$C_{16}H_{17}NS_2O_5$: C,44.04: H,4.63: N,3.81%. Found: C,43.68: H,4.45: N,3.66%.

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Kinetics and Thermodynamic Studies on the Reaction of Cysteine with Cinnamaldehyde

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The reaction of cysteine with cinnamaldehyde have been studied kinetically and thermodynamically. It was found that the reaction proceeds in two steps; formation of the monoadduct by a Michael type addition followed by the nucleophilic attack of the second cysteine to the carbonyl carbon of the monoadduct to afford the thiazolidine derivative. A reaction profile for the reaction of cysteine with cinnamaldehyde was constructed based on the thermodynamic parameters analyzed for the forward and the reverse reactions. It was assumed that the second step of this reaction accompanies an intermediate, a Schiff base.

Introduction

Michael obtained the addition product of ethyl malonate with ethyl cinnamate in sodium ethoxide solution, and Ingold formulated the mechanism of Michael addition in an alkaline solution.[1]

Strong nucleophiles having sulfhydril groups can be added to benzalaceto-phenone or acrylonitril without acid or base catalyst.[2] The formation of thiazolidine-4-carboxylic acid from formaldehyde and cysteine was explained by Ratner.[3] The mechanism of the reaction of sulfhydril compounds with α,β-unsaturated carbonyl compounds has been studied by Esterbauer.[4-6] In this work, we have studied the mechanism of the reaction between cinnamaldehyde and cysteine. Spectroscopic and polarographic techniques have been employed to follow the rate of the reaction. The concentrations of the cinnamaldehyde and the cysteine were determined by the polarographic wave heights corresponding to the oxidation and the reduction of the respective substrates.

Experimental

General procedure

A. Perkin Elmer UV spectrophotometer and a Shimadz RP-50 polarograph were used. All chemicals were commercially available reagent grade and were used as received. Ionic strength of the solution was maintained at 0.1 by adding appropriate amount of sodium chloride.

Kinetic Studies

The rate of the reaction was determined by spectroscopic and polarographic methods.

Spectrophotometric method: 98 ml of buffer solution in 100 ml volumetric flasks were immersed into the thermostat at 25°C, and 1 ml of 2×10^{-3} M cinnamaldehyde alcohol solution and 1 ml of cysteine solution of several different concentrations ($10^{-2} \sim 10^{-1}$M) were added. In order to prevent the oxidation of cysteine by oxygen in the solution, they had to be in nitrogen environment. Initial concentration of cinnamaldehyde was 2×10^{-5} M and that of cysteine were from 10×10^{-5} M to 100×10^{-5} M. The concentration of cinnamaldehyde in each reaction mixture were determined at 293 nm.

Polarographic method: 5 ml of 1×10^{-3} M solution of cinnamaldehyde in buffer and 10 ml 1×10^{-3} M solution of cysteine in buffer were mixed in the polargraphic cell. Every procedure was carried out in nitrogen environment in order to prevent the oxidation of cysteine and 25°C water was passed around the reaction vessel to keep the temperature constant. Dropping mercury electrode and saturated calomel electrode were applied. The initial cocentration of cinnamaldehyde and cysteine were 3.3×10^{-4} M and 6.6×10^{-4} M, respectively. The wave height, current -0.25 V v.s. S.C.E for the cysteine and at -1.40 V v.s. S.C.E for the cinnamaldehyde were recorded against time. Thermodynamic parameters: The rate constants at temperature of 13°C, 25°C, 32°C and 38°C were determined, respectively.

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Results and Discussion

Spectroscopic method: The change of concentration of cinnamaldehyde under the reaction of various concentration of cysteine were observed at pH 8.5 and 25°C.

The pseudo first-order rate constants for this reaction were plotted against concentration of cysteine (Figure 1). From this slope, the second-order rate constant at various pH, 25°C, and 0.1 ionic strength were determined (Table 1).

Figure 2 shows the pH-rate profile for the reaction of cysteine with cinnamaldehyde.

Polarographic method: From the calibration current curves of cinnamaldehyde and cysteine we could obtain Figure 3 and Table 3, where the concentration of monoadduct and diadduct were calculated by following reactions, (1) and (2), and equation (3)~(6).
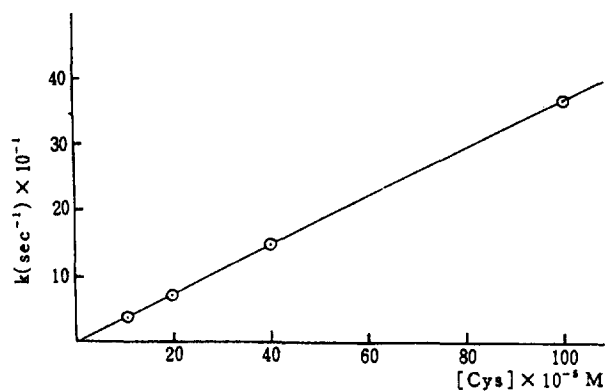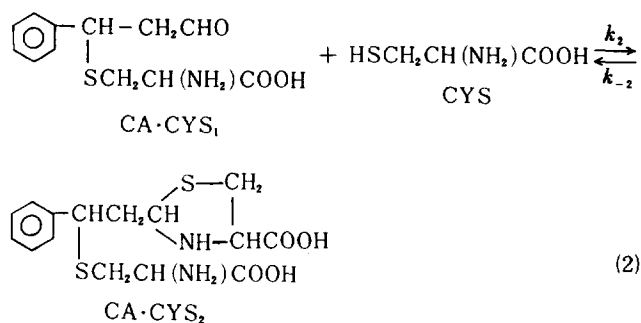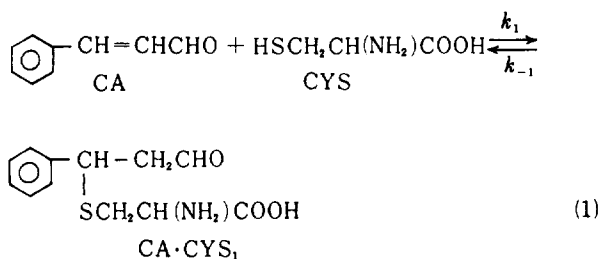
$$\underset{CA}{C_6H_5-CH=CHCHO} + \underset{CYS}{HSCH_2CH(NH_2)COOH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

$$\begin{array}{c} C_6H_5-CH-CH_2CHO \\ | \\ SCH_2CH(NH_2)COOH \\ CA \cdot CYS_1 \end{array} \qquad (1)$$

$$\begin{array}{c} C_6H_5-CH-CH_2CHO \\ | \\ SCH_2CH(NH_2)COOH \\ CA \cdot CYS_1 \end{array} + HSCH_2CH(NH_2)COOH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \\ CYS$$

$$\begin{array}{c} C_6H_5-CHCH_2CH \overset{S—CH_2}{\underset{NH—CHCOOH}{<}} \\ | \\ SCH_2CH(NH_2)COOH \\ CA \cdot CYS_2 \end{array} \qquad (2)$$

Figure 1. Plot of pseudo first-order rate constant vs concentration of cysteine.

Table 1. The Rate Constants for the Reaction of Cysteine with Cinnamaldehyde by Spectrophotometry at Various pH, 25°C, and 0.1 ionic Strength

pH	Buffer soln.	Observed value		Calculated value	
		k_1 (sec^{-1}, M^{-1})	$\log k_1 + 3$	k_1 (sec^{-1}, M^{-1})	$\log k_1 + 3$
1.0	HCl + KCl			5.50×10^{-3}	0.74
2.0	HCL + KCl	5.62×10^{-3}	0.75	5.50×10^{-3}	0.74
2.5	HCL + KCl	5.75×10^{-3}	0.76	5.51×10^{-3}	0.74
3.0	HCL + KCl	5.85×10^{-3}	0.77	5.53×10^{-3}	0.74
3.5	HCL + KCl	5.59×10^{-3}	0.78	5.61×10^{-3}	0.75
4.0	HOAc + NaOAc	6.00×10^{-3}	0.78	5.84×10^{-3}	0.77
4.5	HOAc + NaOAc	7.02×10^{-3}	0.85	6.58×10^{-3}	0.82
5.0	HOAc + NaOAc	1.02×10^{-2}	1.08	8.92×10^{-3}	0.95
5.5	HOAc + NaOAc	1.62×10^{-3}	1.21	1.63×10^{-2}	1.21
6.0	KH$_2$PO$_4$+Borax	5.72×10^{-2}	1.76	3.95×10^{-2}	1.60
6.5	KH$_2$PO$_4$+Borax	1.39×10^{-1}	2.14	1.12×10^{-1}	2.05
7.0	KH$_2$PO$_4$+Borax	4.88×10^{-1}	2.69	3.34×10^{-1}	2.52
7.5	KH$_2$PO$_4$+Borax	1.00	3.00	9.62×10^{-1}	2.98
8.0	KH$_2$PO$_4$+Borax	3.52	3.55	2.43	3.39
8.5	KH$_2$PO$_4$+Borax	3.79	3.58	4.67	3.67
9.0	KH$_2$PO$_4$+Borax	4.98	3.70	6.39	3.81
9.5	NaOH + NaCl	4.75	3.68	6.48	3.81
10.0	NaOH + NaCl	4.40	3.64	4.90	3.69
10.5	NaOH + NaCl	1.25	3.10	2.65	3.42
11.0	NaOH + NaCl	0.90	2.77	1.10	3.04
11.5	NaOH + NaCl	0.29	2.47	4.12×10^{-1}	2.61
12.0	NaOH + NaCl			1.68×10^{-1}	2.23
12.5				8.77×10^{-2}	1.94
13.0				6.19×10^{-2}	1.79
13.5					
14.0					

The Reaction mechanism of Cysteine with Cinnamaldehyde

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$$[CA]_0 = [CA] + [CACys_1] + (CA[Cys]_2) \qquad (3)$$

$$[Cys]_0 = [Cys] + [CACys_1] + 2[CA(Cys)_2] \qquad (4)$$

Then

$$[CACys] = 2[CA]_0 - 2[CA] + [Cys] - [Cys]_0 \qquad (5)$$

$$[CA(Cys)_2] = [Cys]_0 - [Cys] + [CA] - [CA]_0 \qquad (6)$$

The rate constants k_1, k_{-1}, k_2 and k_{-2} were calculated by simultaneous equation[9] (7) on the basis of Fig. 3.

$$-\frac{d[Cys]}{dt} = k_1[CA][Cys] - k_{-1}[CACys] + k_2[Cys][CACys]$$
$$- k_{-2}(CA[Cys]_2) \qquad (7)$$

The rate constants, k_1 were very conformable with the value obtained from spectrophotometric measurement. (Table 2, Fig. 2). The observed reaction rate of the first step is looked upon as a sum of the results of cinnamaldehyde with the individual ionic species of cysteine and the solution. An equilibrium pattern of the ionic species of cysteine and their equilibrium constants were given[10]:

$$I \rightleftharpoons II + III + H^+,$$
$$K_1 = 4.07 \times 10^{-9}$$
$$II + III \rightleftharpoons IV + H^+,$$
$$K_2 = 6.98 \times 10^{-11}$$
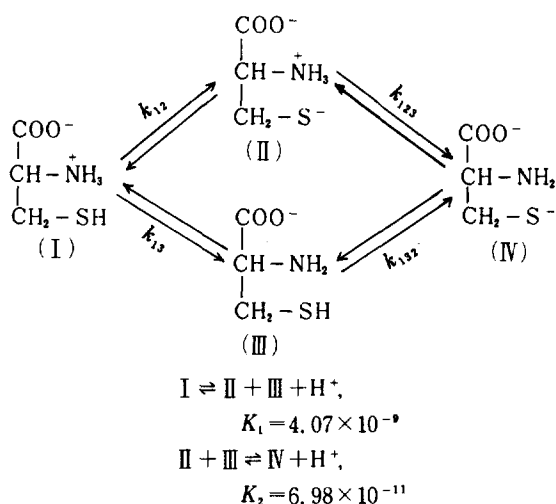
It was assumed that the fraction ratio of species II and III are equal,[10] the species which are likely to be controlled by general base are species I and III, and species IV reacts as same as species II.

From the experimental results and above considerations, we could explain the pH dependent reaction rate of the first step.
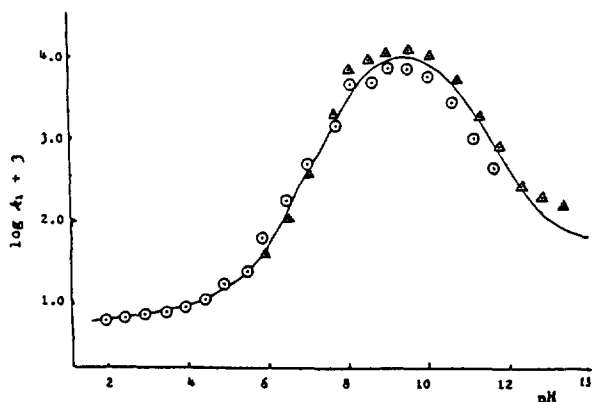

Figure 2. pH-rate profile for the reaction of cysteine with cinnamaldehyde at 25°C and 0.1 ionic strength. △: by polarography. ⊙: by spectrometry.

The rate equation of the first step was given by equation (8).

$$rate = k_1[CA]\{[I] + [II] + [III] + [VI]\} \qquad (8)$$

Since the general base effect was actually negligible, k_1 in equation (8) was given by equation (9).

$$k_1 = \{k_1'[H^+]^2 + \frac{K_1[H^+]}{2}(k_2' + k_3') + k_4'K_1K_2\}$$

$$\times \frac{1}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (9)$$

Where k_1', k_2', k_4' are rate constants in the individual rate equation.

The value of these rate constants were obtained by analysis of experimental results (Fig. 2). The individual rate constant

Table 2. The rate constants for the reaction of cysteine with cinnamaldehydes by polarograph at various pH, 25°C and 0.1 ionic strength

pH	Buffer solution	k_1 obs (sec^{-1}, M^{-1})	$\log k_1 + 3$
6.0	KH$_2$PO$_4$ + Borax	3.96×10^{-2}	1.60
6.5	KH$_2$PO$_4$ + Borax	1.02×10^{-1}	2.01
7.0	KH$_2$PO$_4$ + Borax	4.05×10^{-1}	2.61
7.5	KH$_2$PO$_4$ + Borax	1.05	3.02
8.0	KH$_2$PO$_4$ + Borax	12.19	4.08
8.5	KH$_2$PO$_4$ + Borax	13.89	4.14
9.0	KH$_2$PO$_4$ + Borax	12.22	4.08
9.5	NaOH + NaCl	8.75	3.94
10.0	NaOH + NaCl	6.40	3.80
10.5	NaOH + NaCl	3.02	3.48
11.0	NaOH + NaCl	1.20	3.10
11.5	NaOH + NaCl	0.51	2.70
12.0	NaOH + NaCl	0.22	2.30
12.5	NaOH + NaCl	0.20	2.30
13.0	NaOH + NaCl	0.20	2.30

Table 3. Concentrations of reactants and products for the reaction of cysteine with cinnamaldehyde at pH 8.0, 0.1 ionic strength and 25°C

time (sec)	Concentrations of the reactants and products			
	Cinnamaldehyde	Cysteine	Monoadduct	Diadduct
0	3.30×10^{-4} mole*	6.60×10^{-4} mole*	0	0
12	3.12×10^{-4}	6.24×10^{-4}	1.5×10^{-5}	0.18×10^{-4}
24	2.95×10^{-4}	5.93×10^{-4}	3.00×10^{-6}	0.32×10^{-4}
36	2.88×10^{-4}	5.86×10^{-4}	1.00×10^{-5}	0.32×10^{-4}
54	2.82×10^{-4}	5.60×10^{-4}	6.00×10^{-6}	0.50×10^{-4}
140	2.52×10^{-4}	8.00×10^{-6}	0.70×10^{-4}	
230	2.35×10^{-4}	4.76×10^{-4}	6.00×10^{-6}	0.89×10^{-4}
350	2.13×10^{-4}	4.44×10^{-4}	1.80×10^{-4}	0.99×10^{-4}
590	1.90×10^{-4}	4.08×10^{-4}	2.80×10^{-6}	1.12×10^{-4}
720	1.80×10^{-4}	3.92×10^{-4}	3.20×10^{-5}	1.18×10^{-4}
900	1.70×10^{-4}	3.75×10^{-4}	3.50×10^{-5}	1.25×10^{-4}
1,200	1.67×10^{-4}	3.60×10^{-4}	2.60×10^{-5}	1.37×10^{-4}
1,500	1.60×10^{-4}	3.45×10^{-4}	2.50×10^{-5}	1.45×10^{-4}

*Initial concentrations of the substances as indicated for zero time.

equation where could be corresponding to the experimental results was as follows:

$$k_1 = \frac{5.50 \times 10^{-3} [H^+]^2 + 8.40\, K_1\, [H^+] + 0.05\, K_1 K_2}{[H^+]^2 + K_1\,[H^+] + K_1 K_2} \quad (10)$$

Fig. 2 shows that the value of rate constants k_1 calculated by equation (10) were in good agreement with the observed value (cf. Table 1).

The reactivity of species IV of cysteine, however, was supposed to have greater reactivity than that of species II and III. Accordingly, the decrease of k_1 at above pH 9.5 (Fig. 2) suggests a change in the rate determining step. Up to pH 9.5, the rate is controlled by the addition of Scys, whereas, at higher pH the second step, the formation of the thiazolidine
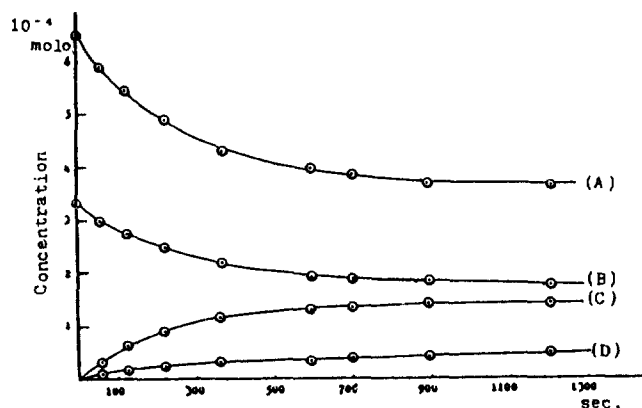

Figure 3. Concentration of reactants and products vs time for the reaction of cysteine with cinnamaldehyde at pH 8.0, 0.1 ionic strength, and 25°C A: Cysteine B: Cinnamldehyde C: Diadduct D: Monoadduct.
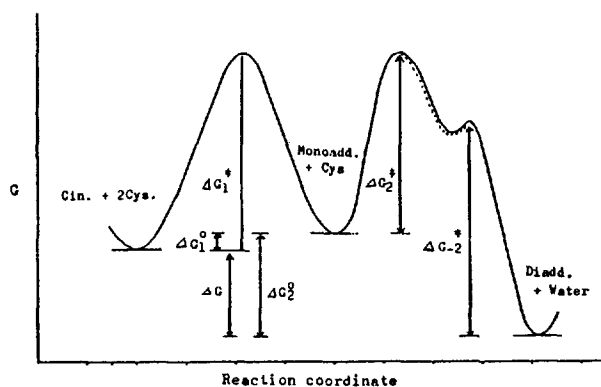

Figure 4. Reaction profile for the reaction of cinnamaldehyde with cysteine at 25°C, pH 8.0 and 0.1 ionic strength.

derivative, probably becomes rate limiting. In order to reveal these detaield reaction mechanism at high pH, more systematic works has been done.
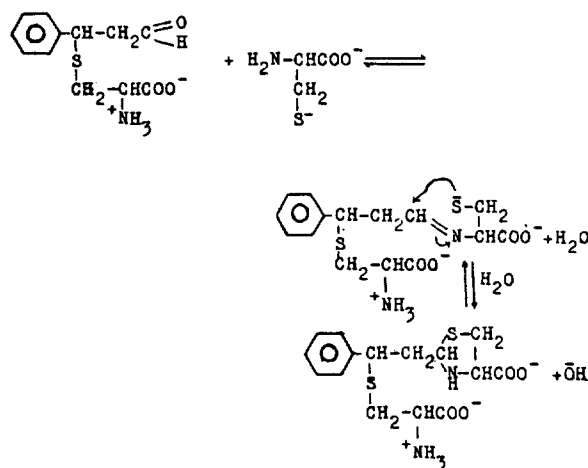
Thermodynamic Parameters: The rate and equilibrium constants determined at various temperature were given in Table 4, and the thermodynamic parameters in the reaction of cysteine with cinnamadehyde at pH 8.0, 25°C and 0.1 ionic strength were given in Table 5.

The energy diagram obtained from the analysis of k_1, k_{-1}, k_2 and k_{-2} shows that the first and second steps are both partially rate determining at pH 8.0. However, the second step appears more complicated than Eq.2. The fact that $\Delta G + \Delta G_2^{\ddagger} > \Delta G_{-2}^{\ddagger}$ requires at least one intermediate in the second step. To understand the mechanism of the second step in more detail, further study has to be done. The proposed mechanism at this stage is as follows:

Table 5. Thermodynamic parameters in the reaction of cysteine with cinnamaldehgde at pH 8.0, 25°C, and 0.1 ionic strength

	Step (1)	Step (-1)	Step (2)	Step (-2)	Overall
Ea	9.17	14.9	6.11	5.96	
ΔH*	8.58	14.3	5.52	5.37	
ΔS*	-24.9	-1.16	-30.5	-40.4	
ΔG*	16.0	14.65	14.6	17.4	
ΔH	-5.39		1.18		-4.21
ΔS	-22.4		32.2		9.8
ΔG	1.31		-8.42		-7.11

*Energy: Kcal entropy: e.u

Table 4. Rate and equilibrium constants for the reaction of cysteine with cinnamaldehyde at pH 8.0, 0.1 ionic strength, and 25°C

Temperature (°C) Constants	13.0	25.0	32.0	38.0
k_1 (mole⁻¹, sec⁻¹)	5.852	12.19	17.45	25.08
k_{-1} (sec⁻¹)	35.34	116.1	194.4	319.8
k_2 (mole⁻¹, sec⁻¹)	78.33	122.3	148.4	184.9
k_{-2} (mole⁻¹, sec⁻¹)	5.820×10^{-5}	8.185×10^{-5}	9.855×10^{-5}	11.49×10^{-5}
K_1	16.56×10^{-2}	10.50×10^{-2}	7.840×10^{-2}	7.840×10^{-2}
K_2	13.56×10^5	14.94×10^5	15.06×10^5	16.09×10^5
K_1, K_2	2.229×10^5	1.569×10^5	1.352×10^5	1.262×10^5

Nonstoichiometric Empirical Formulas

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A Study of Nonstoichiometric Empirical Formulas for Semiconductive Metal Oxides

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An empirical formula for semiconductive metal oxides is proposed relating nonstoichiometric value x to a temperature or an oxygen partial pressure such that experimental data can be represented more accurately by the formula than by the well-known Arrhenius-type equation. The proposed empirical formula is $\log x = A + B \cdot 1000/T + C \cdot \exp(-D \cdot 1000/T)$ for a temperature dependence and $\log x = a + b \cdot \log P_{O_2} + c \cdot \exp(-d \cdot \log P_{O_2})$ for an oxygen partial pressure dependence. The A,B,C,D and a,b,c,d are parameters which are evaluated by means of a best-fitting method to experimental data. Subsequently, this empirical formula has been applied to the n-type metal oxides of $Zn_{1+x}O$, $Cd_{1+x}O$, and $PrO_{1.8003-x}$, and the p-type metal oxides of CoO_{1+x}, FeO_{1+x}, and Cu_2O_{1+x}. It gives a very good agreement with the experimental data through the best-fitted parameters within 6% of relative error. It is also possible to explain approximately qualitative characters of the parameters A,B,C,D and a,b,c,d from theoretical bases.

Introduction

Since Wagner and Schottky[1] had shown that inorganic compounds could have defects in crystals and nonstoichiometric compositions, experimental and theoretical studies for these behaviors have been performed actively.[2-19] Among these, the enthalpy and entropy changes of point defect formations in metal oxides were usually determined by the deviation from stoichiometry, electrical conductivities, and diffusions as a function of temperature or partial pressures of oxygen. In this respect, compositional variations in many nonstoichiometric oxides are often discussed as a function of temperature or partial pressure of oxygen[7-11,20,21] and approximate empirical relations between these have been proposed.[22-26]

Usually the relationships between nonstoichiometric quantity, log x and inverse temperature (1000/T) or oxygen partial pressure (log P_{O_2}) have been considered to be linear. The linear relationship is based on the fact that the defects are randomly distributed and noninteracting to each other with mass action law. This is probably true only in the range of very small deviations from stoichiometry. Consequently, in many cases, to fit experimental data, one has to adopt two linear relationships[7-11] with so called a break point even though there is no apparent phase transition. Moreover, the slopes of lines in ex-

perimental data changes gradually with increasing or decreasing nonstoichiometry. From these facts, it seems that the relationship of real defect system is well represented by curvature rather than linear.

In the present work a new empirical formula is proposed with four parameters which can represent the real defect system. The formula would give a curvature rather than a straight line and would show a consistent result for metal oxides. Characters of parameters A,B,C,D and a,b,c,d obtained from calculations are attempted to be explained qualitatively. The enthalpy of formation of nonstoichiometric composition, $\Delta H_f'$ and the characteristic number, $1/n'$ are obtained from the new formula.

Empirical Formulas and Calculation

The previous relationships between nonstoichiometric quantity and temperature or oxygen partial pressure were derived theoretically. The usual relationships are the Arrhenius-type equation, which is given by;

$$\log x = a + b \cdot 1000/T$$
$$\log x = a' + b' \cdot \log P_{O_2},$$

where both a and a' are constants, b is $-\Delta H_f/2.3R$, b' is $1/n$.