CALCULATIONS OF HENRY CONSTANTS
AND PARTITION COEFFICIENTS*

R.Zahradník[a], P.Hobza[b] and Z.Slanina[a]

[a] *J. Heyrovský Institute of Physical Chemistry and Electrochemistry,*
Czechoslovak Academy of Sciences, 121 38 Prague 2, and
[b] *Institute of Hygiene and Epidemiology,*
Center of Industrial Hygiene and Occupational Diseases, 100 42 Prague 10

Theoretical problems connected with calculations of the Henry and Nernst constants are outlined. A dissolution of an inert gas in a solvent is treated in terms of enthalpy and entropy changes which can be expressed in terms of two contributions: the cavity formation process, and the interaction between a solute molecule (introduced into the cavity) and the surrounding solvent molecules. Calculation of ΔH for the solute–solvent pair interaction is based on empirical estimates of Coulomb, polarization, dispersion, and repulsion terms. A simple statistical-thermodynamic treatment has been used for estimates of ΔS of interaction. The computational scheme has been used for systems of CH_4 in CCl_4, CH_4 in H_2O, and for partitioning of CH_4 between CCl_4 and H_2O.

The importance of the Nernst partition coefficients in some separation processes[1] and in partition chromatography[2] is well known. Moreover, for nearly eighty years it has been known that these coefficients have played an important role for quantitative evaluation of narcotic effects[3,4]. Work during the past $10-15$ years has provided strong evidence that partition coefficients[5,6] and Henry constants do play a fundamental role in quantitative correlations between the magnitude of biological activity and structural characteristics.

As early as 1939 Eley[7,8] published the first study on calculations of solubility of inert gases in water (Henry constants) and on the comparison of organic solvents with water. Pierotti described a method which permits to calculate thermodynamic characteristics of dissolution of simple molecules in nonpolar[9] and polar solvents[10]. No attempt has yet been made on the same level of sophistication to calculate partition coefficients. However, Cammarata and coworkers[6,11,12] have used a simplified perturbation treatment[13,14] for the estimation of enthalpy changes of the partitioning processes. Their final expression for calculating the logarithms of partition coefficients between oil and water includes electron densities, and superdelocalizabilities of positions in the system under study.

The most serious objection to this approach is the assumption that the entropy term is constant which is most definitely not the case. Seemingly, one can pass to a less rigorous requirement using the linear relationship between enthalpy and entropy changes:

$$\Delta H = m\Delta S + n \,, \qquad (1)$$

---

where m and n stand for empirical constants. It is well known that Eq. (1) is nearly generally fulfilled[15,16]. There is strong evidence, however, that in our particular case Eq. (1) is not satisfied. Evans and Polanyi[17] have found that Eq. (1) holds for polyatomic compounds (possessing at least 4 or 5 atoms) only in case of a given compound with a series of solvents but not in the opposite case. *i.e.* a given pair of solvents with a series of compounds. On the one hand, the results obtained by Cammarata and coworkers[6] suggest that this circumstance is not too serious at least not for rough estimates. On the other hand, however, it is sufficient incentive to incite work on calculations of the entropy changes.

It is well known that in case of partitioning of a nonpolar substance between a polar and nonpolar phase the equilibrium is shifted in favor of the nonpolar phase. It is so in spite of the fact that very frequently (perhaps always) the passage from a nonpolar to a polar phase is connected with a negative change[18] of ΔH. Clearly, in all these cases when equilibrium is reached, the nonpolar substance is preferentially dissolved in the nonpolar phase and therefore ΔG is positive. The partitioning process must be accompanied by a relatively high and negative entropy change. This is qualitatively understandable: the solute is distributed in the polar phase[18] more regularly than in the nonpolar phase. Let us add that a similar entropy changes is connected with a process of dissolution of a gas in a solvent: here the significant entropy decrease is due to the strong reduction of the translational partition function. (A more sophisticated treatment requires also an adequate reduction of the rotational partition function which, however, is usually included in the configurational integral.)

The subject of this work is the investigation of the application of theory of weak intermolecular interactions and of statistical thermodynamics to the calculation of the Henry constants and the Nernst partition coefficients. The aim is to calculate absolute values of these characteristics for the simplest systems with minimal use of experimental data.

CALCULATIONS

Thermodynamic relations. Both processes under study are typical thermodynamic (equilibrium) processes. Schematically we write:

(Henry's law) $$A^{(1)} \rightleftharpoons A^{(g)} \tag{2}$$

(Nernst law) $$A^{(1)} \rightleftharpoons A^{(2)} \tag{3}$$

$$K_{(H)} = \frac{p_A^{(g)}}{c_A^{(l)}} = \frac{Q_A^{(g)}}{Q_A^{(l)}} \, e^{-\Delta H_0^0/RT} \tag{4}$$

$$K_{(N)} = \frac{c_A^{(2)}}{c_A^{(1)}} = \frac{Q_A^{(2)}}{Q_A^{(1)}} \, e^{-\Delta H_0^0/RT} = \frac{K_{(H1)}}{K_{(H2)}} \, . \tag{5}$$

For the thermodynamic equilibrium constants the following relationships are valid:

$$\Delta G^0 = -RT \ln K \, , \tag{6}$$

$$\Delta G^0 = \Delta H^0 - T \Delta S^0 . \tag{7}$$

The symbols in Eqs $(2)-(7)$ have their usual meaning, $Q_A^{(p)}$ stands for the partition function of the system A in the phase p. In order to evaluate absolute values of K the respective values of ΔH^0 and ΔS^0 must be known. Calculations of these changes are based on quantum and statistical mechanics.

Let us deal with the dissolution process which, basically, consists of two steps[7,8]. The first one is the cavity formation connected with the respective enthalpy and entropy changes $(\Delta H_c, \Delta S_c)$. The second step corresponds to the introduction of a molecule into the hole; this introduction is characterized by interaction contributions ΔH_I, and ΔS_I, to the total enthalpy and entropy changes

$$\Delta H^0 = \Delta H_c + \Delta H_I , \tag{8}$$

$$\Delta S^0 = \Delta S_c + \Delta S_I . \tag{9}$$

Before passing to the evaluation of these contributions we need to specify models of polar and nonpolar phases. Water seems to be the most important representative of a polar phase and tetrachloromethane is chosen as a representative of a nonpolar phase which consists of quasisphere molecules. It has been shown[19] that it is pos-
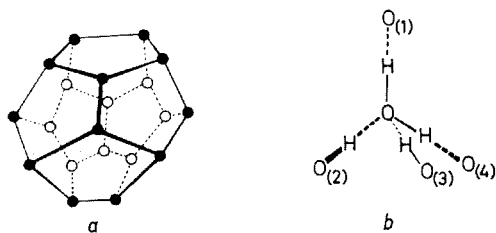

FIG. 1

The Basic Coordination Unit in Water

Regular pentagon dodecaeder ($\bullet$, $\circ$ mean oxygen atoms of water molecules) (a), each bond is associated with a hydrogen atom (b).
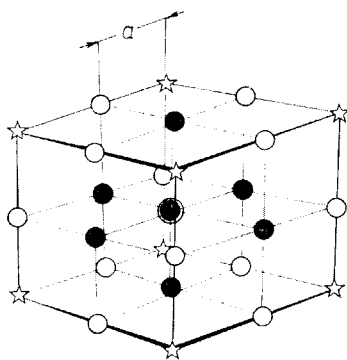
FIG. 2

A Naive Model of a Nonpolar Liquid Phase

Central molecule ($\odot$) is surrounded by ligands in the simple cubic structure. Atoms of first, second, and third shell are indicated by $\bullet$, $\circ$, and $\star$, and their distances from the central molecule are equal to a, $\sqrt{2}a$, and $\sqrt{3}a$.

sible to form cavities in water very easily (with negligible enthalpy and entropy changes) consisting of 20 (regular pentagonal dodecaeder), 24, and 26 molecules of water at about 277 K, each being coordinated by four other water molecules. In Fig. 1 the basic coordination unit is visualized together with a regular pentagonal dodecaeder. There is a strong evidence[19] that atoms (*e.g.* He, Rn) and small molecules (*e.g.* CH_4, C_2H_6, N_2O, PH_3, SO_2, ClO_2, CH_3SH) are accomodated in these dodecaeders. Larger molecules (*e.g.* C_3H_8, $(CH_3)_3CH$, CH_3J, $CHCl_3$) enter holes belonging to tetradecaeders and hexadecaeders, the former having two and the latter four hexagons.

The situation with nonpolar molecules is less clear. Because of lack of data on structure of solid CCl_4 and its solutions we have chosen as the first approximation the simple cubic structure. Clearly enough, choice of another lattice would lead to a somewhat different value of interaction characteristics. In the lattice positions are located sphere-shaped molecules of the solvent (Fig. 2). In this figure the maximum number of ligands and their distances from the central molecule are specified. Obviously, some of the ligands are, depending on the temperature, substituted by holes.

Enthalpy changes. Let us turn our attention to the evaluation of the right-hand terms of Eq. (*8*). A classical thermodynamic treatment[16] leads, in case of ΔH_c, to the following expression:

$$(\Delta H_c)_{T,p} = \frac{\alpha_1}{\beta_1} TV_2 , \qquad (10)$$

where α_1, β_1, and V_2 stand for the coefficient of the isobaric expansion of the solvent, the coefficient of the isothermic compression of the solvent, and the molar volume of the solute.

For the second term in Eq. (*8*) the following expression is valid[16]

$$\Delta H_1 = Nc\, \Phi_{12} - RT \qquad (11)$$

if we limit ourselves to the near-neighbours. Φ_{12} is the pair interaction energy solvent-solute, N is the Avogadro number, and c is the common coordination number of a molecule 1 in the bulk of the molecules 1, and of a molecule 2 in bulk of the molecules 2, and of 1 (solute) in bulk of 2 (solvent).

For the sake of simplicity let us start with dissolution of an inert gas in a solvent. In the majority of cases the forces acting between solute and solvent molecules are weak and, therefore, ΔH is small relative to changes found in chemical reactions. These forces are due to multipole–multipole interactions (*e.g.* dipole–quadrupole), to dipole–induced dipole, and induced dipole–induced dipole interactions (polarization and dispersion interactions). Dispersion energy forms a part of the correlation energy and, therefore, we cannot describe this contribution by means of the Hartree––Fock SCF method. This problem can be solved in principle by allowing for con-

figuration interaction in the total wave-function. Because at least doubly excited configurations must be included, calculations on systems of chemical interest are of prohibitive size. Moreover, any variational type of calculation is connected with an inherent difficulty because what we need is a difference between two large and almost identical values. Therefore, a perturbation treatment is more suitable for this purpose.

Expressions based on the CNDO/2 formalism are available in the literature[20] concerning the Coulomb, polarization, dispersion, charge-transfer, and repulsion terms. This formalism can be used for treatment of small molecules (e.g. methane and water) but at present is hardly applicable for extensive organic molecules. Therefore, an empirical (but theoretically sound) expression seems to be the only realistic possibility. For our purposes a simplified form of the Buckingham[21,22] potential augmented by terms describing the Coulomb and polarization interactions is relevant: the contributions due to the individual atoms of both subsystems are summed up (Eq. (12)).

$$
E^{INT} = -C_1 \sum_i^R \sum_j^T \left(\frac{r_{ij}}{R_i + R_j} \right)^{-6} + C_2 \sum_i^R \sum_j^T \exp\left(-C_3 \frac{r_{ij}}{R_i + R_j} \right) +
$$
$$
+ \sum_i^R \sum_j^T \frac{q_i q_j}{r_{ij}} - \frac{1}{2} \{ \sum_p^R [\alpha_p^T(\xi_p \xi_p) + \delta_p(\xi_p \alpha_p^L)^2] + \sum_q^T [\alpha_q^T(\xi_q \xi_q) + \delta_q(\xi_q \alpha_q^L)^2] \}, \quad (12)
$$

where $C_1, C_2,$ and C_3 are constants, $R_i(R_j)$ are the van der Waals atomic radii, r_{ij} is the distance between the i-th and j-th atoms, q_i is the net charge in position i, $\alpha_p^{T(L)}$ is the transversal (longitudinal) polarizability of the bond p, α_p^L, and r_{jp} are unit vectors, R_{jp} is the distance between the atom j (in system T) and the center of the bond p (in system R), δ_p is the difference between α_p^L and α_p^T. Finally $\xi_p = \sum_j^T (q_j/R_{jp}^3) r_{jp}$. The terms in Eq. (12) correspond to the dispersion, repulsion, Coulombic, and polarization interactions.

Partition functions. It remains now to evaluate the constituents of the total entropy change (Eq. (9)) in terms of statistical thermodynamics; it is connected with more uncertainties than the evaluation of the enthalpy changes. For the sake of simplicity we shall again deal with a simple process of dissolution of an inert gas in a solvent.

The calculation of the ΔS_c part, however, is simple and straightforward. It has been shown[7] that with plausible assumption the following expression holds:

$$
\Delta S_c = \frac{\alpha_1}{\beta_1} V_2, \quad (13)
$$

where the symbols have the same meaning as in Eq. (10).

The ΔS_I term is given as a difference between entropy of gas in cavities and entropy of the gas in the gas phase[7]. A derivation of the corresponding expression[7,8] in terms of partition functions is rather involved and exceeds the scope of this contribution. Therefore, only a general comment will be made and final formulas will be presented.

The total partition function for a molecule in the gas phase is usually given as a product of translational, vibrational, and rotational functions. Its evaluation is straightforward, which is not the case with solutions. The main complications are as follows. The potential under which dissolved molecules move must be considered. This manifests itself in the configurational integral which forms a part of the translational partition function. The influence of the external field is also certainly not negligible with rotational functions. In the first approximation, however, the same vibrational partition function for the solute in both phases can be used. The total partition function for the solution consists of function for both, the solute, and the solvent.

The following expressions may be used for estimates of the total partition functions[7,8]

$$\text{CH}_4 \text{ in } \text{H}_2\text{O:} \quad Q = \frac{N_c!}{N_2!(N_c - N_2)!} \, \Phi_1^{N_1} \Phi_2^{N_2} , \tag{14}$$

$$\text{CH}_4 \text{ in } \text{CCl}_4: \quad Q = \frac{(N_1 + N_2)!}{N_1! N_2!} \, \Phi_1^{N_1} \Phi_2^{N_2} , \tag{15}$$

where

$$\Phi = \frac{(2\pi m k T)^{3/2}}{h^3} \, V J ,$$

where N_1 and N_2 stand for the number of solvent and solute molecules, N_c is the number of cavities per mol, V is the available volume for the solute molecules, and J is the partition function of the internal movements.

More specifically we can write the following expressions for the interaction terms of the entropy changes:

$$\text{CH}_4 \text{ in } \text{H}_2\text{O:} \quad S_I = R\left[\ln \frac{N_c - N_2}{N_2} + \frac{3}{2} \ln \frac{m_{2-1}}{m_2} + \ln \frac{V_F N}{V} + \right.$$

$$\left. + T \frac{\partial \ln V_F}{\partial T} + T \frac{\partial}{\partial T} \frac{N_c - N_2}{N_2} - 1 \right], \tag{16}$$

$$\text{CH}_4 \text{ in } \text{CCl}_4: \quad S_I = R\left[\ln \frac{N_1 + N_2}{N_2} + \frac{3}{2} \ln \frac{m_{2-1}}{m_2} + \ln \frac{V_F N}{V} + \right.$$

$$\left. + T \frac{\partial \ln V_F}{\partial T} - 1 \right], \tag{17}$$

where N is the Avogadro number, m_2 is the mass of the solute, m_{2-1} is the reduced mass of the system solute-solvent, V_F is the free volume of the gas molecule in solution, and V is the volume of the gas phase under standard conditions $(1\ atm,\ 298\ K)$.
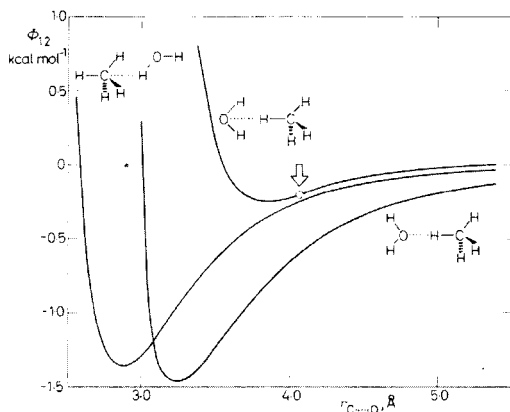

FIG. 3

Potential Energy Curves for the CH_4—H_2O Pair Interaction (Eq. (12)) for Three Mutual Orientations

The $C{\cdots}O$ distance (based on our model considerations) used in further calculation is indicated by an arrow.

FIG. 4

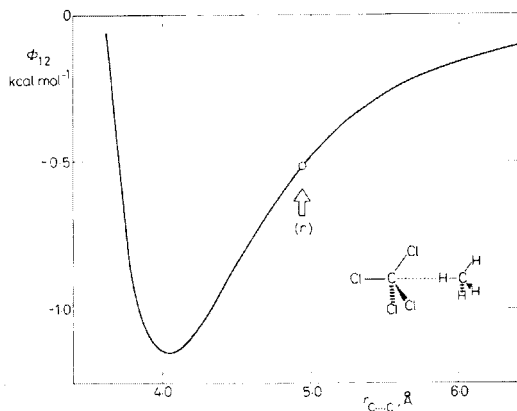Potential Energy Curve for the CH_4—CCl_4 Pair Interaction (Eq. (12))

The $C{\cdots}C$ distance used in further calculations is indicated by an arrow.

EXAMPLES

Let us start with the calculations of the ΔH_c terms which is a very simple task. The resulting values are presented together with the constants of Eq. (*10*) in Table I.

The next step deals with the calculation of the ΔH_I terms and is based on potential energy curves (Fig. 3) and on geometrical considerations: For the experimentally found[26] $O \cdots O$ distance of 2·90 Å in liquid water, the $C \cdots O$ distance between the C atom in methane and the O atoms in twenty molecules of water amounts to 4·06 Å. Accordingly, the respective potential curve of Fig. 3 leads to the pair interaction energy of -0.201 kcal mol^{-1}; by means Eq. (*11*) we obtain easily for ΔH_I -4.612 kcal mol^{-1}. A formally analogous treatment fot the CH_4–CCl_4 system (Fig. 4) leads to values also included in Table I. The $C \cdots C$ distance (between the C atom in CH_4 and the C atom in CCl_4) for the first coordination sphere amounts to 4·94 Å. This distance corresponds to the pair interaction energy of -0.521 kcal mol^{-1} (Fig. 4) and the coordination number c, of the first coordination sphere is equal to 6. For the next coordination sphere c equals 12 and the pair interaction energy amounts to -0.061 kcal mol^{-1}. The interaction between solute and molecules of the third coordination sphere amounts only to -0.017 kcal mol^{-1}.

We performed, moreover, a direct calculation of ΔH_I for a model based on Stackelberg's[19] results on the solvation of methane by water molecules. Twenty water molecules were located at apexes of a regular pentagonal dodecaeder and a methane molecule was placed in the centre. The interaction energy between methane and twenty water molecules was found to be -5.431 kcal mol^{-1} which corresponds to -6.023 kcal mol^{-1} for the ΔH_I value.

TABLE I

Enthalpy of Cavity Formation and Enthalpy of Interaction (298 K)

Process	ΔH_c, kcal mol$^{-1 a}$	ΔH_I, kcal mol^{-1}
CH_4 in CCl_4	4·253	-4.586
CH_4 in H_2O	1·442	-4.612

[a] $10^4 \alpha_1$ (deg^{-1}) amounts to [16,23] 12·2 and 2·57 (CCl_4 and H_2O); $10^6 \beta_1$ (atm^{-1}) amounts to[23] 108 and 45·8 (CCl_4 and H_2O); V_2(cm^3 mol^{-1}) for CH_4 in CCl_4 and for CH_4 in H_2O amounts to[24,25] 52·4 and 35·6, resp.

TABLE II

Entropy of Cavity Formation and Entropy of Interaction (298 K)

Process	ΔS_c (eu)	ΔS_I (eu)
CH_4 in CCl_4	14·27	-19.93
CH_4 in H_2O	4·84	-24.36

TABLE III

Thermodynamic Characteristics of Dissolution and Partition Processes (298 K)

Process	ΔH^0 kcal mol^{-1}		ΔS^0 (eu)		ΔG^0 kcal mol^{-1}		log K	
	obs[27]	calc	obs[27]	calc	obs[27]	calc	obs[27]	calc
(H$_1$): CH$_4$ in CCl$_4$	-0.70	-0.33	-9.4	-5.7	2.09	1.35	1.53	0.99
(H$_2$): CH$_4$ in H$_2$O	-3.18	-3.17	-23.8	-19.5	3.92	2.65	2.88	1.94
(N): CH$_4$(CCl$_4$) $\rightleftarrows$								
$\rightleftarrows$ CH$_4$(H$_2$O)	-2.48	-2.84	-14.5	-13.9	1.83	1.30	1.34	0.95

The entropy changes will be evaluated by means of Eqs (13), (16), and (17). The obtained values of ΔS_c and ΔS_I are presented in Table II.

It is an easy task to calculate the ΔG^0 values, and the corresponding equilibrium constants by using the already obtained ΔH^0 and ΔS^0 changes. The tabulated characteristics concern (a) dissolution of CH$_4$ in CCl$_4$, (b) dissolution of CH$_4$ in H$_2$O, and (c) the partitioning of CH$_4$ between H$_2$O and CCl$_4$ (assuming that the mutual solubility of H$_2$O and CCl$_4$ is negligible) (Table III). In conclusion we can say that the procedure used could lead in near future to results of sufficient accuracy for practical purposes. Moreover, it seems realistic to expect a broad and deep expansion of our knowledge in the field of weak intermolecular interactions and of statistical thermodynamics of solutions during the next decade. Then calculations of the Henry and Nernst constants could be an easy task.

REFERENCES

1. Prausnitz J. M., Chueh P. L.: *Computor Calculations for High-Pressure Vapor–Liquid Equilibria*. Prentice Hall, Englewood Cliffs, N.Y. 1968.
2. Locke D. C.: Advan. Chromatog. *8*, 47 (1969).
3. Overton E.: Z. Phys. Chem. (Leipzig) *22*, 189 (1897).
4. Meyer H.: Arch. Exp. Pathol. Pharmacol. *42*, 109 (1899).
5. Hansch C. in the book: *Drug Design*, Vol. I (E. J. Ariens, Ed.). Academic Press, New York 1971.
6. Cammarata A. in the book: *Molecular Orbital Studies in Chemical Pharmacology* (L. B. Kier, Ed.). Springer, Berlin 1970.
7. Eley D. D.: Trans. Faraday Soc. *35*, 1281 (1939).
8. Eley D. D.: Trans. Faraday Soc. *35*, 1421 (1939).
9. Pierotti R. A.: J. Phys. Chem. *67*, 1840 (1963).
10. Pierotti R. A.: J. Phys. Chem. *69*, 281 (1965).
11. Rogers K. S., Cammarata A.: J. Med. Chem. *12*, 692 (1969).
12. Rogers K. S., Cammarata A.: Biochim. Biophys. Acta *193*, 22 (1969).
13. Klopman G., Hudson R. F.: Theoret. Chim. Acta *8*, 165 (1967).
14. Klopman G.: J. Am. Chem. Soc. *90*, 223 (1968).
15. Leffler J. E.: J. Org. Chem. *20*, 1202 (1955).

16. Moelwyn-Hughes E. A.: *Chemical Statics and Kinetics of Solutions.* Academic Press, London 1971.
17. Evans M. G., Polanyi M.: Trans. Faraday Soc. *32*, 1333 (1936).
18. Kauzmann W.: Advan. Protein Chem. *14*, 37 (1959).
19. v. Stackelberg M., Müller H. R.: Z. Elektrochem. *58*, 25 (1954).
20. Fueno Z., Nagase S., Tatsumi K., Yamaguchi K.: Theoret. Chim. Acta *26*, 43 (1972).
21. Kitaygorodskij A. I.: Tetrahedron *14*, 230 (1961).
22. Eliel E. L., Alinger N. L., Angyal S. J., Morrison G. A.: *Conformational Analysis.* Interscience, New York 1965.
23. Weast R. C.: *Handbook of Chemistry and Physics.* The Chemical Rubber Co., Cleveland 1972.
24. Smith E. B., Walkley J.: J. Phys. Chem. *66*, 597 (1962).
25. Glew D. N.: J. Phys. Chem. *66*, 605 (1962).
26. Wells A. F.: *Structural Inorganic Chemistry.* Clarendon Press, Oxford 1962.
27. Frank H. S., Evans M. W.: J. Chem. Phys. *13*, 507 (1945).

Translated by P. Čársky.