

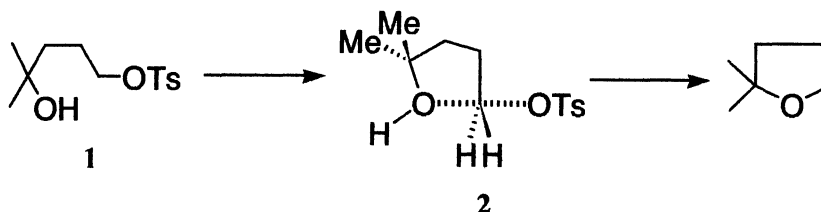
Cyclization of 4-Hydroxy-4-methyl-1-pentyl p-Toluenesulfonate as a Model to Evaluate Inherent Medium Effect on S_N2 Solvolysis

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Solvent effect on the cyclization of 4-hydroxy-4-methyl-1-pentyl p-toluenesulfonate, a mechanistic equivalent to the S_N2 solvolysis, was successfully analyzed by the Taft LSER equation as $\log k = 3.2\pi^* + 1.4\alpha + 1.9\beta - 8.36$, indicating that three independent factors are operative, i.e., solvent polarity and H-bond donor ability which promote ionization, and H-bond acceptor ability which enhances nucleophilicity of the internal OH group.

Solvent effect on S_N2 solvolysis can be analyzed by the extended Winstein equation (Eq. 1) as a linear combination of two solvent parameters, solvent ionizing power Y and solvent nucleophilicity N .^{1,2)} This analysis, however, does not directly lead us to estimate pure medium effect on bond-breaking and bond-forming processes involved in the transition state of the S_N2 solvolysis because the observed solvent effect is not free from concentration of nucleophilic solvents.

$$\log k/k^0 = mY + lN \quad (1)$$



In order to estimate pure medium effect, we selected cyclization of 4-hydroxy-4-methyl-1-pentyl tosylate (=p-toluenesulfonate) (1). The ester cleanly underwent the cyclization even in nucleophilic solvents including methanol, ethanol, 2,2,2-trifluoroethanol (TFE), and aq. acetone as well as in inert solvents like acetone and acetonitrile; we could not detect the

Table 1. Rate constants for cyclization of **1** at 25.0 ± 0.05 °C

Solvent ^{a)}	$10^5 k/s^{-1}$	Solvent ^{a)}	$10^5 k/s^{-1}$	Solvent ^{a)}	$10^5 k/s^{-1}$
H ₂ O	111	80A	11.8	TFE	12.0
20A	76.2	30E	59.8	97T ^{b)}	12.9
30A	51.8	50E	34.9	80T	19.0
40A	44.6	80E	20.6	HCO ₂ H	13.5
50A	30.5	EtOH	9.03	AcOH	1.49
60A	22.8	MeOH	9.47	MeCN	0.938
70A	16.0	i-PrOH	11.0	Me ₂ CO	0.639

a) A: acetone/water, E: ethanol/water, T: 2,2,2-trifluoroethanol (TFE)/water mixtures by volume. b) 97/3 (w/w) TFE/water mixture.

formation of solvolysis products under buffered or unbuffered reaction conditions indicative of pronounced intramolecular reactivity. The first-order rate constant for the cyclization in 97% aq. TFE (Table 1)³⁾ was $1.29 \times 10^{-4} s^{-1}$ at 25 °C which was estimated to be 1.50×10^4 times greater than the solvolysis rate of methyl tosylate in the same solvent⁴⁾ suggesting strong anchimeric assistance by the 4-hydroxy group, as in the ionization of 4-methoxyalkyl derivatives.⁵⁾ The cyclization must proceed via the transition state **2** the structural feature of which is identical to the S_N2 solvolysis. In this case, the reaction is unimolecular and hence we can measure pure medium effect on the bond-breaking and bond-forming processes involved in S_N2 displacement of alkyl tosylate with neutral oxygen nucleophiles.

Figure 1 shows a plot of $\log k$ vs. solvent ionizing power Y_{OTs} ²⁾ for the cyclization in various solvents. Interestingly, despite the

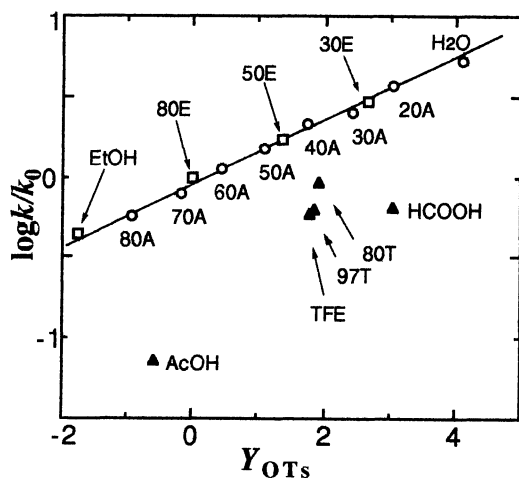
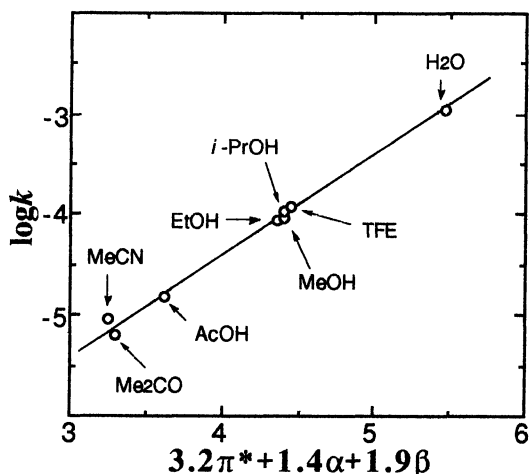
Fig. 1. Plot of $\log k / k_0$ vs. Y_{OTs} .

Fig. 2. Correlation with Taft parameters.

Table 2. Analysis of solvent effect on the cyclization of **1**

Parameters	Correlation	n	r
E_T^N a)	$\log k = 2.9E_T^N - 6.18$	8 ^{e)}	0.85
Y_{OTs}, N_{OTs} b)	$\log k_{rel} = 0.24Y_{OTs} + 0.30N_{OTs}$	18 ^{f)}	0.95
A_j, B_j c)	$\log k = 1.9A_j + 1.3B_j - 6.26$	12 ^{g)}	0.77
π^*, α, β d)	$\log k = 3.2\pi^* + 1.4\alpha + 1.9\beta - 8.36$	8 ^{e)}	0.996

a) Ref. 7. b) Ref. 2. c) Ref. 8. d) Ref. 9. e) Solvent set A: H₂O, MeOH, EtOH, i-PrOH, TFE, AcOH, MeCN, Me₂CO. f) Aq. acetone, aq. ethanol, aq. TFE, MeOH, AcOH, and HCO₂H. g) 80E, 50E, 80A, 70A, and HCO₂H in addition to the solvent set A.

unimolecular process, the cyclization shows a striking resemblance in response to the solvent ionizing power to the S_N2 solvolysis of methyl tosylate. Aq. acetone exhibits a linear response to Y_{OTs} with a slope (m) of 0.20, while ethanol and 80% aq. ethanol slightly deviate upward but TFE, acetic acid, and formic acid markedly deviate downward from the aq. acetone line as if the cyclization involved nucleophilic solvent assistance; the application of Eq. 1 gave, in fact, a fairly improved correlation (m=0.24 and l=0.30 for 18 solvents; correlation coefficient r=0.95). Actually, however, **1** did not undergo intermolecular reactions; so the apparent dependence on the solvent nucleophilicity should be attributed to the specific solvation of the 4-hydroxy group indicative of importance of the medium effect on the bond-forming process. Such specific interaction changes nucleophilicity of the internal alcohol; the downward deviations for TFE and acids suggest that the nucleophilicity of the 4-OH group is significantly lower in these solvents than in aq. acetone.

A linear response of acetone/water binary mixtures covering a wide range of Y_{OTs} scale clearly indicates that the nucleophilicity of the internal OH group does not change with solvent polarity. The m value of 0.20 represents the extent of ionization of the leaving group in the transition state **2** and this value provides a reasonable estimate of the inherent dependence on the solvent ionizing power for the S_N2 solvolysis of alkyl tosylates.

It is worth noting the fact that the nucleophilicity of the internal alcohol of **1** does change with solvent not because of change in solvent polarity but because of solvent-hydroxy group interactions. Since such solvent-hydroxy group interactions can be regarded as a model for solvent-nucleophilic solvent interactions, the present result provides an experimental support for the idea that the solvent nucleophilicity varies

with solvent composition through specific solvent-nucleophilic solvent interactions, which otherwise is not readily verified.⁶⁾

A wide range of solvents listed in Table 1 allows us to discuss the origin of the medium effect on the bond-forming and bond-breaking processes in the transition state 2. Table 2 shows results of correlation of total 21 nucleophilic and non-nucleophilic solvents with various solvent parameters. The solvent effect on the cyclization did not exhibit a linear response to any single parameters available including the Kirkwood parameter $(\epsilon-1)/(2\epsilon+1)$ and $E_T^{N7)}$; the Swain two-parameter treatment⁸⁾ did not give a good linear correlation either. The Taft LSER treatment⁹⁾ provided a successful result expressed by Eq. 2 where π^* , α , and β are indices of solvent polarity, solvent hydrogen-bond donor (HBD) acidity, and hydrogen-bond acceptor (HBA) basicity, respectively.

$$\log k = 3.2\pi^* + 1.4\alpha + 1.9\beta - 8.36 \quad (2)$$

It is now clear that solvent polarity and two types of specific interactions are operative with comparable importance to each other. Since the first two terms on the right of Eq. 2 are associated mainly with the bond-breaking process,⁹⁾ the major factor which changes the nucleophilicity of the internal hydroxy group is the solvent HBA basicity rather than the HBD interaction.

References

- 1) S. Winstein, E. Grunwald, and H. W. Jones, *J. Am. Chem. Soc.*, **73**, 2700 (1951); S. Winstein, A. H. Fainberg, and E. Grunwald, *ibid.*, **79**, 4146 (1957).
- 2) T. W. Bentley, F. L. Schadt, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 992 (1972); **98**, 7667 (1976).
- 3) The rates of the cyclization were followed spectrophotometrically at 25 ± 0.05 °C ($r > 0.99995$ for most cases).
- 4) D. J. Raber, M. D. Dukes, and J. Gregory, *Tetrahedron Lett.*, **1974**, 667.
- 5) E. L. Allred and S. Winstein, *J. Am. Chem. Soc.*, **89**, 3991 (1967).
- 6) Y. Karton and A. Pross, *J. Chem. Soc., Perkin Trans. 2*, **1978**, 595; J. Kaspi and Z. Rappoport, *J. Am. Chem. Soc.*, **102**, 3829 (1980).
- 7) C. Reichard, "Solvent and Solvent Effects in Organic Chemistry," VCH, Weinheim, Germany (1988).
- 8) C. G. Swain, M. S. Swain, A. L. Powell, and S. Alunni, *J. Am. Chem. Soc.*, **105**, 502 (1983).
- 9) J. -L. M. Abboud, M. J. Kamlet, and R. W. Taft, *Progr. Phys. Org. Chem.*, **13**, 485 (1981); M. H. Abraham, R. M. Doherty, M. J. Kamlet, J. M. Harris, and R. W. Taft, *J. Chem. Soc., Perkin Trans. 2*, **1987**, 1097.

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