	24	26	28	Calcd[b]	Found[5]
Ar	−3.76	−1.57	+4.32	+2.16	20 (24)	20, 24
Kr	−5.87	−3.07	+2.80	+1.00	20 (24)	20, 24
Cl_2	−11.93	−8.93	−2.38	−3.26	20 (24)	20, 24
CH_4	−7.16	−4.40	+1.94	+0.14	20 (24)	20, 24
C_2H_6	−13.26	−9.04	−2.50	−3.30	20 (24)	20, 24
$CH_2{=}CH_2$	−9.55	−7.03	−0.82	−3.10	20 (24)	20, 24
CH_3F	−9.62	−6.97	−0.66	−2.33	20 (24)	20, 24
CCl_4	lp	lp	lp	−14.44	28	28
	−13.60	−10.01	−3.56	−4.38	20	24
Br_2	−8.00	−8.91	−6.96	−6.82	24 (20)	26
I_2		−12.50	−8.80	−12.46	24, 28	
C_3H_8		−11.10	−4.82	−9.75	24 (28)	28
$HC(CH_3)_3$		−13.42	−8.40	−12.72	24 (28)	28
$C(CH_3)_4$			−7.81	−14.27	28	
$HC{\equiv}CH$	−3.90	−4.45	+1.93	−0.12	24 (20)	20, 24
$CH_3C{\equiv}CH$		−6.10	−0.12	−5.27	24 (28)	
$(CH_3)_2C{=}CH_2$		−9.71	−2.80	−10.57	28 (24)	
CH_3Cl	−9.60	−6.14	−3.90	−4.97	20	20, 24
CH_3Br	−10.89	−7.99	−1.53	−6.39	20	24
Benzene		−7.43	+1.96	−9.78	28	28
CS_2		−7.12	−1.62	−6.03	24 (28)	28

a) kcal·mol^{-1}. b) In parentheses are shown the number of water molecules of the penultimate unit clathrate which is the second most stable and less stable only within 2 kcal·mol^{-1} than the most stable unit clathrate.

bonded networks of water molecules, and the rotational freedom of the bound guest are the most important term which govern the formation of the water clathrates with hydrophobic molecules. The present study successfully provides the semiempirical basis for *a priori* computation of the number of water molecules in the first layer of the crystalline water clathrate and the present method may be fruitful enough to be extended to the significant problems of water clusters in solutions.

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7) We have encountered a difficulty that the number of sites possibly occupied by oxygens rapidly increases as the execution proceeds. A simple way of the counting to save the computing time was; two independently assigned positions of new oxygen atoms were compared after every loop of computer mapping, and if a site is judged to be doubly occupied within an error of 0.1 Å, then the computer program excludes one and reassigns a new serial number for all oxygens.

8) a) The pentagon method (Eqs. 4—6) employs preferential release of the strain energy (bond length and bond angle strain varying from 1.1 to 8.7 kcal·mol^{-1}) of an unit clathrate since van der Waals stabilization decreases only gradually with the increase of the distance of water molecule from the apolar guest. It, therefore, lightens restriction on the number of water molecules, leading to incorporation of sufficiently remote water molecules. The maximum limit allowed for the remote molecules is given by the elimination of the second layer water molecules from the present counting (Fig. 2). b) We deal with many different guest molecules which are in the gaseous state or in the liquid state at 0 °C, 1 atm. Therefore, it was necessary to constitute crystalline water clathrate from appropriate number of water molecules and a guest molecule, both in the same appropriate standard state, to allow comparison of the different ways that water molecules from the networks around apolar guest molecules of different shape and different size. Thus, for the present thermodynamic calculation, the clathrate was constituted from ice I and a guest molecule whose motional freedoms are freezed in a hypothetical isolated state.

9) a) At $r=\infty$, where r is the interatomic distance between the water molecule and the guest molecule, E_{vdw} equals zero. Therefore, the E_{vdw} value which was calculated by using Eq. 8 equals the van der Waals stabilization, ΔE_{vdw}. b) The "strain" energy of the unit clathrate, ΔE_{strain}, is given by $\Delta E_R+\Delta E_\theta+\Delta E_\alpha$ and designates the energy to form the unit clathrate from ice I whose "strain" energy is zero. c) Configuration change of a unit cell should be reflected in that of neighbors but as the first order approximation these trans-

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10) a) Parameter ε is a geometrical mean of values for each of the two interacting atoms.

	H	C_{sp^3}	C_{sp^2}	C_{sp}	N
kcal·mol^{-1}	0.042	0.107	0.020	0.020	0.095
Ref	9d	10e	10b	10b	10b
	O	F	Cl	Br	I
kcal·mol^{-1}	0.116	0.109	0.314	0.434	0.623
Ref	10c	10b	10b	10b	10b
	S	He	Ne	Ar	Kr
kcal·mol^{-1}	0.314	0.017	0.07	0.235	0.326
Ref	10b	9d	9d	9d	9d

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