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Application of the transition state theory to water transport across cell membranes

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Abstract

We have applied the transition state theory of Eyring et al. (The Theory of Rate Processes, McGraw-Hill, 1941) to water transport across cell membranes. We have then evaluated free energy ($\Delta F^{\neq}$), enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) of activation for water permeation across membranes, such as *Arbacia* eggs, *Xenopus* oocytes with or without aquaporin water channels, mammalian erythrocytes, aquaporin proteoliposomes, liposomes and collodion membrane. $\Delta H^{\neq}$ was found to be correlated with $\Delta S^{\neq}$. This is so-called $\Delta H^{\neq}$ and $\Delta S^{\neq}$ compensation over the ranges of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ from 2 to 22 kcal/mol and from −26 to 45 e.u., respectively, indicating that low $\Delta H^{\neq}$ values correspond to negative $\Delta S^{\neq}$. Large positive $\Delta S^{\neq}$ and high $\Delta H^{\neq}$ values might be accompanied by reversible breakage of secondary bonds in the membrane, presumably in membrane lipid bilayer. Largely negative $\Delta S^{\neq}$ and low $\Delta H^{\neq}$ values for aquaporin water channels, aquaporin proteoliposomes and porous collodion membrane could be explained by the immobilization of permeating water molecules in the membrane, i.e., the partial loss of rotational and/or translational freedoms of water molecules in water channels.

Keywords: Activation enthalpy; Activation entropy; Enthalpy–entropy compensation; Membrane lipid; Water channel; Water transport

1. Introduction

It has been reported by several authors that water in the vicinity of surfaces and particularly within small volume bounded by surfaces is remarkably different from that in a bulky space (see [1] and references therein). Therefore, it might be of interest to study the kinetic characteristics of water within small volume bounded by surfaces, such as pores in desalination membranes [2], water channels [3–7], and collodion membranes [8–10]. Although applications of the transition state theory, i.e., free energy ($\Delta F^{\neq}$), enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) of activation [11], on osmotic water transport across *Arbacia* egg membrane [12], porous collodion membrane [8–10] or liposomes [13], and on gas permeation through rubber membranes [14] have been reported, few transition state analyses on cell membranes were reported

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more recently. According to the transition state theory of Eyring [11], $\Delta S^{\neq}$ values for permeation across membranes seem to give biophysical and molecular insights into the mechanism of water movements (diffusion or flow in the physiological field) across the membrane [8–10,12]. While there are many reports on classical Arrhenius activation energy ($\Delta E_a = \Delta H^{\neq} + RT$, where $\Delta H^{\neq}$ is enthalpy of activation ([15], pp. 187–285) for the osmotic water transport across the membranes, few studies on $\Delta S^{\neq}$ values have been reported [10,12,13] since 1949. Therefore, we evaluated $\Delta F^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for the osmotic water permeation across cell membranes.

2. Materials and methods

Applications of the transition state theory (kinetic analyses) to water transport across porous collodion membrane and *Arbacia* egg membrane were reported by Laidler et al. [8–10] and Zwolinski et al. [12], respectively, in 1949. Zwolinski et al. [12] derived the following equation for permeability constant (P (cm/s)) of solvent or solute molecules across cell membrane

$$P = (k_{\mathrm{sm}} k_{\mathrm{m}} \lambda)/(2k_{\mathrm{m}} + m k_{\mathrm{ms}}) \tag{1}$$

where k_{sm} and k_{ms} are the rate constants for transfer from the water phase to the membrane phase and vice versa, k_{m} is the rate constant for transfer in the membrane, λ is the average distance between energy minima as a permeating molecule hops from site to site within the membrane and $m\lambda$ is membrane thickness [12]. When the rate-determining step is permeation in the membrane, i.e., $k_{\mathrm{m}} \ll k_{\mathrm{sm}} \ll k_{\mathrm{ms}}$, P is then given by the relation

$$P = (k_{\mathrm{sm}} k_{\mathrm{m}} \lambda)/(m k_{\mathrm{ms}}) = K D_{\mathrm{m}}/\delta \tag{2}$$

where K, the partition coefficient, is $k_{\mathrm{sm}}/k_{\mathrm{ms}}$, δ is the membrane thickness ($m\lambda$) and D_{m} is diffusion constant of a molecule in the membrane ($k_{\mathrm{m}}\lambda^2$). According to the transition state theory of Eyring [11], we may write

$$P = K(\lambda^2/\delta)(kT/h)\exp(-\Delta F^{*}/RT) \tag{3a}$$

$$= (\lambda^2/\delta)(kT/h)\exp(-\Delta F^{\neq}/RT) \tag{3b}$$

where k is Boltzmann's constant, h is Planck's constant, $\Delta F^{\neq}$ is free energy of activation for permeation (Eq. 3b), i.e., $\Delta F^{\neq} = (\Delta E_a - RT) - T\Delta S^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$, where $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are enthalpy and entropy of activation, respectively, and ΔF^{*} is free energy of activation for permeation in the membrane (Eq. 3a). So, $\Delta F^{\neq}$ represents the difference in free energy of a permeating molecule between its initial position in the outside of the membrane, i.e., the outside solution, and the top of the highest potential barrier over which the permeating molecule must pass within the membrane.

Analogous transition state analyses for water and solute transport through porous collodion membrane were extensively studied by Laidler's group [8–10]. When k_{ms} is sufficiently large compared with k_{sm} and k_{m}, i.e., $k_{\mathrm{m}} \ll k_{\mathrm{ms}} \gg k_{\mathrm{sm}}$ (k_{sm}, k_{ms} and k_{m} correspond to k_1, k_{-1} and k_2 in Laidler's reports [8–10], respectively), they derived permeation constant, $Q = k_1/k_{-1} D_{\mathrm{m}} = (k_{\mathrm{sm}}/k_{\mathrm{ms}}) D_{\mathrm{m}} = K D_{\mathrm{m}}$ (cm^2/s), where K is the partition coefficient given in Eqs. 2 and 3a [8–10]. According to Laidler's group [10], Q (cm^2/s) may be written as

$$Q = K D_{\mathrm{m}} = \lambda^2 (kT/h)\exp(-\Delta F^{\neq}/RT) \tag{4}$$

where $\Delta F^{\neq}$ is nearly equivalent to those in Eq. 3b. While an effective thickness of collodion membrane was not available in Shuler's report [10], $\Delta S^{\neq}$ values, obtained by Eq. 4, may be less negative compared with those by Q/δ, where δ is membrane thickness. It may be possible to say that from the physiological standpoint, Laidler's porous membrane model is not diffusive but the transport by another physical mechanism which involves hydraulic forces. However, as pointed out by Hill [16,17], water transfer by osmosis through pores occurs either by viscous flow or diffusion depending on the size of osmolyte in relation to pore radius. Therefore, as given in Eqs. 3a, 3b and 4, rate-determining mechanisms in Laidler's porous membrane model [8–11] and Zwolinski's model [12] are the similar molecular process from the standpoint of the transition state theory of Eyring [11] and may be applicable to membrane transport of water.

The conventional permeability constants (p^*) for water transport were evaluated from the following equation exhibiting the swelling of cell in the hypotonic solution; $p^* = \mathrm{d}V/\mathrm{d}t[A\Delta\pi]$ (cm^2/dyn per s), where A and $\Delta\pi$ are surface area of cell and osmotic pressure difference between internal and external solutions. Conversion of p^* (cm^2/dyn per s) to permeability constant (P (cm/s)) is given by Zwolinski et al. [12] and Johnson et al. ([15], pp. 754–762), i.e., $p^*(RT/V_1)$, where V_1 is partial molar volume of water. Permeability constant (P), introduced by Zwolinski et al. [12] and Johnson et al. [15], is equivalent to osmotic water permeability (P_f), used recently by many groups [18–31]. So, $\Delta F^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values were evaluated using $-RT\ln(P_f)$, $(\Delta E_a - RT)$ and $-(\Delta F^{\neq} - \Delta H^{\neq})/RT$ relations, respectively.

A large number of data on osmotic water permeation in *Xenopus* oocytes with or without aquaporin water channels, aquaporin proteoliposomes, human and rabbit erythrocytes have been reported during the last decade [18–28].

3. Results and discussion

Assuming λ and δ in Eqs. 3a, 3b and 4 to be 2.5 and 50 Å, respectively, $\Delta F^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for osmotic water permeation were calculated using the reported P_f values and Arrhenius activation energies ($\Delta E_a = \Delta H^{\neq} + RT$). $\Delta F^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for *Arbacia* egg membranes ([12]; Fig. 1, closed circles), lipid black films ([18]; Fig. 1, open circles), collodion membranes ([10]; Fig. 1, closed triangles) and various cell membranes, such as *Xenopus* oocytes with or without aquaporin water channels, mammalian erythrocytes and aquaporin proteoliposomes [19–28] are given in Table 1 and Fig. 1 (open squares).

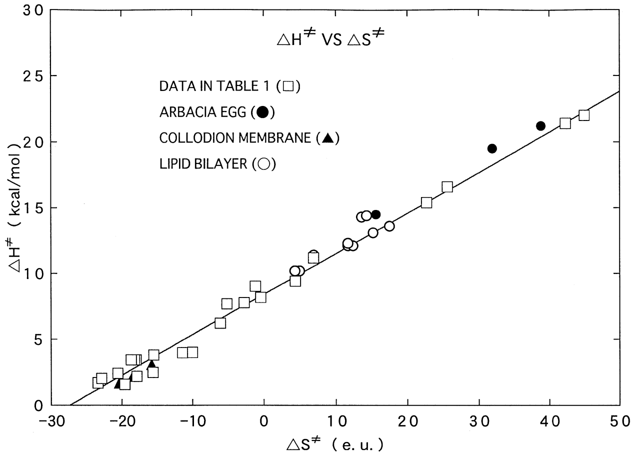

Fig. 1. Plot of $\Delta H^{\neq}$ vs. $\Delta S^{\neq}$ for osmotic water permeabilities of *Arbacia* egg (●), lipid bilayer (○), porous collodion membrane (▲) and data given in Table 1 (□).

$\Delta F^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for endosmotic water transport of *Arbacia* eggs at 24°C, shown in Fig. 1 (closed circles), were very similar to those for *Xenopus* oocytes without aquaporin water channels given in Table 1 [19,22,23,25], thereby suggesting that there are few water channels in *Arbacia* eggs. $\Delta S^{\neq}$ values of 32∼40 e.u. for water transport across *Arbacia* egg cell membrane are approximately twice as large as those found by Barrer et al. [14] for the diffusion (permeation) of nitrogen or methane across vulcanized rubber membranes (7.15% or 11.3% sulfur). A large positive $\Delta S^{\neq}$, which is correlated with a high $\Delta H^{\neq}$ for diffusion, seems to indicate that either a greater region of disorder (a larger zone of activation [14]) or the reversible loosening of more chain segments might arise when water molecules are diffusing (permeating) in a cell membrane of Arbacia eggs than in more rigid structures like the vulcanized rubber membranes [10,12,14]. Therefore, these $\Delta S^{\neq}$ and $\Delta H^{\neq}$ values indicate that a larger number of secondary bonds in the membrane structure, presumably the lipid bilayer, might be being broken reversibly during the permeation of water molecules in a cell membrane of *Arbacia* egg [10,12,14]. The above statements might be equivalent to the kinks model that thermal fluctuation in membrane lipid can cause conformational changes in hydrocarbon chains which lead to the generation of mobile structural defects (mobile packets of free volume) [29–31]. So, the mobile packets (kinks model) may be dynamic pores compared with static pores of water channels or collodion membrane. The ranges of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for water transport across lipid black films at 20∼37°C [13] and liposomes at 37°C (Table 1) were 10∼15 kcal/mol and 4∼23 e.u., respectively, as shown in Fig. 1 (open circles). These large positive $\Delta S^{\neq}$ and high $\Delta H^{\neq}$ values seem to be due to the mechanisms, which are similar to those in *Arbacia* eggs and *Xenopus* oocyte given in Table 1 and Fig. 1 [10,12,14,29–31].

$\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for water transports across porous collodion membrane were 2∼3 kcal/mol and −25∼−16 e.u., respectively, at 30°C, as shown in Fig. 1 (closed triangles). Largely negative $\Delta S^{\neq}$ values

Table 1

Free energy ($\Delta F^{\neq}$), enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) values of activation for osmotic water permeation across cell membranes[a]

Membrane	Substance	$\Delta F^{\neq}$ (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (e.u.)	Temperature[b] (°C)	Ref.
P25-proteoliposome-injected *Xenopus* oocyte (*X.* o.)	H_2O	8.56	2.42	−20.6	25[c]	[19]
AQPI-proteoliposome-injected *X.* o.	H_2O	8.68	1.70	−23.4	25[c]	[19]
Liposome-injected *X.* o.	H_2O	9.11	11.2	6.87	25[c]	[19]
Sheep distal air way epithelium	H_2O	8.41	3.81	−15.5	23	[20]
Human erythrocyte (normal)	H_2O	7.52	3.99	−11.4	37	[21]
Human erythrocyte (proband-1)	H_2O	8.64	7.79	−2.75	37	[21]
Human erythrocyte (proband-2)	H_2O	8.33	8.19	−0.45	37	[21]
CHIP28-proteoliposome-injected *X.* o.	H_2O	7.31	2.49	−15.6	37	[22]
Liposome-injected *X.* o.	H_2O	8.37	15.4	22.7	37	[22]
Water-injected *X.* o.	H_2O	9.04	21.4	42.3	20	[23]
Rat renal medulla mRNA-injected *X.* o.	H_2O	8.15	9.42	4.34	20	[23]
Rat renal medulla mRNA and cAMP-injected *X.* o.	H_2O	8.01	6.22	−6.09	20	[23]
CHIP28-proteoliposome	H_2O	7.31	2.49	−15.6	37	[24]
Liposome	H_2O	8.37	15.4	22.7	37	[24]
CHIP28 mRNA-injected *X.* o.	H_2O	7.47	2.20	−17.9	22	[25]
Control-injected *X.* o.	H_2O	8.70	22.0	45.0	22	[25]
CHIP28 proteoliposome	H_2O	7.67	1.59	−19.6	37	[26]
$HgCl_2$-treated CHIP28 proteoliposome	H_2O	8.66	16.6	25.6	37	[26]
Rabbit erythrocyte (normal)	H_2O	6.97	4.01	−10.0	23	[27]
pCMBS-treated rabbit erythrocyte[e]	H_2O	9.24	7.71	−5.15	23	[27]
Rabbit reticulocyte mRNA-injected *X.* o.	H_2O	8.53	2.04	−22.9	10	[27]
Water-injected *X.* o.	H_2O	9.37	9.04	−1.18	10	[27]
Rabbit reticulocyte mRNA-injected *X.* o.	H_2O	8.52	3.44[d]	−18.0	10	[28]
Rabbit renal papilla mRNA-injected *X.* o.	H_2O	8.66	3.44[d]	−18.4	10	[28]
Rat renal papilla mRNA-injected *X.* o.	H_2O	8.59	3.44[d]	−18.2	10	[28]
Rat renal cortex mRNA-injected *X.* o.	H_2O	8.72	3.44[d]	−18.7	10	[28]

[a] Values of λ and δ in Eqs. 3a, 3b and 4 were assumed to be 2.5 and 50 Å, respectively. Assuming λ and δ to be 5 and 100 Å, 8 and 50 Å or 2.5 and 50 Å, obtained $\Delta S^{\neq}$ values for unfertilized *Arbacia* eggs during endosmosis are 31.6, 29.2 or 31.9 e.u., respectively.

[b] Values of osmotic water permeability were reported at written temperature.

[c] Experimental temperature for given P_f values was assumed to be 25°C.

[d] Zhang et al. [28] reported Arrhenius activation energies (ΔE_a) being <4 kcal/mol. Therefore, we assumed $\Delta H^{\neq} = \Delta E_a - RT$ to be 3.44 kcal/mol for numerical calculations of $\Delta S^{\neq}$ values.

[e] pCMBS, *p*-chloromercuribenzene sulfonate.

for permeation of water through porous collodion membrane could be explained by the partial immobilization of permeating molecules, because the process of partial immobilization brings about a decrease in $\Delta S^{\neq}$ ([10,11], p. 398). Typical negative values of $\Delta S^{\neq}$ arising from loss of freedom in adsorption of molecules, which have the moments of inertia of 10^{-40} g cm^2 and the mass of 1 atomic weight unit at 27°C, were reported by Eyring and his co-workers ([11], p. 398). If the adsorbed molecules were mobile on the surface, $\Delta S^{\neq}$ value, due to loss of one translational freedom, may be −38 e.u. On the other hand, $\Delta S^{\neq}$ value, due to loss of 3 rotational freedoms, may be −10.1 e.u. So, the obtained $\Delta S^{\neq}$ values for water permeation through porous membrane seem to suggest the partial loss of rotational and/or translational freedoms of permeating water molecules in the membrane as they permeate it without irreversible breaking or loosening of the membrane structure ([10,11], p. 398). The present findings, i.e., negative $\Delta S^{\neq}$ values for permeation of water through porous collodion membrane, might be in good agreement with results obtained by the molecular dynamics simulation on water in channel, i.e., reduction of rotational and translational relaxation rates [32].

$\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for water transport of control *Xenopus* oocytes [19,25,27,28] were $1 \sim 22$ kcal/

mol and $-1 \sim 45$ e.u., respectively; these values were similar to those of *Arbacia* eggs (Fig. 1, closed circles). $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values of aquaporin proteoliposome- or mRNA-microinjected *Xenopus* oocytes [19,22,25,27,28], aquaporin proteoliposomes [24,26] and human erythrocytes [21,27] were $1.7 \sim 4.0$ kcal/mol and $-25 \sim -11$ e.u., respectively, except for data on rat renal mRNA-microinjected *Xenopus* oocytes [23] given in Table 1. Low $\Delta H^{\neq}$ and largely negative $\Delta S^{\neq}$ values for *Xenopus* oocytes with aquaporin water channels, aquaporin proteoliposomes and human erythrocytes were very similar to those for water permeation through porous collodion membrane (Fig. 1, closed triangles), and could be explained by the partial immobilization of permeating water molecules, i.e., the partial loss of rotational and/or translational freedoms of permeating water molecules in the membrane ([11], p. 398; [10,32]). Indeed, electron crystallography of frozen-hydrated two-dimensional crystals of human erythrocyte aquaporin revealed an aqueous vestibule in each monomer ($8 \sim 20$ Å in diameter), leading to water-selective channel which is enclosed by multiple *trans*-membrane α-helices [3–7]. Murata et al. [33] recently reported the pore diameter of human erythrocyte aquaporin of ~ 3 Å and the mechanism of permeation by water but not by protons. It might be worthwhile to note that in desalination membranes, significant desalting is expected when their pore sizes are below $20 \sim 22$ Å [2].

There are two passive pathways for water permeation across cell membrane, i.e., simple diffusion across the lipid bilayer and flow through hydrophilic pores (water channels) [34–36]. However, as shown in Eqs. 3a, 3b and 4, the transition state theory [11] indicated that rate-determining mechanisms for two passive water transports are transfer processes with positive or negative $\Delta S^{\neq}$ values. These two passive processes could be distinguished by various techniques, such as osmotic water permeability (P_f), P_f/P_d ratio where P_d is diffusional water permeability monitored with labeled water molecules, Arrhenius activation energy ($\Delta E_a = \Delta H^{\neq} + RT$), radiation inactivation, mercurial inhibition [35] and our $\Delta S^{\neq}$ values. In fact, kinetic parameters for osmotic water permeability (P_f) of CHIP28 proteoliposomes were changed by $HgCl_2$ treatment from $\Delta H^{\neq}$ of 1.59 kcal/mol and $\Delta S^{\neq}$ of -19.6 e.u. to 16.6 kcal/mol and 25.6 e.u., respectively, as given in Table 1 [26].

The ranges of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for osmotic water permeability given in Table 1 were $2 \sim 21$ kcal/mol and $-26 \sim 45$ e.u., respectively, i.e., over the ranges from porous collodion membrane to *Arbacia* egg. $\Delta H^{\neq}$ vs. $\Delta S^{\neq}$ plots showed a good linear regression between them as shown in Fig. 1 (open squares), indicating that low ΔE_a values ($\Delta E_a < 6$ kcal/mol) in water transport across cell membrane correspond to negative $\Delta S^{\neq}$ values. This is so-called $\Delta H^{\neq}$ and $\Delta S^{\neq}$ compensation, as reported by Barrer et al. [14], Cohen [13] and Lumry et al. [37]. Therefore, in spite of large differences in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values among different water transport processes given in Table 1, ranging from 2 to 21 kcal/mol and from -26 to 45 e.u., respectively, the mean of $\Delta F^{\neq}$ values seems to be 8.34 ± 0.63 kcal/mol ($n = 26$). However, we have no knowledge of the detailed mechanism of the so-called $\Delta H^{\neq}$ and $\Delta S^{\neq}$ compensation on water transport at present.

In calculating $\Delta F^{\neq}$ and $\Delta S^{\neq}$ values, it is necessary to assume appropriate values for δ and λ in Eqs. 3a, 3b and 4, as reported by Shuler et al. [10] and Zwolinski et al. [12]. However, variations in δ of $50 \sim 100$ Å and λ of $2.5 \sim 5.0$ Å corresponded to variations in $|\Delta S^{\neq}|$ of < 3 e.u. (see footnote in Table 1). Difference in $\Delta S^{\neq}$ between two data ($\Delta(\Delta S^{\neq})$) in Table 1, such as CHIP28 liposomes [17] and liposomes [17], was 38 e.u. and independent of δ and λ. These results might indicate that variations in δ and λ values only show the slight parallel shift of a regression line for $\Delta H^{\neq}$ vs. $\Delta S^{\neq}$ plot (Fig. 1) to the right- or left-hand side.

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