a glass-stoppered quartz cell, and submitted to absorption measurement. The temperature of the cell compartment was kept at 20° throughout the measurements. As shown in Fig. 1, when the time at the point of maximum absorbance of the solution is defined as zero time, the rate of change in the absorbance of the solution with time was automatically recorded at 265 nm with $Al(NO_3)_3$ solution as blank. After the addition of Al ion, the absorbance reached maximum value within 3 min and the difference in absorbance ΔA was measured after 20 min. From the calibration plots of ΔA *vs.* concentration, the amount of oxalacetic acid was calculated.

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Quantum Statistical Calculation for the Correlation of Biological Activity and Chemical Structure. IV.[1] Subtrates for a Rabbit Kidney Reductase

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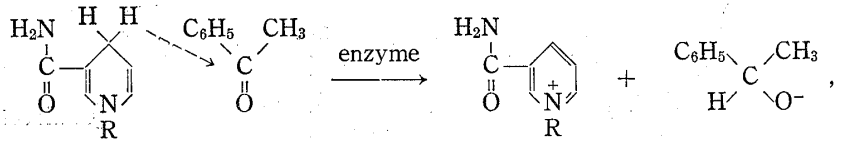
A structure-activity relationship based on a quantum statistical model was pursued in this study. The results of the calculations show that the model is good in relating the maximum velocity of the different acetophenone substrates for rabbit kidney reductase to the stretching vibrational frequency of the carbonyl group.

Keywords——structure-activity relationship; quantum statistical model; mathematical model; substrates; acetophenone derivative; infrared spectroscopic data; enzyme

In order to investigate the structure-activity relationship for compounds of substituted acetophenones, which are used as substrates for rabbit kidney reductase,[3] we have computed an equation based on the quantum statistical model.[1,4] The results of these calculations are shown in Table I and II.



According to the following reaction model of Hermann, *et al.*[5] the relationship between the maximum velocity of the different acetophenone substrates for rabbit kidney reductase was established in terms of quantum chemical parameters. We decided to use Eq. (1) developed in our early publications[4] to correlate their data:

$$-\log(k_0) = c_1 - c_2\theta, \tag{1}$$

$$\ln(1/C) = k_1 - k_2\theta, \tag{2}$$

where $\theta = \boldsymbol{h}c\tilde{\nu}/2\boldsymbol{k}T$, $\tilde{\nu}$ is the wave number of the stretching vibrational mode of the carbonyl group, $\boldsymbol{c}$ is the speed of light, $\boldsymbol{h}$ is the Planck constant, $\boldsymbol{k}$ is the Boltzman constant, and T is

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3) H.W. Culp and R.E. McMahon, *J. Biol. Chem.*, **243**, 848 (1968).
4) Part I: T.K. Lin, *J. Med. Chem.*, **17**, 151 (1974); Part II: T.K. Lin, *ibid.*, **17**, 749 (1974).
5) R.B. Hermann, H.W. Culp, R.E. McMahon, and M.M. Marsh, *J. Med. Chem.*, **12**, 749 (1969).

the absolute temperature. For the theoretical derivation of Eq. (2) one may refer to Ref. (4). The C represents the concentration of a drug available at receptor sites to reach a constant biological response (*i.e.*, ED_{50}, LD_{50}, *etc.*).

The data used for the linear regression analysis to obtain constants c_1 and c_2 in Eq. (1) was obtained from different sources. The infrared spectroscopic data (the wave number of the stretching vibrational mode of the carbonyl group) was taken from the work of Soloway and Friess,[6] and the relative activities, expressed in logarithms of the rate constants ($k_0 \times 100$), were taken from Table I of Ref. (5). The resulting equation of the present method (from the quantum statistical point of view) and the correlation based on the concept of incipient transition states and Hansch's method are summarized as follows:

Method

	n	r	s	$F_{1,4}$	
Crude enzyme					
Quantum statistics					
$-\log(k_0 \times 100) = 133.989 - 33.736\theta$	6	0.96	0.25	46.1	(3)
Transition states					
$\log(k_0 \times 100) = 0.582\delta_E + 0.943$	6	0.85	0.47	10.4	(4)
Hansch–Hammett					
$\log(k_0 \times 100) = 1.530 + 1.440\sigma^+$	6	0.96	0.24	52.0	(5)
Purified enzyme					
Quantum statistics					
$-\log(k_0 \times 100) = 133.852 - 33.702\theta$	6	0.95	0.28	38.0	(6)
Transition states					
$\log(k_0 \times 100) = 0.555\delta_E + 0.972$	6	0.81	0.53	7.3	(7)
Hansch–Hammett					
$\log(k_0 \times 100) = 1.533 + 1.393\sigma^+$	6	0.93	0.34	23.8	(8)

Where

$$\delta_E = [-(E_{IT}-E_G)_{compd} + (E_{IT}-E_G)_{acetophenone}] \times 100,$$

Table I. Data for Crude Enzyme Treatment

Substrate (substituted acetophenone)	Wave[a] number cm^{-1}	$\theta = h c\tilde{\nu}/2kT$[b]	δ_E[c]	σ^+[d]	log ($k_0 \times 100$) Obsd[c]	Calc. Present	Calc. Hermann[e]	Calc. Hansch[f]
1. *p*-OCH_3	1658	3.9782	0.05	−0.78	0.204	0.219	0.972	0.407
2. *p*-$NHCOCH_3$	1661	3.9854	−0.10	−0.60	0.634	0.462	0.885	0.667
3. *m*-NO_2	1681	4.0334	2.39	0.67	2.114	2.081	2.334	2.495
4. *p*-NO_2	1686	4.0454	3.07	0.79	2.883	2.486	2.730	2.668
5. *p*-CH_3	1675[g]	4.0190	−0.25	−0.31	1.398	1.595	0.798	1.084
6. *m*-OCH_3	1681[g]	4.0334	0.45	0.05	1.690	2.081	1.205	1.602

a) Values were taken from Ref. 6), Nujol mulls for compound No. 1 to 4, and pure liquids for No. 5 and 6.
b) $T = 300°$ K.
c) Values were taken from Ref. 5).
d) Values were taken from C. Hansch, *J. Med. Chem.*, **13**, 964 (1970).
e) Calculated from Eq. (4).
f) Calculated from Eq. (5).
g) These values were obtained in pure liquid forms.

6) A.H. Soloway and S.L. Friess, *J. Am. Chem. Soc.*, **73**, 5000 (1951).

E_{IT}=total energy of incipient transition state, E_G=total energy of ground state, σ^+ represents the Hammett electronic constant, n is the number of compounds used to derive the constants, r is the correlation coefficient, s is the standard deviation, and $F_{1,4}$ is the calculated F statistics[7] with degrees of freedom 1 and 4. For comparison, the results of the calculation of the incipient transition states and Hansch's method are included in Tables I and II. In order to make a fair comparison, the calculation for the methods used six compounds whose spectroscopic data are available from Ref. 6.

Discussion

From Tables I and II, it is evident that the present calculation using Eq. (1), when compared with the methods of Hermann and Hansch, shows a better overall result. For example, the first compound in Table I has an experimental value of 0.204. Using Hermann's transition states method gives a value of 0.972 which is more than four times greater than the observed experimental value. Using Hansch's sigma approach gives a value of 0.407 which is about two times greater than the experimental value. Using the present method gives a value of 0.219 which is relatively much closer to the experimental value.

Apparently, the chemical reaction rate between the series of substituted acetophenones and the rabbit kidney reductase is related to the vibrational frequency of the carbonyl group within the molecules of substituted acetophenones. Hence, the result of this calculation suggests that the present physical model is better than Hermann's or Hansch's physical models.

Table II. Data for Purified Enzyme Treatment

Substrate (substituted acetophenone)	Wave[a] number cm^{-1}	$\theta=hc\bar{\nu}/2kT$[b]	δ_E[c]	σ^+[d]	log ($k_0\times100$) Obsd[c]	Calc. Present	Calc. Hermann[e]	Calc. Hansch[f]
1. p-OCH_3	1658	3.9782	0.05	−0.78	0.204	0.224	1.000	0.446
2. p-$NHCOCH_3$	1661	3.9854	−0.10	−0.60	0.591	0.466	0.917	0.697
3. m-NO_2	1681	4.0334	2.39	0.67	1.965	2.084	2.298	2.466
4. p-NO_2	1686	4.0454	3.07	0.79	2.944	2.488	2.675	2.633
5. p-CH_3	1675[g]	4.0190	−0.25	−0.31	1.628	1.599	0.834	1.101
6. m-OCH_3	1681[g]	4.0334	0.45	0.05	1.613	2.084	1.222	1.602

a) Values were taken from Ref. 6), Nojol mulls for compound No. 1 to 4, and pure liquids for No. 5 and 6.
b) T=300° K
c) Values were taken from Ref. 5).
d) Values were taken from C. Hansch, *J. Med. Chem.*, **13**, 964 (1970).
e) Calculated from Eq. (7).
f) Calculated from Eq. (8).
g) These values were obtained in pure liquid forms.

7) Documenta Geigy. Scientific Tables. Geigy (1962).