20605-01-0; 2-carboxy-1,3-propanedithiol, 20605-01-0; 3-(acetylthio)-2-methenyl-1-propanoic acid, 56140-22-8; sodium 2-hydroxyethanethiolate, 37482-11-4; potassium 2-hydroxyethanethiolate, 7450-31-9; sodium butylthiolate, 4779-86-6; potassium butylthiolate, 26385-25-1; potassium 2,2-dimethylpropylthiolate, 124357-90-0; potassium 2-hydroxy-2-methylpropylthiolate, 124357-91-1; potassium 3-hydroxy-2,2-dimethylpropylthiolate, 124357-92-2; bis(2-hydroxyethyl) disulfide, 1892-29-1; 4-carboxy-1,2-dithiolane, 2224-02-4; sodium 2,2-dideuterio-2-hydroxyethanethiolate, 124357-93-3; bis(2,2-dideuterio-2-hydroxyethyl) disulfide, 124357-94-4; butyl disulfide, 629-45-8; selenylbenzene, 645-96-5.

Quantitative Analysis of Solvent Effects in Highly Aqueous Media. Application of the SWAG Procedures and a Critical Appraisal of the Additivity Principle

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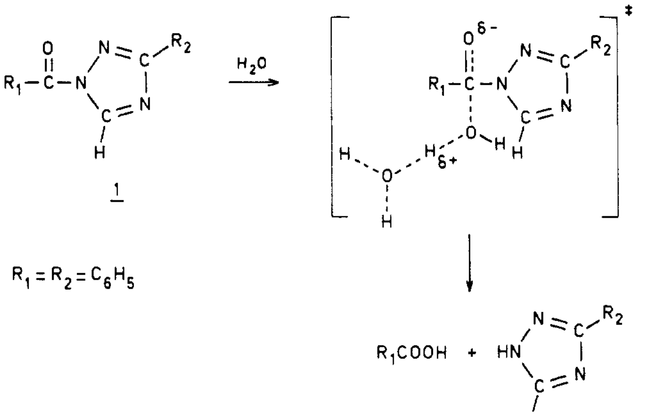
Abstract: This paper describes a study on medium effects of 25 monohydric and polyhydric alcohols on the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in highly aqueous media. Dependences of pseudo-first-order rate constants on molality of added alcohol are quantitatively analyzed in terms of pairwise Gibbs energy interaction parameters for initial state and transition state. Additivity of pairwise group interaction parameters (SWAG procedure) is applied, and the validity of additivity is critically examined. Excellent additivity is observed in series of monohydric alcohols and vicinal diols. In series of polyhydric alcohols, group contributions to the observed rate effects, as expressed in pairwise group interaction parameters, are, however, strongly dependent on the position of hydroxyl groups in the alcohol. This (apparent) nonadditivity behavior is discussed in terms of the hydration characteristics of the cosolvents. The importance of hydration shell overlap in determining medium effects is supported by kinetic data in ternary 1-propanol–urea–water mixtures.

Specific noncovalent interactions in aqueous media are responsible for stabilization of proteins,[1] biological membranes,[2] micelles, and other aggregates[3] in aqueous solutions. Chemical reactivity in aqueous media is also largely governed by these types of interactions, and the presence of inert cosolvents in the reaction medium can seriously affect the rate of the reaction.[4] A valuable approach to analyze intermolecular interactions in aqueous solutions has been introduced by Wood and co-workers,[5,6] who proposed that thermodynamic pairwise intermolecular interaction parameters can be calculated as the sum of independent pairwise group interaction parameters (SWAG procedure). Recently we used this "additivity principle" in a quantitative analysis of rate effects of inert cosolvents on a hydrolysis reaction in highly aqueous media.[7,8] Here, we present a study of the medium effects of 25 monohydric and polyhydric alcohols on the neutral hydrolysis of the activated amide bond in 1-benzoyl-3-phenyl-1,2,4-triazole (**1**) in water-rich mixtures. These cosolvents retard the hydrolysis reaction. The observed rate effects, expressed in pseudo-first-order rate constants, are quantitatively analyzed in terms of the Gibbs energies of pairwise intermolecular interactions of the cosolvents with both the initial state (IS) and the transition state (TS) of the reaction. The consequence of gradual changes of the structure of the cosolvent for the rate effect is monitored. Additivity schemes have been frequently invoked to analyze intermolecular solute–solute interactions in aqueous mixtures.[6,9-24] Anomalies in these analyses have been noted because additivity schemes do not accommodate conformational and configurational aspects of intermolecular interactions in solutions.[10,14,20,21,25-30] The rate effect of monohydric and polyhydric alcohols on the hydrolysis of **1** can be expressed in terms of group contributions of merely two groups, i.e., CH and OH. In this analysis, these are the groups in the cosolvent that directly interact with solutes and solvent molecules in the reaction medium. Within series of structurally related alcohols, the rate effects can be understood in terms of two unique values of these group contributions and excellent additivity is observed. However, attempts to express the rate effects of all

Scheme I



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cosolvents in two parameters gave less satisfactory results. Most likely, this is caused by neighboring group effects of hydroxyl groups that modify the water structure in the hydration shell surrounding the cosolvent. The importance of hydration shell overlap for intermolecular interactions in water, and consequently for observed rate effects of inert cosolvents on reactions in aqueous media, is enormous. This is further emphasized by kinetic experiments in ternary 1-propanol–urea–water mixtures. Urea reduces the rate effects of hydrophobic cosolvents to nearly zero due to a mechanism that is probably similar to denaturation.

Results

Theoretical Background. In aqueous media at pH 3–5, the hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole (**1**) proceeds via a dipolar transition state in which two water molecules are involved[31,32] (Scheme I). The reaction medium consists of 1 kg of water, m_{is} and m_{ts} moles of the initial state and the transition state of the reaction, respectively, and m_c moles of an inert cosolvent C. The concentration of the reacting substrate is very low ($\approx 10^{-5}$ M). As a consequence, every observed rate effect has to be the result of interaction of IS and TS with the added cosolvent.[33] These interactions affect the activity coefficient of the IS and the TS. The observed medium effect of cosolvent C now characterizes the differences in the {IS↔C} and {TS↔C} interactions. The activity coefficients can be expressed[34,35] in terms of pairwise Gibbs energy interaction parameters $g(\mathrm{S}\leftrightarrow\mathrm{C})$:

$$\ln \gamma_s = 2/[RT\, g(\mathrm{S}\leftrightarrow\mathrm{C})\ [m_c/m_0^2]] \qquad (1)$$

Table I. Neutral Hydrolysis of **1** with SWAG Analysis Applied to Monohydric Alcohols at 25 °C

cosolvent[a]	G(C)(exptl),[b] J·kg·mol^{-2}	G(C)(calcd),[c] J·kg·mol^{-2}
methanol	27 ± 2	22
ethanol	−120 ± 6	−114
1-propanol	−258 ± 6	−250
2-propanol	−231 ± 6	−250
1-butanol[d]	−474 ± 39	−386
2-butanol[d]	−405 ± 12	−386
2-methyl-1-propanol	−425 ± 24	−386
2-methyl-2-propanol	−392 ± 14	−386
cyclopentanol	−379 ± 18	−386

[a] Concentration 0–2 M. [b] Experimental value. [c] Calculated value using G(CH) = −68 J·kg·mol^{-2} and G(OH) = 226 J·kg·mol^{-2}. [d] Concentration 0–1 M because of solubility constraints.

In this equation S represents either the IS or the TS of the reaction. By definition, m_0 = 1 mol·kg^{-1}. According to Wood et al.[5,6] $g(\mathrm{S}\leftrightarrow\mathrm{C})$ can be calculated as the sum of independent pairwise Gibbs energy group interaction parameters $G(i\leftrightarrow j)$, describing the interactions of n^s groups i in compound S with n^c groups j in compound C:

$$g(\mathrm{S}\leftrightarrow\mathrm{C}) = [\sum_{i=1}^{k} \sum_{j=1}^{l} n^s(i)\ n^c(j)\ G(i\leftrightarrow j)] - M_1RT/2 \qquad (2)$$

The term $M_1RT/2$ arises because of a scale conversion.[7,8] M_1 is the molar mass of water.

The hydrolysis of the activated amide or, in general, a hydrolysis reaction can be schematically depicted as

$$\mathrm{S(aq)} + N\mathrm{H_2O} \rightleftarrows [\mathrm{S}\text{–}N\mathrm{H_2O}]^{\ddagger} \rightarrow \text{products}$$

In this scheme, N designates the number of water molecules bound in the transition state for hydrolysis.

The pseudo-first-order rate constants in the presence of a cosolvent are related to the rate constants in pure water by the activity coefficients of all reactants according to[36,37]

$$\ln [k(m_c)/k(m_c{=}0)] = \ln \gamma_{is} - \ln \gamma_{ts} - NM_1\phi m_c \qquad (3)$$

Herein, ϕ is the osmotic coefficient of the reactant water.[8] By combining eq 1–3, we obtain

$$\ln [k(m_c)/k(m_c{=}0)] = 2/RT(1/m_0^2)m_c \times \sum_{i=1}^{k} \sum_{j=1}^{l} n^c(i)\ n^{is}(j)\ [G(i\leftrightarrow j) - \sum_{i=1}^{k} \sum_{j=1}^{m} n^c(i)\ n^{ts}(j)\ G(i\leftrightarrow j)] - NM_1\phi m_c \qquad (4)$$

The medium effect, expressed by ln $[k(m_c)/k(m_c{=}0)]$, can now be analyzed and calculated in terms of a difference sum of pairwise Gibbs energy group interaction parameters, describing the intermolecular interactions between IS and TS of the reaction and the added cosolvent as a function of the composition of the reaction medium.[8]

Of course, a valid description of the interactions involving TS is a matter of considerable concern. In the present study we focus our attention on the cosolvent. Therefore, we rewrite eq 4 in a more amenable form:

$$\ln [k(m_c)/k(m_c{=}0)] = 2/RT(1/m_0^2)m_c[\sum_{i=1}^{k} n^c(i)\ G(\mathrm{IS}\leftrightarrow i) - \sum_{i=1}^{k} n^c(i)\ G(\mathrm{TS}\leftrightarrow i)] - NM_1\phi m_c \qquad (5)$$

Herein, $G(\mathrm{IS}\leftrightarrow i)$ and $G(\mathrm{TS}\leftrightarrow i)$ represent the pairwise Gibbs function interactions of, respectively, IS and TS with n^c groups

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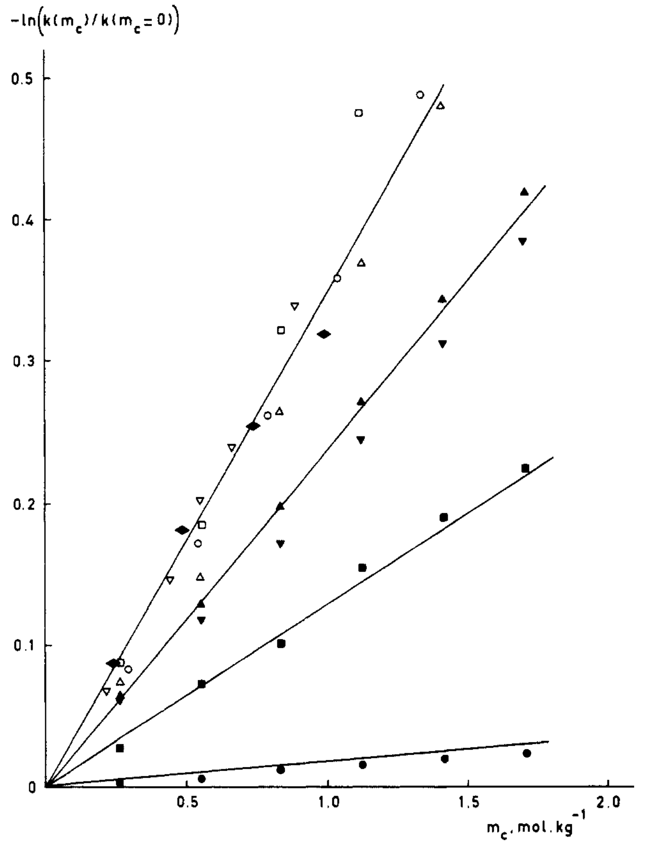

Figure 1. Plots of ln $[k(m_c)/k(m_c=0)]$ vs molality of monohydric alcohol for the neutral hydrolysis of **1** at 25 °C: ●, methanol; ■, ethanol; ▲, 1-propanol; ▼, isopropyl alcohol; □, 1-butanol; △, 2-methyl-2-propanol; ○, 2-butanol; ▽, 2-methyl-1-propanol; ◆, cyclopentanol. The solid lines represent calculated reaction rates (see text).

i in the cosolvent. Only those groups are taken into account that directly interact with surrounding solvent and solute molecules (vide supra). Assuming that $\phi = 1$ in the dilute solutions, the term between brackets in the right-hand side of eq 5 multiplied by $1/m_0^2$ (symbolized as $G(\mathrm{C})$) can be easily evaluated from the experimental results and expressed in terms of group contributions $G(i)$. In the case of alcohols, this analysis is particularly simple. If complete additivity is observed, the rate effects of alcohols on the hydrolysis of **1** should be governed by merely two parameters, the contribution of the OH group, expressed as $G(\mathrm{OH})$, and the contribution of the CH groups, expresssed as $G(\mathrm{CH})$.

Alcohol–Water Mixtures. Pseudo-first-order rate constants for hydrolysis of **1** have been measured in a large series of dilute (0–1.5 mol·kg^{-1}) alcohol–water mixtures. In these media, alcoholysis may compete with hydrolysis and therefore the nature of the reaction products (carboxylic acid vs carboxylic ester; see the Experimental Section) was carefully examined. However, it was found that the presence of the most reactive alcohol, i.e., methanol (1 mol·kg^{-1}), only led to a 3% yield of methyl benzoate. Therefore, in our analysis of medium effects, the contribution of alcoholysis can be safely neglected. Of course, alcohol could also function as a general base in the hydrolysis of **1**, but in view of the large excess of water molecules, this process will not contribute significantly to the overall reaction rates.

Monohydric Alcohols. The medium effect of a series of monohydric alcohols on the hydrolysis of **1**, expressed as ln $[k(m_c)/k(m_c=0)]$, is plotted against the molality of the added alcohol in Figure 1. All functions show, in particular at low molalities, perfect linearity. All alcohols induce a decrease in rate. This is, except for methanol, the result of the negative value of $G(\mathrm{C})$ (Table I), which is a consequence of the less favorable sum of pairwise Gibbs energy group interactions between the added alcohol and the TS than between the alcohol and the IS. This clearly reflects the loss of hydrophobicity of the substrate during the activation process and the hydrophobicity of the alcohols. A methyl group can be represented by three CH groups, according to[20-23]

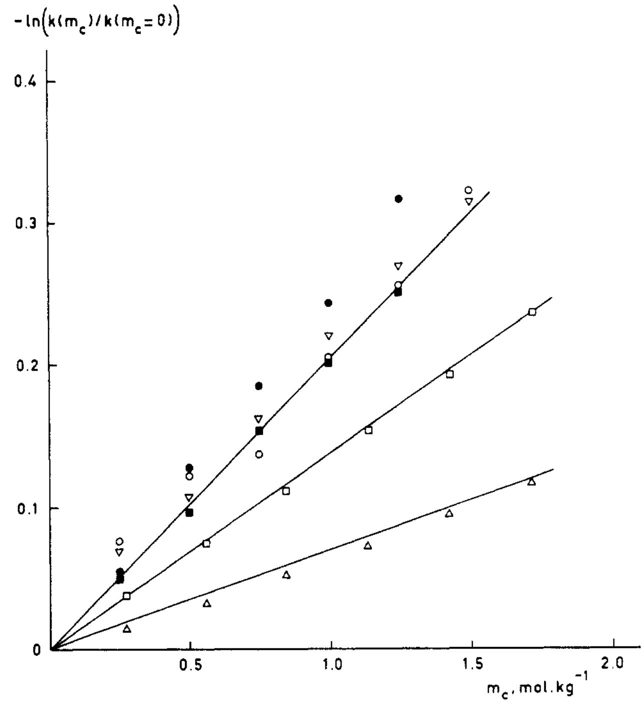

Figure 2. Plots of ln $[k(m_c)/k(m_c=0)]$ vs molality of dihydric alcohol for the neutral hydrolysis of **1** at 25 °C: △, glycol; □, 1,2-propanediol; ○, 1,2-butanediol; ▽, 2,3-butanediol; ●, *trans*-cyclopentane-1,2-diol; ■, *cis*-cyclopentane-1,2-diol. The solid lines represent calculated reaction rates (see text).

$$G(\mathrm{CH_3}) = 1.5G(\mathrm{CH_2}) = 3G(\mathrm{CH})$$

Now $G(\mathrm{CH_2})$ can be derived from the increments between the slopes of the lines in Figure 1, for example

$$G(\mathrm{CH_3CH_2CH_2OH}) - G(\mathrm{CH_3CH_2OH}) = G(\mathrm{CH_2}) = 2G(\mathrm{CH})$$

We find $G(\mathrm{CH}) = -68$ J·kg·mol^{-2}. From $G(\mathrm{C})$ and $G(\mathrm{CH})$ the value of G(OH) can be calculated, for example

$$G(\mathrm{CH_3CH_2OH}) - 5G(\mathrm{CH}) = G(\mathrm{OH})$$

and we find $G(\mathrm{OH}) = 226$ J·kg·mol^{-2}. Clearly the hydroxyl group exerts a rate-increasing effect whereas the hydrophobic CH groups retard the hydrolysis. Calculated values of $G(\mathrm{C})$, from the derived values of $G(\mathrm{OH})$ and $G(\mathrm{CH})$, are in close agreement with experimental values (Table I). Theory predicts, as a result of the application of the additivity principle, a unique value of $G(\mathrm{C})$ for all isomers of propanol and butanol. Moreover, even cyclopentanol should induce a similar rate effect as all isomers of butanol. In fact, isomeric cosolvents induce a different rate effect. The differences between the calculated and the experimentally obtained values of $G(\mathrm{C})$ are, however, small. This indicates that the configuration of the alkyl group is not a very important factor in the determination of the magnitude of the overall medium effect of monohydric alcohols.

Dihydric Alcohols. Dihydric alcohols also induce a decrease of the rate of hydrolysis of **1**. In Figure 2 the medium effect, expressed as ln $[k(m_c)/k(m_c=0)]$, of vicinal dihydric alcohols is plotted as a function of the molality. Similar plots of other dihydric alcohols show also excellent linear behavior. Again, the rate retardation is governed by a negative value of $G(\mathrm{C})$ (Table II), indicating that dihydric alcohols exhibit a predominantly hydrophobic behavior. With use of the values of $G(\mathrm{OH})$ and $G(\mathrm{CH})$ as derived for monohydric alcohols, $G(\mathrm{C})$ parameters are also calculated. Obviously (Table II) the discrepancy between theoretical and experimental values is in most cases dramatic. Generally, dihydric alcohols exhibit more hydrophobic character than anticipated. Only when both hydroxyl groups are not in close

Table II. Neutral Hydrolysis of **1** with SWAG Analysis Applied to Dihydric Alcohols at 25 °C

cosolvent[a]	G(C)(exptl),[b] J·kg·mol^{-2}	G(C)(calcd),[c] J·kg·mol^{-2}	G(C)(calcd),[d] J·kg·mol^{-2}
glycol	-40 ± 6	180	-44
1,2-propanediol	-124 ± 6	44	-128
1,3-propanediol	-69 ± 6	44	-128
1,2-butanediol	-214 ± 14	-92	-212
2,3-butanediol	-212 ± 14	-92	-212
1,3-butanediol	-172 ± 6	-92	-212
1,4-butanediol	-108 ± 6	-92	-212
1,5-pentanediol	-216 ± 6	-228	-296
1,6-hexanediol[e]	-410 ± 14	-396	-380
cis-1,2-cyclopentanediol	-208 ± 12	-92	-212
trans-1,2-cyclopentanediol	-268 ± 14	-92	-212

[a] Concentration 0–2 M. [b] Experimental value. [c] Calculated value using G(CH) = -68 J·kg·mol^{-2} and G(OH) = 226 J·kg·mol^{-2}. [d] Calculated value using G(CH) = -42 J·kg·mol^{-2} and G(OH) = 62 J·kg·mol^{-2}. [e] Concentration 0–1 M because of solubility constraints.

Table III. Neutral Hydrolysis of **1** with SWAG Analysis Applied to Polyhydric Alcohols at 25 °C

cosolvent[a]	G(C)(exptl),[b] J·kg·mol^{-2}	G(C)(calcd),[c] J·kg·mol^{-2}	G(C)(calcd),[d] J·kg·mol^{-2}
glycerol	-91 ± 6	38	-24
erythritol	-170 ± 10	496	-4
arabitol	-229 ± 14	654	16
sorbitol	-172 ± 14	812	36
mannitol	-159 ± 14	812	36

[a] Concentration 0–2 M. [b] Experimental value. [c] Calculated value using G(CH) = -68 J·kg·mol^{-2} and G(OH) = 226 J·kg·mol^{-2}. [d] Calculated value using G(CH) = -42 J·kg·mol^{-2} and G(OH) = 62 J·kg·mol^{-2}.

proximity (e.g., in 1,4-butanediol) is agreement between the calculated and experimental value satisfactory. Obviously, it is not possible to express the medium effects of both monohydric and vicinal dihydric alcohols in two *unique* pairwise Gibbs energy interaction parameters. Therefore, the interaction of IS and TS with these polyols cannot be analyzed in terms of an additivity of group interactions approach. However, from the increments that emerge from Figure 2, an alternative set of contributions can be derived that describe the rate effect of vicinal dihydric alcohols. We find G(CH) = -42 J·kg·mol^{-2} and G(OH) = 62 J·kg·mol^{-2}. Apparently, the value of G(CH) derived for the vicinal diols, and consequently also G(OH), is significantly smaller than those for monohydric alcohols. Our data suggest that 1,3-diols show behavior in between that of monohydric alcohols and vicinal diols. But most strikingly, 1,4-, 1,5-, and 1,6-diols exhibit medium effects that can be analyzed conveniently with the parameters derived for monohydric alcohols. To probe the nature of the OH proximity effect, the rate effects of *cis*- and *trans*-1,2-cyclopentanediol were studied. The positioning of the vicinal hydroxy groups also appears to be relevant for the induced rate effect (Table II). The relative values of G(C) indicate that intramolecular OH···OH hydrogen bonding in the cosolvent is not primarily the cause of the observed reduction of the OH group contribution due to a second OH group in close proximity.

Polyhydric Alcohols. Even hydrophilic polyols, as listed in Table III, are found to induce a significant *decrease* of the rate of hydrolysis of the activated amide. Plots of ln $[k(m_c)/k(m_c{=}0)]$ against the molality of the polyols show good linearity. The experimental values of G(C) are all negative (Table III). The calculated values of G(C), with use of the estimates for G(OH) and G(CH) as derived for monohydric alcohols as well as for vicinal dihydric alcohols, show bad agreement with the experimental results. Again, the presence of a series of OH groups in close proximity troubles the analysis on the basis of the additivity principle. We find for monohydric alcohols that [G(CH) + G(OH)] = 158 J·kg·mol^{-2}, whereas for vicinal diols [G(CH) + G(OH)] = 20 J·kg·mol^{-2}. In the case of polyols, the value of [G(CH) + G(OH)] even becomes negative, which illustrates dramatically the decreasing medium effect of the hydroxyl groups when they are positioned in close proximity in the molecule.

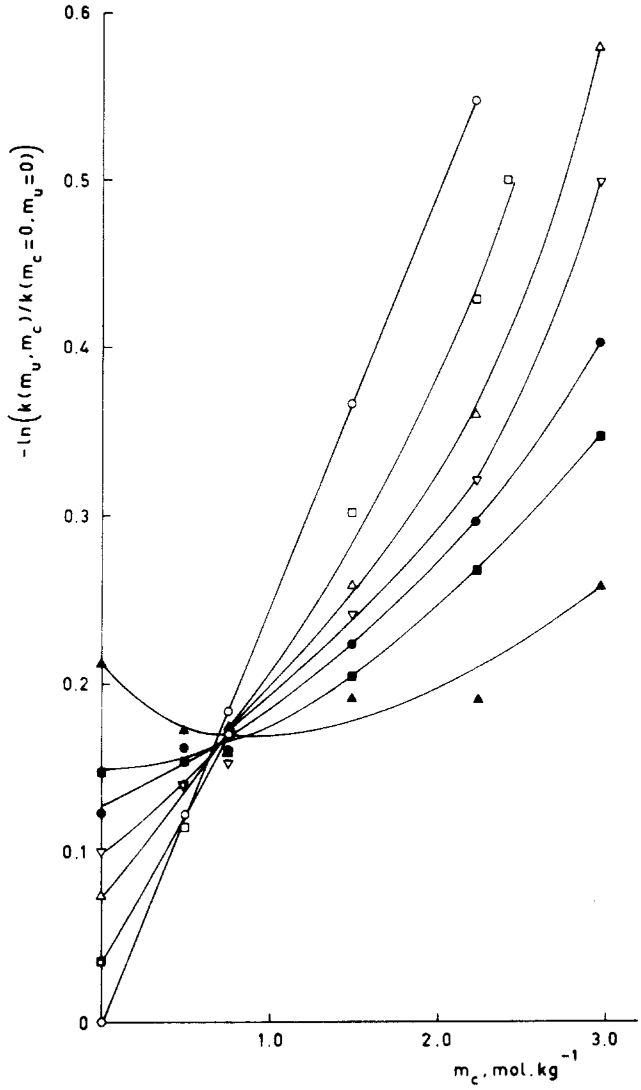

Figure 3. Plots of ln $[k(m_c,m_u)/k(m_c{=}m_u{=}0)]$ vs molality of 1-propanol for the neutral hydrolysis of **1** at 25 °C in the presence of different concentrations (m_u) of urea; ○, m_u = 0; □, m_u = 1 mol·kg^{-1}; △, m_u = 2 mol·kg^{-1}; ▽, m_u = 3 mol·kg^{-1}; ●, m_u = 4 mol·kg^{-1}; ■, m_u = 5 mol·kg^{-1}; ▲, m_u = 10 mol·kg^{-1}.

1-Propanol–Urea–Water Mixtures. In Figure 3 the rate effect of 1-propanol, expressed as ln $[k(m_c,m_u)/k(m_c{=}m_u{=}0)]$, on the hydrolysis of **1** is plotted as a function of the molality of 1-propanol at different molalities of urea. Generally, addition of 1-propanol to the reaction medium results in a decrease of the rate of hydrolysis. Urea, a thermodynamically nearly ideal cosolute, reduces the rate-decreasing effect of 1-propanol dramatically. In a solution containing 10 mol·kg^{-1} of urea, addition of 1-propanol causes even an effective rate *acceleration*. This situation contrasts with the effect of adding ethanol to the aqueous propanol system; under these conditions the medium effects of both cosolvents show normal additivity. We note that the urea–water system has been studied extensively in relation to the denaturing properties of these solutions.[30,38–41] Despite the fact that the denaturation of proteins by urea in aqueous solutions is still not completely understood, breaking of hydrophobic interactions by disturbing the hydrophobic hydration shells surrounding apolar groups is now generally accepted as one of the mechanisms of denaturation.[38] Hence, the reduction of the medium effect of 1-propanol by addition of urea

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suggests that the strong reduction of $G(\mathrm{CH})$ by the presence of urea is the result of the urea-induced disturbance of the hydrophobic hydration sphere around the *n*-propyl group in the alcohol and a concomitant decrease of hydrophobic interactions.

Discussion

The present results emphasize the overwhelming importance of *hydration shell overlap effects* in determining kinetic medium effects in highly aqueous reaction media. We contend that the observed medium effects are primarily the result of a reordering of hydration shells during the activation process. Thus, the hydration characteristics of the cosolvent are of paramount importance.

However, particularly in the case of polyols, classification of these molecules as hydrophilic or hydrophobic is rather ambiguous.[42] Measurements of temperatures of maximum density, ultrasonic relaxation, and microcalorimetry show significant differences in the solution properties of, e.g., isomeric diols.[42-44] Our kinetic medium effects of alcohols are clearly governed by a rate-decreasing contribution of the CH groups and a counteracting, rate-enhancing contribution of OH groups. Comparison of the medium effects induced by monohydric alcohols and their vicinal diol analogues illustrates the delicacy of this balance. For the vicinal diols, the contribution of the CH groups is much smaller, but the OH contributions appear to be even more reduced. This results in an apparent less "hydrophilic" behavior of vicinal diols than anticipated on the basis of additivity schemes. The balance of the CH/OH contributions can be expressed in the value of $[G(\mathrm{CH}) + G(\mathrm{OH})]$. For monohydric alcohols, $[G(\mathrm{CH}) + G(\mathrm{OH})] = 158$ J·kg·mol^{-2}, for vicinal diols the value is only 20 J·kg·mol^{-2}. Interestingly, comparison of the medium effects induced by 1,3-propanediol ($G(\mathrm{C}) = -69$ J·kg·mol^{-2}) and glycerol ($G(\mathrm{C}) = -91$ J·kg·mol^{-2}) indicates that introduction of a third OH group results in even a stronger rate inhibition.

In fact, the contributions of CH and OH groups tend to become small with the introduction of more OH groups. This explains why carbohydrates often exhibit thermodynamically almost ideal behavior.[10,45] That the stereochemistry of the polyhydric alcohol is important for the observed interactions is already illustrated by the rate effects induced by *trans*- and *cis*-1,2-cyclopentanediol.

Conclusions

The present results strongly suggest that the observed rate effects in the highly aqueous reaction media directly reflect the hydration characteristics of the cosolvent. The overlap of the hydration layers surrounding the IS and TS with the hydration shell of the cosolvent is governed by the balance between hydrophilic and hydrophobic groups in the cosolvent. Introduction of more OH groups leads to a further breakdown of the hydrophobic hydration shells around the apolar sites in the cosolvent. This effect results in a better hydration and a better "fit" of the cosolvent in the water structure.

However, the observation that solvation of individual functional groups in sufficiently close promixity in the cosolvent is mutually obstructive is the main reason that intermolecular interactions governing the medium effects cannot be treated uncritically by additivity schemes of group interaction parameters. Interestingly, excellent additivity is observed in cosolvents in which only the alkyl "backbone" is varied, keeping the relative positions of the functional groups constant.

The present study shows that the SWAG approach, using pairwise Gibbs energy interaction parameters, offers a highly useful procedure for a quantitative analysis of medium effects on reactions in highly aqueous media. This type of analysis does full justice to the notion that medium effects result from a delicate balance between competing group contributions. Thus, the analysis leads to a better understanding of the molecular origin of medium effects on reactivity in highly aqueous media. It is also possible to use pairwise group interaction parameters to analyze and calculate rate effects in a series of cosolvents that have a more or less similar "hydrophilic framework", e.g., carbohydrates.[46] In addition, SWAG-type analysis of medium effects can provide valuable information about details of reaction mechanisms.[47] Work along these lines will be reported in due course.

Experimental Section

Materials. 1-Benzoyl-3-phenyl-1,2,4-triazole was prepared according to a standard procedure.[48] Glycol and glycerol were distilled in vacuo before use. Erythritol was crystallized twice from ethanol. *trans*- and *cis*-cyclopentane-1,2-diol were prepared from cyclopentene according to the methods of Owen and Smith.[49] 1,3-Propanediol was purified as follows: 1,3-Propanediol (1.0 mol) was added to acetone (1.3 mol) and benzene (50 mL). A few crystals of *p*-toluenesulfonic acid were added, and the mixture was refluxed under removal of water. After 24 h, benzene and the excess of acetone were removed in vacuo, and the trimethylene acetal was purified by distillation; bp 125 °C (72 mm). The acetal (10.4 g, 0.090 mol) was hydrolyzed by addition of 10 mL of 0.5 N HCl. Acetone and water were removed in vacuo, and 1,3-propanediol was distilled twice: yield 6.0 g, 0.079 mol; bp 120 °C (15 mm) [lit.[50] bp 108 °C (11 mm)].

All other alcohols were used as supplied. Demineralized water was distilled twice in an all-quartz distillation unit. Urea (Merck) was used as supplied.

All solutions were made up by weight and contained ca. 3×10^{-4} mol·kg^{-1} HCl to suppress catalysis by hydroxide ions.

Product Analysis. Reaction products for the solvolysis of **1** in alcohol–water mixtures were analyzed quantitatively. Hereto reactions were performed in the presence of 0.50, 1.00, and 1.50 mol·kg^{-1} alcohol, with substrate concentrations of ca. 5×10^{-3} M. In all cases the pH was kept at ca. 4.5 to suppress hydroxide ion catalysis. After the reaction was allowed to go to completion, the products were analyzed by gas chromatography (Hewlett-Packard 5890 instrument, equipped with a 15-m wide-bore HPI fused silica column) and by GC–MS (Ribermag R-10-10c instrument). The relative amounts of benzoic acid and the corresponding ester were determined by calibration against known mixtures of authentic ester and benzoic acid. Only in the case of alcohols containing primary OH functions were significant amounts of ester found. Independent experiments showed that the esters were not formed by esterification of benzoic acid after complete hydrolysis of **1**. For different alcohols (1.5 mol·kg^{-1}), the percentage of ester formation was as follows: methanol, 5 ± 1%; ethanol 3 ± 1%; 1-propanol, 2 ± 1%; 2-butanol, ≈1%; glycol, 3 ± 1%; 1-butanol, ≈1%; 2-butanol and 2-methyl-2-propanol, <0.4%. The yield of ester in the presence of 0–1.5 mol·kg^{-1} alcohol depended linearly on the alcohol concentration in the reaction mixture.

Kinetic Measurements. Pseudo-first-order rate constants were determined by following the change in absorbance at 273 nm. About 3×10^{-3} cm^3 of a stock solution of **1** in acetonitrile ($\approx 5 \times 10^{-2}$ mol·dm^{-3}) was added to the reaction medium (≈2.5 mL) in a quartz cell placed in a thermostated (25.0 °C) cell compartment of a Perkin-Elmer λ5 spectrophotometer. The reaction was followed for about 10 half-lives, and excellent first-order kinetics was observed. Pseudo-first-order rate constants were calculated with a data station PE λ5, connected to the spectrophotometer, and were reproducible to within 2%. Reaction rates at each molality of cosolvent were determined at least three times. For the calculation of the value of $G(\mathrm{C})$, data measured for at least six molalities were used.

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