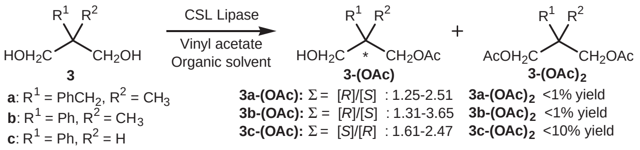
Two-parameter Analysis of Solvent Effects on Selectivity in Chemical Reactions: Information of Polarity and Activation Volume at the Transition State in Organic and Enzymatic Reactions

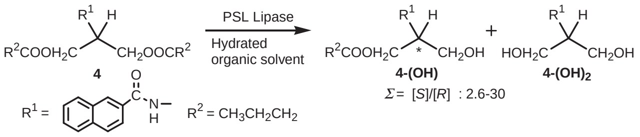
Chunlei Lin, Yoshikazu Hiraga, and Katsuo Ohkata*
Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526

(Received November 15, 2005; CL-051413; E-mail: ohkata@sci.hiroshima-u.ac.jp)

The solvent effects on stereoselectivity in the Diels–Alder reaction of cyclopentadiene, the [2 + 2]photodimerization of 2-cyclopentenone, and the enzymatic asymmetrization of prochiral 1,3-propanediols were analyzed by two-parameter treatment using both the dielectric constant and the solubility parameter to show a good linear relationship.



Scheme 1. Enzymatic reaction.



Scheme 2. Enzymatic hydrolysis.[2g]

The solvent effects on selectivity in some organic and enzymatic reactions gave us important information about the stability difference at the transition states according to the Curtin–Hammett principle.[1] Enzymatic reactions in organic solvent have become of interest in recent years from the point of view of physical organic chemistry as well as biocatalysis.[2]

The solvent effects of *endo*/*exo* selectivity in the Diels–Alder reaction of cyclopentadiene (**1**) with methyl acrylate,[3] *anti*/*syn* selectivity in the [2 + 2]photodimerization of 2-cyclopentenone (**2**),[4] and enantio-selectivity in the enzymatic desymmetrization (Schemes 1 and 2)[2g,5c] were examined by two-parameter analysis. Especially, prochiral substrates such as 2-substituted 1,3-propanediols must be a suitable probe for investigation on the transition state in enzymatic reactions.[6] Acetylation of **3a** and **3b** with a novel CSL lipase[5a,5b] gave exclusively the monoaceteate **3a** and **3b-(OAc)**, while the reaction of **3c** afforded **3c-(OAc)** along with the diacetate **3c-(OAc)$_2$** of less than 10% yield.[5c] There was not observed the racemization of **3a**–**3c-(OAc)** under the same reaction conditions.

The stereo-selectivity of products was abbreviated to "Σ" and calculated by Σ = [major-isomer]/[minor-isomer]). The polarity and the free volume at the transition state are important factors in organic reactions and these two properties influence the reactivity of organic reactions. Notwithstanding, there is not observed a linear relationship in these reactions by one-parameter analysis of the selectivity with either $[(\mathcal{E}-1)/(2\mathcal{E}+1)]$ or δ^2.[1a] Therefore, we applied two-parameter treatment to the solvent analysis in which the solvent effect was considered as a linear function of two independent and complementary parameters describing the polarity and cohesive pressure factors of the given solvent.[1] In this case, the Kirkwood parameter $[(\mathcal{E}-1)/(2\mathcal{E}+1)]$ was used as a measure of polar factor and δ^2 as a measure of cohesive pressure.[1] According to the model, the ln Σ was described in terms of Eq 1, where *a* and *b* are constants describing the sensitivity of ln Σ to the two properties.

$$\ln \Sigma = a[(\mathcal{E}-1)/(2\mathcal{E}+1)] + b\delta^2 + c. \qquad (1)$$

The regression coefficients (*a*, *b*, and *c*) and contributions ($a^{\%}$ and $b^{\%}$)[7] calculated by the least-squares method are summarized in Table 1 and the linear relationship ($r = 0.985$) is illus-

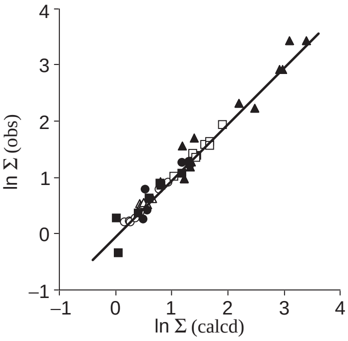


Figure 1. Observed ln Σ vs calculated ln Σ, **1** (□), **2** (■), **3a** (○), **3b** (●), **3c** (△), and **4** (▲).

Table 1. Two-parameter descripition of solvent effects on organic and enzymatic reactions $\ln \Sigma = a[(\mathcal{E}-1)/(2\mathcal{E}+1)] + b\delta^2 + c$

Entry	Reactant	Selectivity Σ	Coefficient			Corr. coefft.	Contribution (%)		Number of solvent
			a	$10^{-2}b$	*c*		$a^{\%}$	$b^{\%}$	
1[a]	**1**	*endo*/*exo*	0.593	0.112	0.622	0.977	18	82	7
2[b]	**2**	*anti*/*syn*	−4.12	−0.152	2.92	0.938	64	36	8
3[c]	**3a**	*R*/*S*	3.81	−0.280	0.252	0.987	55	45	7
4[c]	**3b**	*R*/*S*	4.42	−0.128	−0.0548	0.924	76	24	7
5[c]	**3c**	*S*/*R*	1.53	−0.156	0.650	0.892	47	53	7
6[d]	**4**	*S*/*R*	6.64	0.177	−0.818	0.968	83	17	11

[a]Ref. 3. [b]Ref. 4. [c]Present study. [d]Ref. 2g.

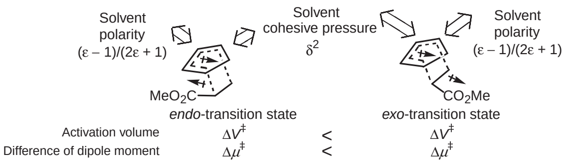


Figure 2. Model of solvent effect on the transition state of Diels–Alder reaction.

trated in Figure 1. Although the absolute values of coefficients of unnormalized parameters are not used for evaluation of the difference of selectivity, the sign and contribution are informative to expect and evaluate the influence of solvent on the selectivity in organic reactions.

The solvent effect of the *endo*/*exo* selectivity of product $\mathbf{1_{DA}}$ in the Diels–Alder reaction of cyclopentadiene **1** with methyl acrylate (Entry 1)[3] showed a good linearity ($r = 0.977$). The positive sign of coefficient for δ^2 suggests that the larger the solvent cohesive pressure become, the higher the *endo* selectivity. The contribution of cohesive pressure factor ($b^{\%}$) for **1** is 82%. According to the free volume model,[8d,9] the coefficient "b" and contribution "$b^{\%}$" for δ^2 would reflect the activation volume ($\Delta V^{\ddagger}$).[1a,9] The large contribution of δ^2 is not inconsistent with the relatively large activation volume and the smaller $\Delta V^{\ddagger}$ of the *endo*-transition state than that of the *exo*-one in the Diels–Alder reaction as shown in Figure 2.[1a,9,10] Furthermore, the relatively small contribution (18%) of polar parameter must result from the concerted mechanism.

The solvent effect of *anti*/*syn* selectivity of product $\mathbf{2_2}$ in the [2 + 2]photocycloaddition of **2** also showed a good linearity (Entry 2). The contribution of polar factor and cohesive factor was 64 and 36%, respectively. The polarity at the transition state seems to affect the solvent effect on *anti*/*syn* selectivity more than the free volume of transition state. The sign of coefficient of polarity factor is understandable in terms of the difference of dipole moment between the *anti*- and *syn*-transition state.

In **3a** (Entry 3), the negative coefficient for δ^2 suggests that the lower the cohesive pressure of solvent is, the higher the *R*-selectivity. The contribution of polar ($a^{\%}$) and cohesive pressure factors ($b^{\%}$) to the solvent effect for **3a** is 55 and 45%, respectively. In **3b** and **3c**, the contribution for the two parameters was almost similar to that of **3a** (Entries 4 and 5). The hydrolysis of **4** showed the positive sign of coefficient and the large contribution (83%) for the polar parameter (Entry 6). It can be considered that the polar factor of solvent mainly affects the selectivity in the enzymatic asymmetrization.

The selectivity ($\ln \Sigma$) relates to the free energy difference (difference in the stability) at the transition state ($\Delta\Delta G^{\ddagger}$) or structure in the stereo-determining transition state according the Curtin–Hammett principle as described above. Thus, it can be explained that the difference of structural fluctuation or conformational changing of enzyme at the transition state due to the induced-fit process.[8] The dependence of δ^2 would relate the difference of free volume at the enantio-determining step in the enzymatic reaction.[8d,9] The sign of coefficient "b" and the contribution "$b^{\%}$" would reflect the conformational mobility or the activation volume ($\Delta V^{\ddagger}$) of external regions of protein of the active sites in the transition states of the *R*- or *S*-enantiomer in consideration of the relation between the free volume of solute and the cohesive pressure δ^2 of solvent as shown in Figure 3.[1a]

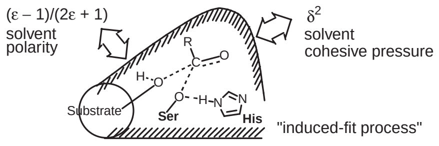


Figure 3. Model of solvent effect on the transition state of enzymatic reaction.

The present analysis by means of the complementary parameters treatment must be informative to expect and evaluate the influence of solvent on the other selectivity in chemical and enzymatic reactions.

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$$a' = |a|\left(\frac{\sum_{i=1}^{n}\{[(\varepsilon-1)/(2\varepsilon+1)]_i - \overline{[(\varepsilon-1)/(2\varepsilon+1)]}\}^2}{\sum_{i=1}^{n}(\ln \Sigma_i - \overline{\ln \Sigma})^2}\right)^{1/2};$$

$$b' = |b|\left(\frac{\sum_{i=1}^{n}\{\delta^2{}_i - \overline{\delta^2}\}^2}{\sum_{i=1}^{n}(\ln \Sigma_i - \overline{\ln \Sigma})^2}\right)^{1/2}$$

$$a^{\%} = 100a'/(a'+b');\ b^{\%} = 100b'/(a'+b')$$

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