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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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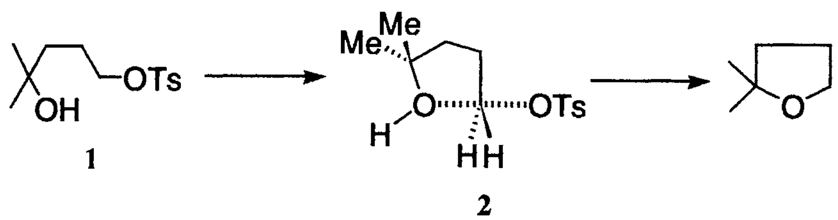
Solvent effect on the cyclization of 4-hydroxy-4-methyl-1-pentyl p-toluenesulfonate, a mechanistic equivalent to the S_N2 solvolysis, was successfully analyzed by the Taft LSER equation as log $k=3.2\pi^*+1.4\alpha+1.9\beta-8.36$, indicating that three independent factors are operative, i.e., solvent 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.

$$\log k/k^{o} = mY + lN \qquad (1)$$



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)]	$10^5k/s^{-1}$	Solvent[a)]	$10^5k/s^{-1}$	Solvent[a)]	$10^5k/s^{-1}$
H_2O	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_2H	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_2CO	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 1.29×10^{-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 solvent[4)] 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

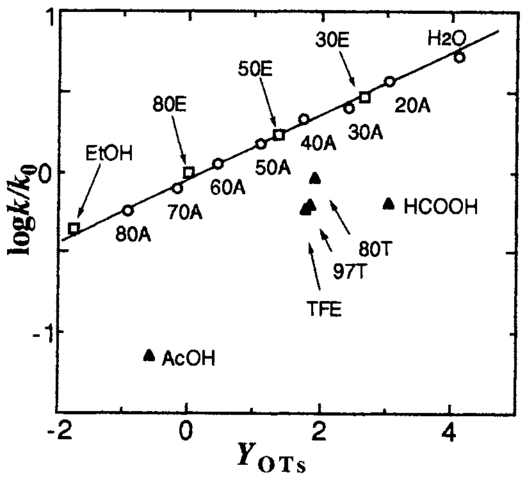


Fig. 1. Plot of $\log k / k_0$ vs. Y_{OTs}.

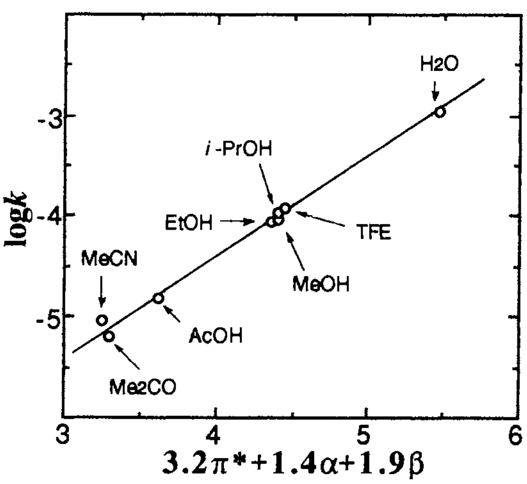


Fig. 2. Correlation with Taft parameters.

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: H_2O, MeOH, EtOH, i-PrOH, TFE, AcOH, MeCN, Me_2CO. f) Aq. acetone, aq. ethanol, aq. TFE, MeOH, AcOH, and HCO_2H. g) 80E, 50E, 80A, 70A, and HCO_2H 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 rang 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^N[7]; the Swain two-parameter treatment[8] did not give a good linear correlation either. The Taft LSER treatment[9] 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.

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

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.

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