Kinetics of Neutral Hydrolysis of Two 1-Acyl-1,2,4-triazoles in Binary Aqueous Mixtures: A Critique of the Evans and Polanyi Proposals Concerning Isochoric Activation Parameters

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Abstract: Kinetic data are reported for hydrolysis of two 1-acyl-1,2,4-triazoles in water and two isodielectric mixtures which belong to different classes of aqueous mixtures. Trends in isothermal and isobaric activation parameters are examined in light of both solvent–solvent and solute–solvent interactions. Comments by Evans and Polanyi concerning an isochoric constraint are considered. Attention is drawn to the difficulties of satisfying the original criteria and to the possibility of using the internal pressure of the solvent as a way of satisfying in part the requirements of the Evans–Polanyi formalism.

Although the rates of chemical reactions in aqueous solutions are controlled to a considerable degree by the quite characteristic properties of water,[1] identifying the role played by this solvent is not a trivial task.[1a,2] In terms of transition-state theory,[3] the rate constant for reaction at fixed temperature and pressure is expressed in terms of a Gibbs function of activation, $\Delta^{*}G^{\ominus}$ which is notoriously insensitive to subtle changes in the various factors which determine the energetics of activation.[1a] However, this theory[3] shows how the dependence of rate constants on temperature can be analyzed[4] to yield an isobaric enthalpy of activation, $\Delta^{*}H^{\ominus}$. Similarly the dependence of rate constants on pressure at constant temperature yields the isothermal volume of activation,[4,5] $\Delta^{*}V^{\ominus}$. The effects are also examined of adding organic cosolvents on rate constants and derived isothermal and isobaric activation parameters. The dependence of these activation parameters on solvent composition is often complicated because each cosolvent exerts a characteristic modification of water–water interactions.[2,6] At the same time, the dielectric properties change when a cosolvent is added. In the study reported here, we counter the latter point by examining the kinetics of reaction in isodielectric aqueous mixtures. Further, we have selected two organic cosolvents, *tert*-butyl alcohol and acetonitrile, in light of the excess molar thermodynamic properties of mixing for their aqueous mixtures (see below) which show that these cosolvents have quite different effects on water–water interactions. The kinetics of reaction are reported for the neutral hydrolysis of the two 1-acyl-1,2,4-triazoles **1** and **2** (Scheme I). These activated amides react in the pH region between ca. 3 and 5 by a mechanism involving water-catalyzed nucleophilic attack of water at the carbonyl group via a transition state in which three protons are in flight.[7,8] Based on Rekker's hydrophobic fragmental constants,[9] the difference in hydrophobicity between **1** and **2** corresponds to 5.5 methylene moieties.

Substrates **1** and **2** provide valuable contrasts in their effects on neighboring water–water interactions in aqueous solutions. We report rate constants *k* and derived activation parameters calculated from the dependence of *k* on both *T* and *P*. This simple statement masks a controversy. By changing the temperature (at fixed *P*) and the pressure (at fixed *T*), the solvent is effectively changed. Evans and Polanyi commented[10] along these lines in a paper published in 1935. The major thrust of their paper was directed toward the calculation of volumes of activation from kinetic data. In a penultimate section, Evans and Polanyi[10] raised the possibility of measuring the dependence of rate constant on temperature at constant volume (i.e., isochoric conditions) rather than at constant pressure. This important suggestion was ignored until the 1960s when, largely at the prompting of Whalley,[11,12] the proposal was reexamined. The importance of this topic is not

confined to chemical kinetics. Rather the subject has wider ramifications,[13] extending to such diverse fields as electron spin resonance spectra,[14] ionic conductances,[15,16] viscosities,[17] and dielectric relaxation.[18] In this paper, we subject the methodology for analysis of kinetic data to close scrutiny prompted by the comments of Evans and Polanyi.[10]

The importance of volumetric considerations to the framework of these discussions highlights advantages of using aqueous systems as test beds for a theory. That water has a minimum in molar volume near 277 K (at ambient pressure) is well-known but, as Kell points out,[1b] the volumetric properties of water are distinctive over the complete *P–T* range. Furthermore, the volumetric properties of aqueous mixtures[1c,19,20] often stand apart from other mixtures.[1c] In general terms, it is convenient to classify[1d,21] aqueous mixtures in terms of their excess molar thermodynamic properties of mixing X_m^E (where $X = G, H, S, V, C_P$, etc.) and the partial molar properties of the nonaqueous component, X_2.

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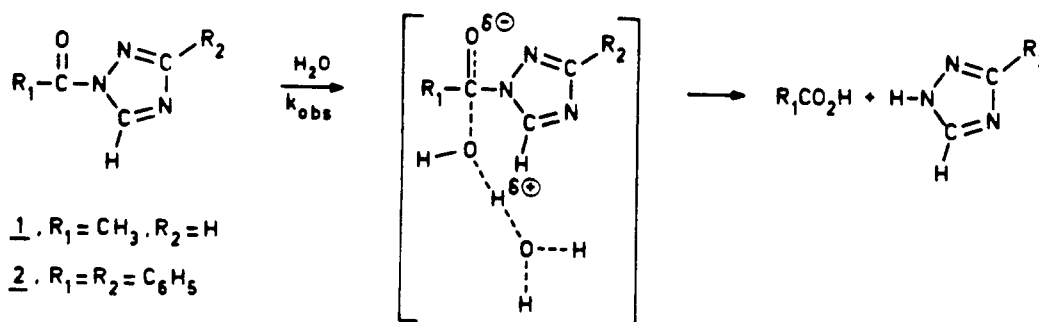(19) Nakegawa, M.; Inubushi, H.; Moriyoshi, T. *J. Chem. Thermodyn.* **1981**, *13*, 171.

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Scheme I

$\underline{1} \cdot R_1 = CH_3, R_2 = H$

$\underline{2} \cdot R_1 = R_2 = C_6H_5$

For typically aqueous (TA) mixtures, $G_m^E > 0$ but $|TS_m^E| > |H_m^E|$, the mixing being dominated by the entropy of mixing. *tert*-Butyl alcohol belongs to this class,[1d,6,21,22] and all evidence points to a general enhancement of water–water interactions at low alcohol mole fractions. The latter is also indicated[1d] by the minimum in V_2 at low n_2. In contrast, acetonitrile–water mixtures[23–26] are classed as typically nonaqueous (TNA) because $|H_m^E| > |TS_m^E|$ although G_m^E is also >0. Moreover, V_2 for acetonitrile shows no minimum at low n_2. All evidence suggests[1e,6,27] that acetonitrile exerts a structure-breaking influence on water.

Here we report the kinetics of hydrolysis for **1** and **2** in water–*tert*-butyl alcohol at a mole fraction ($n_{H_2O} = 0.95$) where hydrophobic interactions play an important role and in an acetonitrile–water mixture of $n_{H_2O} = 0.85$, these mixtures being isodielectric[1f,28] with $\epsilon_r = 66$ at 298 K. Isobaric activation parameters and volumes of activation are discussed in terms of specific intermolecular interactions. We extend the analysis to a consideration of isochoric activation parameters along the lines suggested by Evans and Polanyi[10] and comment on the application of isochoric parameters to an understanding of solvent effects.

Experimental Section

Materials. The substrates **1** and **2** were prepared by a standard procedure involving acylation of the corresponding 1,2,4-triazole and 3-phenyl-1,2,4-triazole, respectively.[29,30] **1**, mp 35.3–37.7 °C [lit.[30] 36.0–37.0 °C]; **2**, mp 78.6–79.9 °C [lit.[30] 83.4–86.0 °C]. Acetonitrile (Aldrich), acetonitrile-d_3 (Merck), *tert*-butyl alcohol (Merck), and deuterium oxide (Merck) were the best grade available and were used as such. Water was demineralized and distilled twice in an all-quartz distillation unit. All solutions were made up by mass and contained 10^{-3} mol kg^{-1} of HCl in order to prevent hydroxide-ion catalysis of the hydrolysis of **1** and **2**.

Kinetic Measurements. Pseudo-first-order rate constants, k_{obsd}, for the neutral hydrolysis of **1** and **2** under atmospheric pressure were determined between 22 and 40 °C by following the disappearance of **1** (at 222 nm) or **2** (at 273 nm) with a Cary 210 spectrophotometer equipped with a thermostated cell compartment. All reactions were followed to completion. In a typical experiment, 20 μL of a stock solution in MeCN containing 10^{-2} M **1** or **2** was added to 3 mL of the reaction medium in the cell.

The hydrolysis reactions under pressures up to 2000 bar (200 MPa) were followed spectrophotometrically at 25 °C in a Nova Swiss high-pressure flow cell (provided with sapphire windows, path length 1.0 cm, volume ca. 2 mL) which was built in a Zeiss PMQII spectrophotometer.[31,32] The optical cell was part of a high-pressure system in which

Table I. Pseudo-First-Order Rate Constants[a] for the Neutral Hydrolysis of **1** and **2** in Different Reaction Media at 25 °C

		1		**2**	
solvent	ϵ_r[b]	$10^4 k_{obsd}$, s^{-1}	k_{rel}[c]	$10^4 k_{obsd}$, s^{-1}	k_{rel}[c]
H$_2$O	78.5	20.9	1	12.4	1
t-BuOH–H$_2$O, n_{H_2O} = 0.975	72.2			7.99	0.644
t-BuOH–H$_2$O, n_{H_2O} = 0.970	71.0	16.2	0.775		
t-BuOH–H$_2$O, n_{H_2O} = 0.950	66.0	12.9	0.617	3.38	0.273
t-BuOH–H$_2$O, n_{H_2O} = 0.925	59.7			1.65	0.133
t-BuOH–H$_2$O, n_{H_2O} = 0.920	58.4	10.5	0.502		
MeCN–H$_2$O, n_{H_2O} = 0.920	72.2	8.77	0.420	2.90	0.234
MeCN–H$_2$O, n_{H_2O} = 0.850	66.1	4.37	0.209	0.907	0.073
MeCN–H$_2$O, n_{H_2O} = 0.770	60.0	2.05	0.098	0.417	0.034

[a] Rate constants in *t*-BuOH–H$_2$O taken from ref 35. [b] Relative dielectric constant.[1f,28] [c] $k_{rel} = k_{obsd}/k_{obsd}^{H_2O}$.

pressures were generated with two manually driven compression pistons. The pressures were monitored with a pressure transducer (range 0–4000 bar, accuracy 6 bar). During a reaction, the pressure was constant to within 10 bar. Temperature stabilization was obtained by circulating water (25.00 ± 0.05 °C) through a copper cylinder surrounding the high-pressure flow cell. In a typical experiment, 100 mL of the reaction medium was circulated through the high-pressure system by means of a membrane pump (Prominent Electronic A1002) for 15 min. The reaction was initiated by adding 20 mL of solvent (containing 400 μL of the stock solution of **1** or **2** in acetonitrile) to the medium under continuous pumping. As soon as the absorbance reached a maximum value (after ca. 1–2 min), the system was closed and raised to the desired pressure. Minor corrections in the pressure were then applied to correct for the temperature rise as a result of compression. All reactions (done at least in triplicate) were followed to about 95% completion.

Kinetic Analysis. k_{obsd} was calculated from absorbances A obtained during the first three half-lives. At atmospheric pressure, a stable A^∞ was obtained and k_{obsd} was reproducible to within 1%. At high pressures, A^∞ was not completely stable, showing a small irreproducible drift. Therefore, A^∞ was adjusted on the basis of the absorbance readings over the first three half-lives with a nonlinear least-squares method.[33] Adjustments up to 10% were, in some cases, necessary. k_{obsd} obtained in this manner was reproducible to within 3% for water and *t*-BuOH–H$_2$O (n_{H_2O} = 0.95) and to within 7% for MeCN–H$_2$O (n_{H_2O} = 0.85).

NMR Measurements. ^{1}H chemical shifts of **1**, (200 MHz Nicolet FT200) are given in hertz (error ±0.5 Hz) downfield from the standard (either tetramethylsilane or sodium 3,3,3-trimethylpropanesulfonate, both give the same values).

Results and Analysis

Pseudo-first-order rate constants for the neutral hydrolysis of **1** and **2** in water, *t*-BuOH–H$_2$O, and MeCN–H$_2$O (at 25 °C and atmospheric pressure) are listed in Table I. The assumption

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implicit in the analysis is that for a given substrate in a particular solvent, the quantity ln $[k/T]$ is defined by the independent variables, T and P. {We use the ratio k/T rather than k because we develop the analysis in terms of transition-state theory.[3]} The relationship is expressed

$$\ln [k/T] = \ln [k/T][T;P] \qquad (1)$$

The general differential of eq 1 is

$$d \ln [k/T] = \left[\frac{\partial \ln [k/T]}{\partial T}\right]_P dT + \left[\frac{\partial \ln [k/T]}{\partial P}\right]_T dP \qquad (2)$$

where the enthalpy of activation is related to the first differential and the volume of activation to the second, eq 3 and 4, respectively.

$$\left[\frac{\partial \ln [k/T]}{\partial T}\right]_P = \frac{\Delta^{\ddagger}H^{\ominus}(\text{sln}; T;P)}{RT^2} \qquad (3)$$

$$\left[\frac{\partial \ln [k/T]}{\partial P}\right]_T = \frac{-\Delta^{\ddagger}V^{\ominus}(\text{sln}; T;P)}{RT} \qquad (4)$$

Equations 3 and 4 have their origins in equilibrium thermodynamics. For a chemical equilibrium at fixed T and P, a closed system is at a minimum in the Gibbs function G where the sum of the chemical potentials of the reactants equals the corresponding sum for the products. Carrying over this idea to chemical reactions using transition-state theory[3] yields the following condition for a first-order unimolecular reaction (r = reactant, ‡ = transition state)

$$\mu_r^{\text{eq}}(\text{sln}; T;P) = \mu_{\ddagger}^{\text{eq}}(\text{sln}; T;P) \qquad (5)$$

These equilibrium chemical potentials are related to the corresponding chemical potentials in standard states and the equilibrium concentration of each substance in solution.[34] For example, $\mu_{\ddagger}^{\ominus}(\text{sln}; T;P)$ is the chemical potential of the transiton state in a dilute ideal solution where $c_{\ddagger}$ is unity at the same T and P. Then $\Delta^{\ddagger}H^{\ominus}(\text{sln}; T;P)$ and $\Delta^{\ddagger}V^{\ominus}(\text{sln}; T;P)$ are the corresponding differences in enthalpies and volumes of reactants and transition states in reference solution states in the same solvent at the same T and P.

In calculating $\Delta^{\ddagger}H^{\ominus}(\text{sln}; T;P)$, the dependence of ln k_{obsd} on T was fitted to eq 6 with a linear least-squares analysis[35]

$$\ln (k_{\text{obsd}}/T) = b_1 + b_2/T \qquad (6)$$

where

$$\Delta^{\ddagger}G^{\ominus}(\text{sln}; T;P) = \Delta^{\ddagger}H^{\ominus}(\text{sln}; T;P) - T\Delta^{\ddagger}S^{\ominus}(\text{sln}; T;P) \qquad (7)$$

From the variety of methods[5,36-38] proposed for the calculation of $\Delta^{\ddagger}V^{\ominus}$ from kinetic data, we have chosen the procedure in which ln k_{obsd} is fitted to the quadratic eq 8. Despite possible drawbacks,[39] eq 8 has remarkable descriptive power and is simple to apply.[37]

$$\ln k_{\text{obsd}} = aP^2 + bP + c \qquad (8)$$

The outcome of the analysis is summarized in Table II for T = 298 K and P = 101325 N m^{-2}. We stress that in the column headed $\Delta^{\ddagger}H^{\ominus}(\text{sln}; T;P)$, the derived quantities refer to systems at the same T and P. Therefore, Table II summarizes quantities which are intrinsic[40] to each system. The variation arises from the dependence on solvent of the partial molar properties in their

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Table II. Isobaric Activation Parameters and Volumes of Activation for the Neutral Hydrolysis of **1** and **2** in Different Reaction Media at 25 °C[a]

compd	solvent	$\Delta^{\ddagger}H^{\ominus}$, kJ mol^{-1}	$\Delta^{\ddagger}S^{\ominus}$, J mol^{-1} K^{-1}	$\Delta^{\ddagger}V^{\ominus}$, 10^{-6} m^3 mol^{-1}
1	H$_2$O	43.1 ± 1.2[b]	−150 ± 4[b]	−17.9 ± 0.8
1	*t*-BuOH-H$_2$O, $n_{\text{H}_2\text{O}}$ = 0.95	41.8 ± 1.2[b]	−159 ± 4[b]	−17.5 ± 0.9
1	MeCN-H$_2$O, $n_{\text{H}_2\text{O}}$ = 0.85	41.4 ± 0.3	−170 ± 1	−20.5 ± 1.2
2	H$_2$O	46.4 ± 1.2[b]	−146 ± 4[b]	−15.8 ± 0.7
2	*t*-BuOH-H$_2$O, $n_{\text{H}_2\text{O}}$ = 0.95	37.6 ± 1.2[b]	−184 ± 4[b]	−30.3 ± 0.5
2	MeCN-H$_2$O, $n_{\text{H}_2\text{O}}$ = 0.85	53.1 ± 0.3	−144 ± 1	−28.1 ± 2.4

[a] Errors calculated from the standard deviation. [b] Taken from ref 35.

standard solution states of initial and transition states. The (equilibrium) molar volume V_m of each solvent, at fixed composition, is also a function of T and P (eq 9). In other words, at

$$V_m = V_m[T;P] \qquad (9)$$

a given T and P, the molar volume of the solvent (in our discussion equivalent to the solution volume) is defined. We turn attention at this stage to isochoric parameters. The thrust of our argument is developed by concentrating attention on eq 1 and 9. Consider a particular temperature θ and pressure π. According to eq 9, there exists at equilibrium a molar volume for a given solvent $V_m(\theta;\pi)$ and according to eq 1 a rate constant $k(\theta;\pi)$. Following a change in temperature from θ to $\theta + \Delta\theta$ at pressure π, the molar volume is $V_m(\theta + \Delta\theta;\pi)$. Consider a change in pressure from π to $\pi + \Delta\pi'$ where, by definition,

$$V_m(\theta;\pi) = V_m(\theta + \Delta\theta;\pi + \Delta\pi') \qquad (10)$$

Equation 10 is an isochoric condition where $\Delta\pi'$ is characteristic of the solvent. Therefore, $k(\theta,\pi)$ and $k(\theta + \Delta\theta;\pi + \pi')$ are rate constants for chemical reaction under conditions where the molar volumes of the solvent are equal. We anticipate that $\Delta\pi'$ will be different for each solvent. In effect, eq 1 describes a three dimensional plot in which a surface represents the dependence of ln (k/T) on T and P, graph A. Equation 9 describes the corresponding plot, graph B, for the dependence of V_m, the molar volume of the solvent, on T and P. Then, at θ = 298.15 K and π = 101325 N m^{-2}, we explore the dependence of ln (k/T) on T along a vector which, when transposed to graph B, conforms to the isochoric condition (cf. eq 10). Alternatively we explore the dependence of ln (k/T) on P in graph A along a vector which in graph B conforms again to the isochoric condition, cf. eq 10. These two dependences are calculated with a calculus operation; eq 11 and 12. The condition, constant V_m, attached to the partial

$$\left[\frac{\partial \ln (k/T)}{\partial T}\right]_{V_m} = \left[\frac{\partial \ln (k/T)}{\partial T}\right]_P - \left[\frac{\partial V_m}{\partial T}\right]_P \left[\frac{\partial P}{\partial V_m}\right]_T \left[\frac{\partial \ln (k/T)}{\partial P}\right]_T \qquad (11)$$

$$\left[\frac{\partial \ln (k/T)}{\partial P}\right]_{V_m} = \left[\frac{\partial \ln (k/T)}{\partial P}\right]_T - \left[\frac{\partial V_m}{\partial P}\right]_T \left[\frac{\partial T}{\partial V_m}\right]_P \left[\frac{\partial \ln (k/T)}{\partial T}\right]_P \qquad (12)$$

derivatives on the left-hand side of eq 11 and 12 refers to graph B and therefore is extrinsic to the kinetic parameters described in graph A.

But

$$\alpha = (1/V_m)(\partial V_m/\partial T)_P \qquad (13)$$

and

$$\kappa_T = -(1/V_m)(\partial V_m/\partial P)_T \qquad (14)$$

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Table III. Isochoric Activation Parameters[a] for the Neutral Hydrolysis of **1** and **2** in *t*-BuOH–H_2O and MeCN–H_2O at 25 °C

compd	solvent	$10^{-8} \pi_i$,[b] N m^{-2}	$\Delta^{\ddagger}\Psi^{\ominus}(V_m)$, kJ mol^{-1}
1	H_2O	1.716	46.2 ± 1.3
1	*t*-BuOH–H_2O, $n_{H_2O} = 0.95$	3.911	48.6 ± 1.6
1	MeCN–H_2O, $n_{H_2O} = 0.85$	4.575	50.8 ± 0.8
2	H_2O	1.716	49.1 ± 1.3
2	*t*-BuOH–H_2O, $n_{H_2O} = 0.95$	3.911	49.5 ± 1.4
2	MeCN–H_2O, $n_{H_2O} = 0.85$	4.575	66.0 ± 1.4

[a] Errors calculated from the errors in the isobaric activation parameters and in $\Delta^{\ddagger}V^{\ominus}$. [b] Internal pressures taken from ref 42 and 43.

where α is the equilibrium expansivity and κ_T is the equilibrium compressibility of the solvent. We define

$$\left[\frac{\partial \ln (k/T)}{\partial T}\right]_{V_m} = \frac{\Delta^{\ddagger}\Psi(V_m)^{\ominus}}{RT^2} \qquad (15)$$

and

$$\left[\frac{\partial \ln (k/T)}{\partial P}\right]_{V_m} = \frac{-\Delta^{\ddagger}\Phi(V_m)^{\ominus}}{RT} \qquad (16)$$

Hence, with eq 3, 4, and 11–16,

$$\Delta^{\ddagger}\psi(V_m)^{\ominus} = \Delta^{\ddagger}H^{\ominus} - (\alpha/\kappa_T)T\Delta^{\ddagger}V^{\ominus} \qquad (17)$$

and

$$\Delta^{\ddagger}\Phi(V_m)^{\ominus} = \Delta^{\ddagger}V^{\ominus} - (\kappa_T/\alpha T)\Delta^{\ddagger}H^{\ominus} \qquad (18)$$

where $\Delta^{\ddagger}\psi(V_m)^{\ominus}$ is expressed in J mol^{-1} and $\Delta^{\ddagger}\Phi(V_m)^{\ominus}$ in m^3 mol^{-1}. The internal pressure[41] of a solvent is given by

$$\Pi_i = (\alpha T/\kappa_T) - P \approx \alpha T/\kappa_T \qquad (19)$$

Hence, from eq 17 and 18, we obtain

$$\Delta^{\ddagger}\psi(V_m) = -\Pi_i\Delta^{\ddagger}\Phi(V_m)^{\ominus} \qquad (20)$$

Equation 20 has a form reminescent of the classic thermodynamic equation, d$w = -P$ dV.

Internal pressures[42,43] Π_i and derived $\Delta^{\ddagger}\psi(V_m)^{\ominus}$ parameters are summarized in Table III. For each entry in Table III, the molar volume of the solvent at 298 K and 1 atm is characteristic of the solvent. In other words, the isochoric condition is not global in Table III but each $\Delta^{\ddagger}\psi(V_m)^{\ominus}$ is calculated for a local isochoric condition in a solvent system. In principle, it is possible to compare rate constants under a global isochoric condition, at temperatures and pressures where the molar volumes of all solvent systems are identical. However, in practice, the differences in T and P through a range of solvents are enormous as judged from the limited amount of data available.[19,44]

Discussion

Before we turn our attention to a discussion of isochoric activation parameters, we present an analysis of the kinetic data in terms of the isothermal/isobaric framework. In both the TA and TNA mixture, k_{obsd} decreases with increasing concentration of the organic cosolvent, the inhibition being most pronounced for substrate **2**. Isobaric activation parameters (Table II) reveal large compensatory changes in $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}S^{\ominus}$ for **2**, but not for **1**. This difference has been noted previously[35] for hydrolysis in *t*-BuOH–H_2O and has been explained in terms of the much larger hydrophobicity of **2** relative to that of **1**.

The negative $\Delta^{\ddagger}V^{\ominus}$ values for hydrolysis of **1** and **2** in water are in the expected range for pH-independent hydrolytic processes.[5]
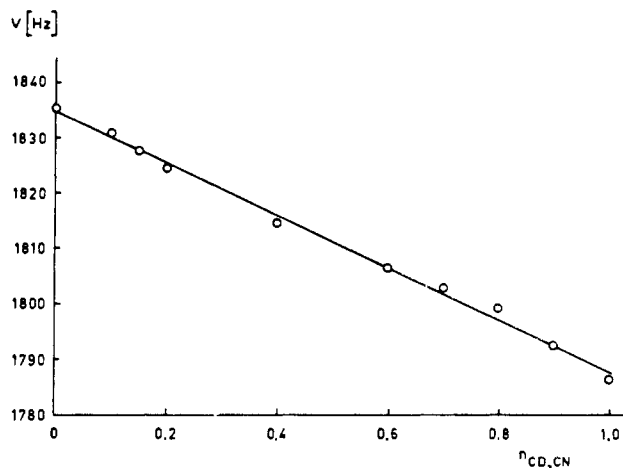

Figure 1. Plot of the chemical shift of the 5-proton in the 1,2,4-triazole ring of **1** vs. mole fraction of CD_3CN in CD_3CN–D_2O mixtures at 20 °C.

Again, the solvent effects on $\Delta^{\ddagger}V^{\ominus}$ are much larger for **2** than for **1**. We suggest that the hydrophilic substrate **1** is preferentially solvated by water molecules in *t*-BuOH–H_2O which will explain the hardly significant changes in $\Delta^{\ddagger}H^{\ominus}$, $\Delta^{\ddagger}S^{\ominus}$, and $\Delta^{\ddagger}V^{\ominus}$ on going from water to *t*-BuOH–H_2O at $n_{H_2O} = 0.95$. Modest changes in the activation parameters occur in MeCN–H_2O ($n_{H_2O} = 0.85$). Several reasons can be invoked to explain the somewhat larger effects in the TNA mixture: the higher mole fraction of MeCN and the higher dipole moment of the organic component (MeCN, $\mu = 3.44$ D; *t*-BuOH, $\mu = 1.66$ D). In addition, the smaller molar volume of MeCN (MeCN, $V_m = 52.2 \times 10^{-6}$ m^3 mol^{-1}; *t*-BuOH, $V_m = 94.0 \times 10^{-6}$ m^3 mol^{-1}) and the more rodlike shape of MeCN vs. the more spherical shape of *t*-BuOH also enhance the possibility of replacing water molecules in the solvation sphere of **1**. The absence of preferential solvation effects[45] in MeCN–H_2O is supported by ^{1}H NMR chemical shift measurements. Figure 1 shows the linear plot of the chemical shift of the 5-proton in the 1,2,4-triazole ring of **1** vs. mole fraction of CD_3CN in CD_3CN/D_2O at 20 °C. Unfortunately, chemical shift differences between D_2O and alcohol were too small to warrant measurements in TA alcohol–D_2O mixtures.

The solvent effects on the activation parameters are quite different for the hydrophobic substrate **2**. The changes in $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}S^{\ominus}$ upon going from water to *t*-BuOH–H_2O ($n_{H_2O} = 0.95$) are best reconcilable with initial state stabilization as a result of hydrophobic interactions[1a,35] between **2** and *t*-BuOH. Solubility measurements[35] using a model substrate fully substantiated this explanation. For hydrolysis in the TNA MeCN–H_2O mixture, however, there occur much smaller changes in $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}S^{\ominus}$, the rate retardation being caused by an increase of $\Delta^{\ddagger}H^{\ominus}$. This effect contrasts with the decrease of $\Delta^{\ddagger}H^{\ominus}$ in the TA mixture and is indicative for essentially different solvation effects. In MeCN–H_2O polar solute–solvent interactions dominate and the kinetic solvent effects reflect the reduced water content and polarity of the medium.[1a]

The changes in $\Delta^{\ddagger}V^{\ominus}$ for hydrolysis of **2** upon going from water to the TA and TNA mixtures are interesting on several counts. First of all, they are rather similar in magnitude but much larger for **2** than for **1**. Most likely, two effects play a role in *t*-BuOH–H_2O. Despite some controversy,[46] there is strong evidence that the volume contribution of hydrophobic interactions is positive with a value in the order of 1–2 cm^3 mol^{-1} per methylene group. These data have been obtained from suitable model processes such as dimerization of carboxylic acids[47] and micellization of am-

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phiphilic molecules.[48] The positive volume contribution is also consistent with the observation that the partial molar excess volume of an apolar solute decreases with increasing hydrophobic hydration.[1g] On the basis of this starting point and taking into account the loss of hydrophobicity going from the initial state to the transition state, the decrease of $\Delta^{\ddagger}V^{\ominus}$ in *t*-BuOH–H$_2$O ($n_{\text{H}_2\text{O}}$ = 0.95) is expected. However, the magnitude of the effect appears to be too large to be accounted for solely in terms of a decrease in hydrophobic interactions during the activation process. For example, the difference in $\Delta^{\ddagger}V^{\ominus}$ for neutral hydrolysis of **2** in water and *t*-BuOH–H$_2$O ($n_{\text{H}_2\text{O}}$ = 0.95) amounts to -14.5 ± 1.2 cm^3 mol^{-1}. The corresponding quantity for **1** is $+0.4 \pm 1.7$ cm^3 mol^{-1}. This difference between **2** and **1** is abnormally large even if complete allowance is made for the total difference in hydrophobicity between both substrates, which is equivalent to ca. 5.5 methylene moieties (vide supra). Thus, an additional effect must be present. We contend that increased electrostriction is the most likely possibility. The decreased polarity of the medium as well as preferential solvation of the initial state and of apolar parts of the transition state by *t*-BuOH both lead to negative contributions to $\Delta^{\ddagger}V^{\ominus}$ as expressed in the Drude–Nernst equations.[39]

In MeCN–H$_2$O ($n_{\text{H}_2\text{O}}$ = 0.85), where specific, polar solute–solvent interactions dominate solvation changes,[1f] $\Delta^{\ddagger}V^{\ominus}$ for hydrolysis of **2** is also strongly decreased. In this TNA solution, isodielectric with the *t*-BuOH–H$_2$O medium, the hydrophobic **2** fully experiences the decreased polarity of the solvent, leading to strongly enhanced electrostriction and a corresponding negative contribution to $\Delta^{\ddagger}V^{\ominus}$. Unfortunately, no ^{1}H NMR chemical shift measurements could be performed with **2** because of its low solubility in water-rich solvents.

The above analysis of isothermal and isobaric activation parameters prompts a reconsideration of "isochoric" parameters. If we had followed the procedures suggested by Whalley,[11,12] we would have written an equation along the following lines rather than, for example eq 15.

$$(\partial \ln (k/T)/\partial T)_V = \Delta^{\ddagger}U_V^{\ominus}/RT^2 \qquad (21)$$

Whalley and co-workers have used this formalism in their extensive kinetic studies.[49] The subscript *V* is ambiguous in that volume is an extensive property. For this reason we specified in eq 9–11 that the quantity of interest is the molar volume of the solvent (either a mixture or a pure liquid). The justification for eq 21 is the Gibbs–Helmholtz equation for the dependence of the Helmholtz function *F* on temperature; $(\partial F/\partial T)_V = -U/RT^2$. This is valid for processes at constant volume because *F* is the thermodynamic potential function for processes at constant *T* and *V*. Under these conditions, all spontaneous processes (e.g., chemical reactions) operate to lower the total *F* of a system. However, under the conditions employed in the present study (and as far as we can judge in those reported in ref 49), the reacting system is held at constant *T* and *P* such that all spontaneous processes operate to lower the *G* of a system. Moreover the standard states for derived activation parameters (e.g., $\Delta^{\ddagger}H^{\ominus}$) are defined for isobaric–isothermal conditions. In a collection of data comparable to that in Table III, there is no global isochoric condition, whereas for the data in Table II the constraints *T* = 298 K and *P* = 101 325 N m^{-2} (1 atm) apply to $\Delta^{\ddagger}H^{\ominus}$, $\Delta^{\ddagger}S^{\ominus}$, and $\Delta^{\ddagger}V^{\ominus}$. It is clear that the solvent dependence of $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}\psi(V_m)^{\ominus}$ is quite different for the hydrophobic substrate **2** as crucially determined by the sign and value of the isothermal activation parameter $\Delta^{\ddagger}V^{\ominus}$. However, the task of interpreting trends in $\Delta^{\ddagger}\psi(V_m)^{\ominus}$ (Table III) is, we would argue, very complicated in the absence of a global condition. Further, considerable experimental problems would

be encountered if attempts are made to hold constant the molar volumes of different solvent systems. Nevertheless, it is useful to trace the argument back to the original proposal made by Evans and Polanyi.[10] Two key sentences in their paper run as follows: "Especial difficulty arises in solution, from the interaction between solvent and solute, which depends strongly on the temperature. This effect would be *to some extent* eliminated by measuring the temperature coefficient at constant volume,...". We have italicized three words in this quotation because they are crucial to the argument. In effect, Evans and Polanyi[10] envisaged a situation in which solvent–solvent and, particularly, solvent–solute distances would be held constant as the temperature increases. Furthermore they obviously recognized, by the words italicized above, that this is not equivalent to holding the volume of a system constant when the temperature is changed. The point is clarified by considering liquid water. At ambient pressure, there exist pairs of temperatures, one above and one below the temperature of maximum density, (TMD) where the molar volumes of water are equal.[1b] On the other hand, many other properties (e.g., the molar isobaric heat capacity) show no extremum in the region of the TMD. Indeed the radial distribution functions for water at these pairs of temperatures differ.[1h,i] The TMD is a consequence of a normal thermal expansion of a liquid with increase in temperature together with an in-filling from a breakdown of the intermolecular hydrogen bonds. Kinetic data for reactions in water over a temperature range spanning the TMD (cf. ref 50 and 51) reveal nothing out of the ordinary.

The task set by Evans and Polanyi,[10] namely to hold the solute–solvent separation constant, is almost impossible, corresponding to a type of Franck–Condon restraint when *T* and *P* are changed. Some attempt to satisfy the criteria might be undertaken by combining information from scattering (X-ray and neutron) and kinetic experiments, as well as molecular dynamic simulations, matching conditions under which nearest-neighbor distances (calculated from the radial distribution function) remain constant within the solvent (cf. ref 52). A related approach is indicated by Grunwald[53] who treats the properties of a solute in the presence of an equilibrium involving the solvent, thereby distinguishing "frozen" and "equilibrium" properties for a solute. Another procedure which accepts the points made by Evans and Polanyi[10] would be to use the internal pressure of the solvent,[54] itself an indicator of solvent–solvent interaction, as a reference. Partial derivatives of ln (k/T) may be formed with respect to *T* and *P* at constant internal pressure. Interestingly the internal pressure close to the TMD for water (and also D$_2$O) is zero. Also the TMD is dependent on pressure[1b,55] and the mole fraction of added solute and cosolvent.[1c,56,57] The latter observations prompt a number of studies which will be reported in due course.

In conclusion, we have shown that isobaric and isothermal activation parameters can be reasonably interpreted for the hydrolysis of **1** and **2** in two mixed solvents. On the other hand, isochoric activation parameters are extremely difficult to interpret, prompting the suggestion that the approach discussed by Evans and Polanyi[10] is difficult to follow in practice.

Supplementary Material Available: Three tables of rate constants as a function of temperature and pressure and least-squares fit of the pressure-dependent rate constants to eq 8 (3 pages). Ordering information is given on any current masthead page.

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