

- Porte, *J. Chem. Soc. (A)*, 545 (1969).
7. See, for example, J.A. Weil, *J. Magn. Resonance*, **18**, 113(1975).
 8. L. Stefaniak, *Org. Magn. Reson.* **12**, 379 (1979).
 9. S.C. Kokkou and V. Schramm, *Acta Cryst.*, **C41**, 1040 (1985).
 10. S.R. Fletcher and A.C. Skapski, *J. Chem. Soc. Dalton*, 635 (1972).
 11. F.A. Cotton, R. Francis, and W.D. Horrocks, *J. Phys. Chem.*, **64**, 1534 (1960).
 12. The organic product from the reaction of S-2-pyridyl benzothioate and cupric nitrate trihydrate was identified as benzoic acid by its NMR spectrum and melting point.
 13. T.H. Fifie and T.J. Przystas, *J. Am. Chem. Soc.*, **107**, 1041 (1985).
 14. L.M. Sayre, *J. Am. Chem. Soc.*, **108**, 1632 (1986).
 15. Reference 4. The color change accompanying reduction of the cupric ion is also observed in acetonitrile.
 16. At 80° more than two moles of a thioate are esterified in the presence of one mole of cupric halide. See reference 1.
 17. R.D. Willett and R.E. Rundle, *J. Chem. Phys.*, **40**, 838 (1964).

Theoretical Study on the Role of Water in Anesthesia

Seung Do Hong and Mu Shik Jhon*

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131. Received July 19, 1986

There are lipid phase theories and aqueous phase theories among the theories of anesthesia. For water clusters induced by anesthetizing molecules, the interaction energies are calculated using an empirical potential function and correlated with the anesthetizing partial pressures for mice. A good agreement was obtained with the theory that the water clusters around anesthetics play an important role on the anesthetic actions.

Introduction

General anesthetics don't possess any common physical or chemical feature. Thus, it is thought that only the simplest intermolecular interactions are involved in anesthetic actions.

The mechanism of general anesthesia is not known fully yet. Among the physico-chemical theories of anesthesia, there are lipid phase theories¹⁻⁴ and aqueous phase theories.^{5,6} Lipid phase theories showed good correlations between anesthetic potencies and physical properties as solubility of anesthetics at lipid phase, and suggested that anesthetics act in the lipid region of nerve membrane.

On the other hand, aqueous phase theories were proposed independently by Pauling⁵ and Miller.⁶ The Pauling theory⁵ is that the hydrate microcrystals of anesthetics involving the protein side chains and other charged groups would be formed and interfere with the central nervous system. While Miller⁶ proposed that the hydrate microcrystals would not be formed in the body, but the anesthetics would induce the ordering referred to as icebergs in the neighboring water molecules. Pauling⁵ pointed out that approximately the same correlation would be found between the anesthetizing partial pressure of non-hydrogen-bonding anesthetic agents and any property involving an intermolecular interaction energy, but water containing ions and proteins with charged side chains is expected to be largely involved in the consciousness actions. Claussen *et al.*⁷ suggested that the water structures which constitute the icebergs would be the same water structures surrounding the voids in the hydrates. Therefore it is thought that anesthetizing molecules are enclosed by the hydrate-like structures in the aqueous phase in the body.

In this work, the interaction energies were evaluated for the systems composed of several anesthetizing molecules and

the surrounding water framework using an empirical potential function.⁸ The resulting interaction energies were correlated with the anesthetizing pressures of the anesthetics.

Model System

Small molecules such as xenon(Xe), krypton(Kr), argon(Ar), helium(He), hydrogen(H₂), nitrous oxide(N₂O), and carbon tetrafluoride (CF₄) are surrounded by the water framework composed of 20 water molecules having the structure of pentagonal dodecahedron. Slightly larger molecules such as chloroform (CHCl₃), dichlorodifluoromethane(CCl₂F₂), and cyclopropane (c-C₃H₆) are surrounded by the water framework composed of 28 water molecules having the structure of hexakaidecahedron. The water frameworks enclosing no anesthetizing molecule are referred to as the reference water frameworks.

X-ray crystallographic results for gas hydrates^{9,10} were used as the initial geometry of water frameworks for energy calculations. The center of each anesthetizing molecule¹¹ is taken as the center of the water framework enclosing the anesthetic molecule. The geometry of water molecule is taken from the experimental values,¹² *i.e.*, r(O-H)=0.9572 Å and <HOH = 104.52°.

Potential Function⁸

The total interaction energy consists of electrostatic, non-bonded, hydrogen-bonding, and polarization energies.

$$E_{tot} = \sum_{i,j \neq hb} (E_{el} + E_{nb}) + \sum_{i,j \neq hb} E_{hb} + \sum_{i,j} E_{pol} \quad (1)$$

Where the first summation is the interaction energy for atoms

except hydrogen-bonding pairs and the second summation is that for hydrogen-bonding pairs.

The electrostatic energy is given by

$$E_{el} = q_i q_j / \epsilon r_{ij} \quad (2)$$

where q_i and q_j are the atomic net charges of atoms i and j , r_{ij} is the distance between atoms i and j , and ϵ is the dielectric constant and is taken to be unity in this work.

The polarization energy is given by

$$E_{pol} = -\frac{1}{2} \sum_i \bar{\alpha}_i E_i^2 \quad (3)$$

where $\bar{\alpha}$ is the atomic static polarizability and E is the electric field due to the interacting molecules.

The nonbonded energy is given by

$$E_{nb} = -K_6(i, j) / z_{ij}^6 (1 - 0.5/z_{ij}^6) \quad (4)$$

where $K_6(i, j) = C_6(i, j) / (r_{ij}^w)^6$

and $z_{ij} = r_{ij} / r_{ij}^w$

Here, $C_6(i, j)$ is the dispersion coefficient and r_{ij}^w is the sum of the van der Waals radii of atoms i and j . The dispersion coefficient is given in the form of London formula.

$$C_6(i, j) = \frac{3}{2} \frac{\bar{\alpha}_i \bar{\alpha}_j I_i I_j}{I_i + I_j} \quad (5)$$

where I_i is the ionization potential of atom i .

The hydrogen-bonding energy is given by

$$E_{hb} = E_{hb}^0(r) \cdot A(\phi) \quad (6)$$

where $E_{hb}^0(r)$ is the hydrogen-bonding energy for the linear OH...O system and $A(\phi)$ is the attenuating factor given by a bent angle.

The atomic net charges and the potential parameters are listed in Tables 1 and 2, respectively.

Energy Calculation

When an anesthetizing molecule is located in the void of the reference water framework, the total interaction energy of the anesthetizing molecule, ΔE_{tot} , is composed of the interaction energy between the anesthetizing molecule and surround-

Table 1. The Atomic net Charges of Each Species

Species	Atomic net charges ^a
H ₂ O ^b	0.326(H), -0.652(O)
N ₂ N ₂ O ^c	-0.101(N ₁), 0.326(N ₂), -0.224(O)
CHCl ₃ ^d	0.056(C), 0.131(H), -0.063(Cl)
CF ₄ ^d	0.684(C), -0.171(F)
CCl ₂ F ₂ ^d	0.426(C), 0.087(Cl), -0.126(F)
c-C ₃ H ₆ ^d	-0.075(C), 0.038(H)

^aUnits in electron. ^bFrom ref 8. ^cJ. Mullay, *J. Am. Chem. Soc.*, **108**, 1770(1986). ^dCalculated from parameters of G. Del Re, *J. Chem. Soc.*, 4031(1958).

Table 2. The Potential Parameters for Each Atom

Atom	$\bar{\alpha}(\text{\AA}^3)$	I(eV)	$r^w(\text{\AA})$
H	0.386 ^a	13.61 ^a	1.20 ^b
O	0.54 ^a	17.76 ^a	1.50 ^b
C	1.064 ^a	14.57 ^a	1.70 ^b
N	1.090 ^a	12.25 ^a	1.55 ^b
Xe	4.01 ^c	12.13 ^c	2.239 ^d
Kr	2.48 ^c	14.00 ^c	2.019 ^d
Ar	1.63 ^c	15.76 ^c	1.918 ^d
He	0.21 ^c	24.56 ^c	1.60 ^d
F	0.38 ^c	17.82 ^e	1.50 ^b
Cl	2.28 ^c	11.42 ^e	1.77 ^b

^aY.K. Kang and M.S. Jhon, *Theoret. Chim. Acta*, **61**, 41(1982). ^bA. Bondi, *J. Phys. Chem.*, **68**, 441(1964). ^cK.S. Pitzer, *Advan. Chem. Phys.*, **2**, 71(1959). ^dR.H. Stokes, *J. Am. Chem. Soc.*, **86**, 979(1964). ^eJ.A.A. Ketelaar, "Chemical Constitution," 2nd Ed., p. 91, Elsevier, New York, 1958. ^fC.E. Melton and H.W. Joy, *J. Chem. Phys.*, **42**, 2982(1965). ^gK. Watanabe, *J. Chem. Phys.*, **26**, 542(1957).

ing water framework, E_{aw} , the water-water interaction energy of the model system, E_{ww} , and the water-water interaction energy of the reference water framework enclosing no anesthetizing molecule, E_{ww}^0 .

$$\Delta E_{tot} = E_{aw} + E_{ww} - E_{ww}^0 \quad (7)$$

For the model system and the reference water framework, energy minimizations were carried out using Quasi-Newton method developed by Fletcher¹³ with a convergence criterion of 0.005kcal/mol.

Results and Discussion

The interaction energies of model systems and reference water frameworks are listed in Table 3, where H₂O(20) and H₂O(28) denote the reference water frameworks composed of 20 and 28 water molecules, respectively. The optimized structures of water frameworks enclosing anesthetics were almost the same regardless of anesthetics. The optimized structure for the system composed of xenon and water framework is shown in Figure 1 and such cluster is referred to as anesthetizing cluster.

According to Miller,⁶ the following relation was obtained:

$$P_A = \frac{X_A}{X_w} \frac{RT}{V_f} \exp(\Delta G_f / RT) \quad (8)$$

where P_A is the equilibrium partial pressure of anesthetizing gas, X_A/X_w the ratio of water forming anesthetizing clusters to liquid water, V_f the free volume per mole, and ΔG_f the free energy to form a mole of anesthetizing cluster from liquid water and anesthetizing gas. Assuming that anesthesia occurs at a constant value of X_A/X_w , the following relation is obtained from Eq. (8):

$$\ln P_{anes} = \Delta G_f / RT + C \quad (9)$$

where P_{anes} is the anesthetizing partial pressure of each

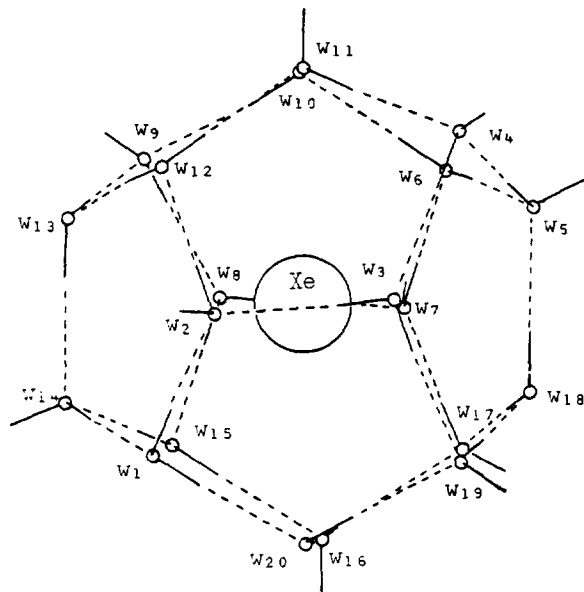


Figure 1. The optimized structure for the system composed of xenon and water framework. The dashed lines represent the hydrogen-bondings.

Table 3. The Interaction Energies of Anesthetics and Water Molecules (kcal/mol)

Species	$-E_{ww}^0$	$-E_{ww}$	$-E_{sw}$	$-\Delta E_{tot}$	ΔH^a
H ₂ O(20) ^b	108.14				
Xe		107.68	4.83	4.37	4.49 ^c
Kr		107.71	3.53	3.10	3.55 ^c
Ar		107.80	2.48	2.14	2.73 ^c
He		107.81	0.37	0.04	0.84 ^c
H ₂		107.76	1.31	0.93	1.28 ^c
N ₂ O		107.63	4.60	4.09	4.84 ^c
CF ₄		107.72	2.83	2.41	
H ₂ O(28) ^b	147.30				
CHCl ₃		146.56	8.58	7.84	9.80 ^c
c-C ₃ H ₆		146.68	6.51	5.89	
CCl ₂ F ₂		146.80	5.86	5.36	

^a ΔH represent the heat of vaporization of anesthetizing gases from aqueous solution. ^bH₂O(20) and H₂O(28) represent the reference water frameworks composed of 20 and 28 water molecules, respectively.

^cData taken from ref 14.

anesthetic and C is a constant which is the function of temperature.

The total interaction energy of anesthetizing molecule corresponds to the minus of the heat of vaporization in the model system or the heat of formation of anesthetic cluster from liquid water and anesthetizing gas, but somewhat deviates from the heat of vaporization of anesthetizing gases in aqueous solution as given in Table 3, because all parts of dissolved gases in aqueous solution would not form anesthetic cluster. The heat of formation of anesthetic cluster from liquid water and anesthetizing gas, ΔE_f , is composed of the total interaction energy of anesthetizing molecule, ΔE_{tot} , and the heat of formation of reference water framework from liquid water,

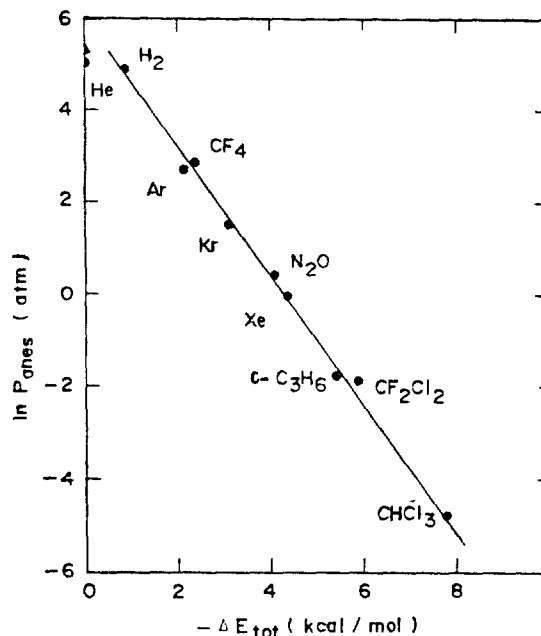


Figure 2. The logarithm of anesthetizing partial pressures for mice are plotted against the total interaction energies of anesthetics.

ΔE_f .

$$\Delta E_f = \Delta E_{tot} + \Delta E_r \quad (10)$$

According to Frank and Evans,¹⁴ the entropy of vaporization of anesthetic gases in the water is proportional to the heat of vaporization. The entropy of formation of anesthetic cluster from liquid water and anesthetizing gas would be proportional to the heat of formation of anesthetic cluster, too. Therefore, the free energy to form a mole of anesthetic cluster, ΔG_f , would be proportional to the heat of formation of anesthetic cluster, ΔE_f . Also, ΔG_f would be proportional to ΔE_{tot} because ΔE_r is a constant in Eq. (10). A similar relation that the hydration energy of metal ions in aqueous solution is proportional to the free energy was shown by Moon and Jhon.¹⁵ Accordingly, Eq. (9) is also written as

$$\ln P_{anes} \propto \Delta E_{tot} \quad (11)$$

In Figure 2, the logarithm of anesthetizing partial pressures for mice¹⁶ are plotted against the total interaction energies of anesthetics. The correlation shown in Figure 2 agrees well with Eq. (11), and supports the assumption that the formations of the same amount of anesthetic clusters play an important role on the anesthetic actions.

At the high pressure, the anesthetic clusters with large volume would be destroyed and the cavity between the anesthetics and surrounding water framework would be filled with bulk water molecules, reducing the volume of the system. As a consequence, the high pressure reversal of anesthesia^{17,18} would occur.

As pointed out by Catchpool *et al.*,¹⁹ the fact that decreasing the temperature makes the anesthetics more potent is in accord with the assumption that anesthesia occurs in the aqueous phase, but contrary to the lipid phase theories. The increased solubility²⁰ and the increased entropy of vaporization¹⁴ of anesthetizing gases in aqueous solution ac-

cording to the temperature decrease support the aqueous phase theory of anesthesia. Also the fact that the presence of a fully active acidic hydrogen in anesthetizing molecule increases anesthetic potency²¹ supports the aqueous phase theory.

Acknowledgement. This work was supported in part by the Korea Research Center for Theoretical Physics and Chemistry and the Korea Science and Engineering Foundation.

References

1. K.H. Meyer, *Trans. Faraday Soc.*, **33**, 1062(1937).
2. L.J. Mullins, *Chem. Rev.*, **54**, 289(1954).
3. (a) K.W. Miller, W.D.M. Paton, and E.B. Smith, *Nature*, **206**, 574(1965); (b) K.W. Miller, W.D.M. Paton, and E.B. Smith, *Anesthesiology*, **36**, 339(1972).
4. H. Eyring, J.W. Woodbury, J.S. D'Arrigo, *Anesthesiology*, **38**, 415(1973).
5. L. Pauling, *Science*, **134**, 15(1961).
6. S.L. Miller, *Proc. Nat. Acad. Sci.*, **47**, 1515(1961).
7. W.F. Clausen and M.F. Polglase, *J. Am. Chem. Soc.*, **74**, 4817(1952).
8. Y.K. Kang and M.S. Jhon, *Bull. Korean Chem. Soc.*, **2**, 8(1981).
9. J.H. van der Waals and J.C. Platteuw, *Advan. Chem. Phys.*, **2**, 1(1959).
10. G.A. Jeffrey and R.K. McMullan, *Progress in Inorganic Chemistry*, **8**, 43(1967).
11. The geometry of each anesthetizing molecule is taken from "Tables of interatomic distances and configuration in molecules and ions," ed. by L.E. Sutton, Special Publication No. 11, Burlington House, London, 1958.
12. D. Eisenberg and W. Kauzmann, "The Structure and Properties of Water," p. 4, Clarendon, Oxford, 1969.
13. R. Fletcher, "Fortran Subroutines for Minimization by Quasi-Newton Methods," A.E.R.E. Report R7125 (1972).
14. H.S. Frank and M.W. Evans, *J. Chem. Phys.*, **13**, 507(1945).
15. M.J. Moon and M.S. Jhon, *Bull. Chem. Soc. Jpn.*, **59**, 1215(1986).
16. R.D. Kaufman, *Anesthesiology*, **46**, 49(1977).
17. P.M. Winter, R.A. Smith, M. Smith, and E.I. Eger, *Anesthesiology*, **44**, 416(1976).
18. M.J. Lever, K.W. Miller, and W.D.M. Paton, *Nature*, **231**, 368(1971).
19. A. Cherkin and J.F. Catchpool, *Science*, **144**, 1460(1964).
20. (a) J.H. Hildebrand and R.C. Scott, "The Solubility of Nonelectrolytes," 3rd Ed., pp. 251-252, Reinhold, New York, 1950; (b) W. Gerrard, "Solubility of Gases and Liquids," pp. 231-234, Plenum, New York and London, 1976.
21. A. Spinks, *Chemistry and Industry*, **18**, 475(1977).

Geometries and Energies of S_N2 Transition States[†]

Ikchoon Lee,* Chan Kyung Kim, and Chang Hyun Song

Department of Chemistry, Inha University, Incheon 160. Received August 1, 1986

MNDO calculations were carried out to determine reactant complexes and transition states of the S_N2 reactions of $CH_3X + Y^- \rightarrow CH_3Y + X^-$ where $X = F, Cl, CN$ and $Y = CN, OH, F, Cl$. The leaving group ability was found to vary inversely with the activation barrier, which in turn was mainly ascribable to the deformation energies accompanied with bond stretching of C-X bond and inversion of CH_3 group. The nucleophilicity was shown to be in the order $Cl^- > F^- > OH^- > CN^-$ but the effect on the activation barrier was relatively small compared with that of the leaving group. The bond breaking and bond formation indices and energy decomposition analysis showed that the TS for the reaction of CH_3Cl occurs in the early stage of the reaction coordinate relative to that of CH_3F . It has been shown that the potential energy surface (PES) diagrams approach can only accommodate thermodynamic effects but fails to correlate intrinsic kinetic effects on the TS structure.

Introduction

Experimental studies of gas-phase S_N2 reactions have been suggested that the potential energy profile will have the double-well form shown in Figure 1; two minima correspond to reactant (RC) and product complexes (PC), while the central barrier is the highest energy point on the minimum energy reaction path from RC to PC and can be identified as the classical S_N2 transition state (TS). The activation barrier is therefore given by the energy difference between the TS and RC, which can be estimated¹ from the intrinsic barriers for

the identity reaction using Marcus equation.²

As S_N2 reaction, $Y^- + CH_3X \rightarrow YCH_3 + X^-$ proceeds via the concerted bond-breaking and bond-formation with a concomitant inversion of the reaction center carbon. Thus at the TS a number of changes in molecular geometry occur; the C-X bond stretches, the C-Y bond shortens and the H-C-H angles deform. These distortions in geometry are accompanied by changes in the total energy of the system. Mitchel *et al.*³, has shown that in the identity S_N2 reaction, the distortion energies are dominated by the C-X stretching deformations which are linearly correlated with the intrinsic barriers.

In the work, we investigated the relationships between geometries and energies of the S_N2 (non-identity) reactions,

[†] Determination of Reactivity by MO Theory (Part 47).