7 Hz), 5.1 (3 H, m); MS, m/z 315 (M^+); HRMS calcd for $C_{21}H_{33}NO$ MW 315.2559, found 315.2558 (M^+).

Acknowledgment. We are grateful to Professor Lewis N. Mander, Australian National University, for supplying us with a sample of 5-methoxy-2-tetralone. This work was supported in part by a Grant-in Aid for the Encouragement of Young Scientists, Japan (to R.Y.).

Supplementary Material Available: Spectral data for compounds **3**, **9**, **17**, **31**, **36**, **49**, and **51** and copies of ^1H NMR and IR spectra of compounds **25**, **37**, **39**, **41**, **43**, and **47** and ^1H NMR spectra of compounds **24** and **46** (15 pages). Ordering information is given on any current masthead page.

Alkyl Substituent Effects on the Neutral Hydrolysis of 1-Acyl-(3-substituted)-1,2,4-triazoles in Highly Aqueous Reaction Media. The Importance of Solvation

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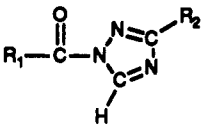
The importance of solvation in determining substituent effects of alkyl groups has been assessed in a quantitative study of the medium effects of ethanol and 1-propanol on the neutral hydrolysis of 18 1-acyl-(3-substituted)-1,2,4-triazoles in highly aqueous solutions. The dependence of the pseudo-first-order rate constants for hydrolysis on the molality of added cosolvent is analyzed in terms of pairwise Gibbs function interaction parameters and individual group contributions to the overall medium effect. It is found that the alkyl substituent effects depend on the presence of the cosolvent and that this medium dependence is different for different alkyl groups. In addition, the effect is sensitive to the position of the substituent and the overall hydrophobicity of the substrate. Alkyl substituent effects have also been examined for the acid-catalyzed hydrolysis of a series of 1-acyl-(3-substituted)-1,2,4-triazoles. The solvation dependence of alkyl substituent effects is discussed in terms of changes in hydration of the substrate during the activation process.

Noncovalent intermolecular interactions in highly aqueous solutions between chemically inert cosolvents and reacting substrates can seriously affect rate constants of many types of reactions.[2,3] These medium effects are largely governed by the overlap of hydration shells of both substrate and activated complex with the hydration shell of the cosolvent. In the case of cosolvents containing hydrophobic groups, the magnitude of the solvent effect is often dominated by the change in hydrophobicity of the reacting molecule(s) during the activation process.[4]

Recently we proposed a quantitative treatment for the analysis of medium effects on (in)organic reactions in highly aqueous solvent systems.[5-7] The medium effects were analyzed in terms of pairwise Gibbs energy interaction parameters, which reflect pairwise interactions of both substrate and activated complex with the cosolvent molecule. The theory has been critically tested on a hydrolysis reaction in water in the presence of N-substituted ureas[6] and mono- and polyhydric alcohols.[7] Careful application of additivity schemes[7] allowed a subdivision of medium effects of cosolvents into group contributions to the overall medium effect.

Here, we present a combined quantitative study of substituent effects of alkyl groups[8] and medium effects of ethanol and 1-propanol on the pseudo-first-order rate constants for the pH-independent hydrolysis of 18 1-acyl-(3-substituted)-1,2,4-triazoles (**1a-j**, **2a,b**, **3a-c**, **4a,b**, **5**) in highly aqueous solutions. A large set of substrates was examined in an attempt to subject our quantitative theory to a rigorous test. Furthermore, kinetic medium effects and substituent effects for the water-catalyzed hydrolysis are compared with a relevant set of data for the acid-catalyzed hydrolysis.



1a, R_1 = Me, R_2 = H
b, R_1 = Et, R_2 = H
c, R_1 = *n*-Pr, R_2 = H
d, R_1 = *i*-Pr, R_2 = H
e, R_1 = *i*-Bu, R_2 = H
f, R_1 = *s*-Bu, R_2 = H
g, R_1 = *t*-Bu, R_2 = H
h, R_1 = *n*-Pent, R_2 = H
i, R_1 = 3-Pent, R_2 = H
j, R_1 = Ph, R_2 = H

2a, R_1 = Me, R_2 = *t*-Bu
b, R_1 = Me, R_2 = Cl
3a, R_1 = Et, R_2 = Me
b, R_1 = Et, R_2 = *t*-Bu
c, R_1 = Et, R_2 = Ph
4a, R_1 = *t*-Bu, R_2 = Me
b, R_1 = R_2 = *t*-Bu
5, R_1 = R_2 = Ph

Substituent effects of alkyl groups on rate constants and equilibrium constants in solution have been studied extensively.[9-15] Although it is now generally agreed that

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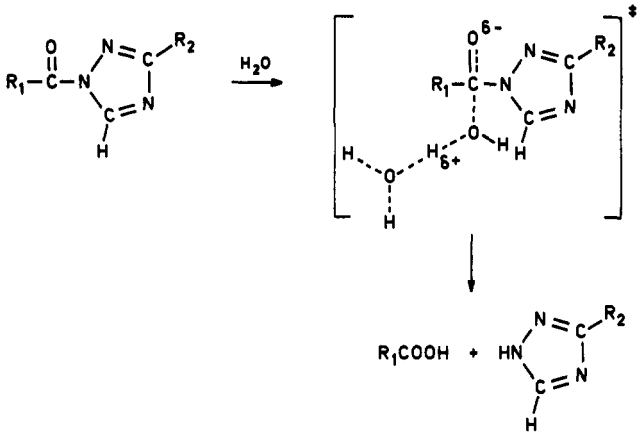
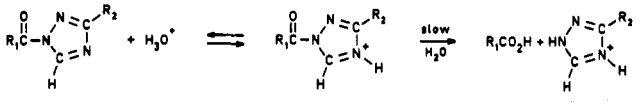
0022-3263/91/1956-1832$02.50/0

Scheme I



Scheme II



solvation effects play an important role,[13] it is difficult to identify the contribution of these effects quantitatively. Usually, solvation effects are incorporated in steric substituent constants.[13,16-19] The contribution of different inductive effects is controversial. Charton[17] argues that such effects represent artifacts in the analysis of the experimental data, but Hanson[15] and others[20-23] stress the importance of different inductive, field, and resonance effects. This situation differs from that for gas-phase alkyl substituent effects, which can be analyzed satisfactorily in terms of polarizabilities.[20,24] Our present results indicate that the change in solvation during the activation process is greatly affected by the specific alkyl substituent near the reaction center in the molecule. More remote alkyl substituents also have significant but smaller effects on the solvation change. The finding that the alkyl substituent effects vary substantially when the composition of the aqueous medium is changed emphasizes the important role of solvation in determining substituent effects of alkyl groups.

Results and Discussion

Theoretical Background. In water-rich media the pH-independent hydrolysis of 1-acyl-(3-substituted)-1,2,4-triazoles proceeds via a general-base-catalyzed process in which water acts both as a nucleophile and a general base.[8,25,26] A likely mechanism is shown in Scheme I. Depending on the effectiveness of acid- and base-catalyzed hydrolysis, the rate constants are pH-independent in a particular pH range (ca. 3–6). However, this range is critically determined by the substituents R_1 and R_2 in the substrate. The acid-catalyzed hydrolysis shows the characteristics of specific-acid catalysis and proceeds via reversible protonation at N-4 in the triazole ring, followed by rate-determining attack of water at the carbonyl moiety (Scheme II).[27] For the neutral hydrolysis, the reaction medium consists of 1 kg of water, m_s and m_{ac} moles of substrate and activated complex, respectively, a small concentration of HCl, and m_c moles of a cosolvent C (ethanol or 1-propanol). In all experiments m_s is small (ca. 10^{-4} mol·kg^{-1}). Product analyses revealed only small amounts of products formed by alcoholysis, which do not complicate the kinetic analyses (see the Experimental Section).[7] Thus, the medium effects reflect interactions between substrate and activated complex with the added cosolvent molecule. Previously,[6] we derived the following equation, which relates the pseudo-first-order rate constant for water-catalyzed hydrolysis in the binary mixture ($k(m_c)$) with the rate constant in bulk water ($k(m_c=0)$):

$$\ln [k(m_c)/k(m_c=0)] = (2/RT)(1/m_0)^2[g(S\leftrightarrow C) - g(AC\leftrightarrow C)]m_c - NM_1\phi m_c \quad (1)$$

Here, N is the number of water molecules covalently bound in the activated complex (i.e., $N = 2$), M_1 is the molar mass of water, and ϕ is the practical osmotic coefficient of water. By definition, $m_0 = 1$ mol·kg^{-1}. The interactions of substrate S and activated complex AC with cosolvent C are described[6,7] by the pairwise Gibbs energy interaction parameters $g(S\leftrightarrow C)$ and $g(AC\leftrightarrow C)$, respectively. The last term in eq 1 describes the effect of C on the activity of water. Since all solutions are dilute in C, triplet and higher order interactions can be neglected. According to the additivity approach, introduced by Wood,[28] intermolecular pairwise interaction parameters can be expressed as the sum of specific pairwise Gibbs energy group interactions. Thus, eq 1 can be rewritten as

$$\ln [k(m_c)/k(m_c=0)] = (2/RT)(1/m_0)^2[\sum_{i=1}^{i=k} n_c(i)\ G(S\leftrightarrow i) - \sum_{i=1}^{i=k} n_c(i)\ G(AC\leftrightarrow i)]m_c - NM_1\phi m_c \quad (2)$$

where $G(S\leftrightarrow i)$ and $G(AC\leftrightarrow i)$ represent the pairwise Gibbs function interaction parameters for interactions of, respectively, substrate and activated complex with n_c groups i in the cosolvent molecule. In the dilute solutions we set $\phi = 1$. The main term in eq 2 represents the difference in the Gibbs function interaction energies of the cosolvent with the substrate and activated complex. It is this term that governs the medium effect.[6,7] The terms between brackets, multiplied by a scale factor $(1/m_0)^2$, is symbolized by $G(C)$ and can be obtained from a plot of $\ln [k(m_c)/k(m_c=0)]$ vs. m_c.

According to eq 2, medium effects of ethanol and 1-propanol can be conveniently expressed in terms of group contributions of the cosolvent OH and CH groups to the overall medium effect, expressed as $G(OH)$ and $G(CH)$. In a next step, substrate and activated complex can be described in terms of constituent groups. Particularly for the activated complex, this is a matter of concern. Two limiting approaches can be considered. In the first, we

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Table I. Neutral and Acid-Catalyzed Hydrolysis of 1a–j: Rate Constants, Solvent Deuterium Isotope Effects, and Medium Effects at 25 °C

	R_1	$k \times 10^5$, s^{-1}	k_{H_2O}/k_{D_2O}[a]	G(EtOH),[a] J·kg·mol^{-2}	G(n-PrOH),[a] J·kg·mol^{-2}	G(CH),[a] J·kg·mol^{-2}	G(OH),[a] J·kg·mol^{-2}	$k_H \times 10^2$, kg·mol^{-1}·s^{-1}
1a	Me	216	3.00	−52 (2)	−97 (2)	−22 (2)	59	20
1b	Et	290	3.13	−103 (2)	−158 (3)	−28 (3)	37	29
1c	n-Pr	175	3.31	−107 (1)	−182 (3)	−38 (2)	82	17
1d	i-Pr	340	3.38	−155 (2)	−237 (3)	−41 (3)	50	56
1e	i-Bu	41.4	3.49	−133 (2)	−226 (3)	−47 (3)	102	5.3
1f[b]	s-Bu	98.0	2.96					
1g	t-Bu	341	3.09	−185 (1)	−289 (2)	−52 (2)	75	68
1h[b]	n-Pent	4.27	4.15					
1i	3-Pent	9.40	4.13	−202 (2)	−324 (5)	−61 (4)	103	2.2
1j	Ph	203	2.62	−83 (2)	−172 (3)	−45 (3)	142	9.4

[a] For the neutral hydrolysis. [b] Data from ref 8.

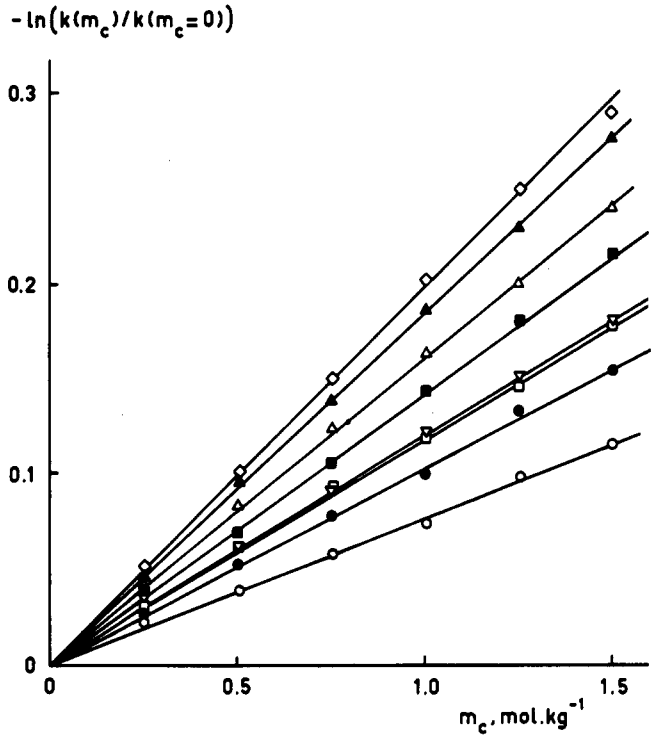

Figure 1. Plots of $-\ln [k(m_c)/k(m_c=0)]$ vs molality of ethanol for the neutral hydrolysis of 1-acyl-1,2,4-triazoles (R_1COTr, R_2 = H) at 25 °C: ○, R_1 = Me; □, R_1 = Et; △, R_1 = i-Pr; ▽, R_1 = n-Pr; ●, R_1 = Ph; ■, R_1 = i-Bu; ▲, R_1 = t-Bu; ◇, R_1 = 3-Pent.

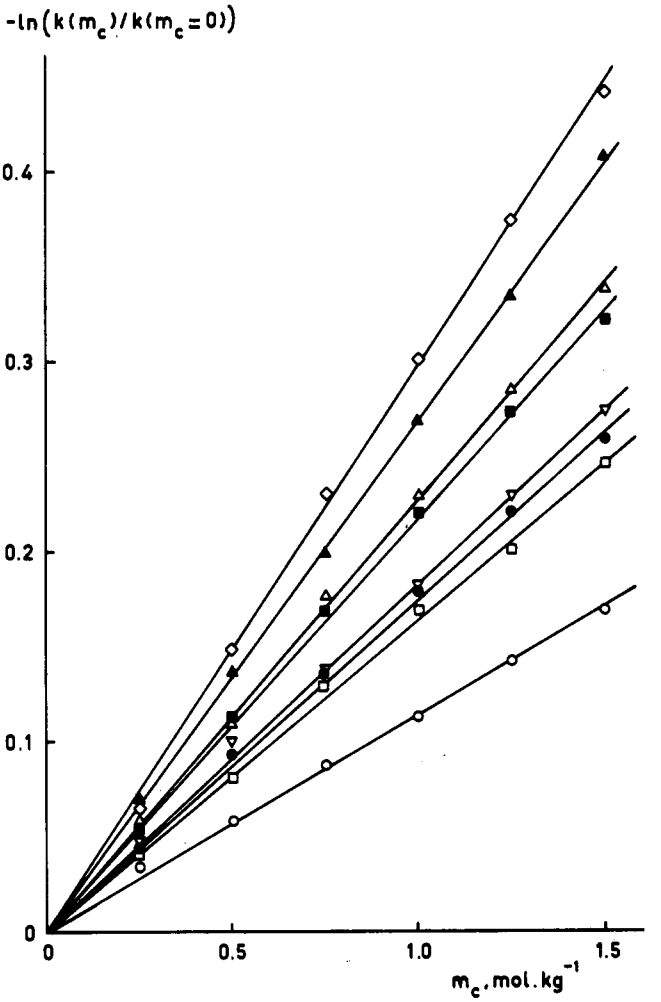

Figure 2. See legend to Figure 1, with cosolvent 1-propanol instead of ethanol.

assume that group interactions of alkyl groups in the substrate and activated complex (described by equivalent methylene groups, i.e., CH_3 = 1.5 CH_2 = 3 CH) remain unchanged during the activation process. Consequently, these pairwise interactions of alkyl groups with groups in the cosolvent cancel, and hence the dependence of rate constants on m_c for sets of related substrates (1–5) will be indistinguishable. In the second approach, an attempt is made to take account of differences in the pairwise interactions of an alkyl moiety in the initial and transition states with added cosolvent. This approach is required if the kinetic data reveal that the dependence of ln $[k(m_c)/k(m_c=0)]$ on m_c is characteristic of a particular substrate molecule.

Kinetic Results. Pseudo-first-order rate constants (k) and solvent deuterium isotope effects (k_{H_2O}/k_{D_2O}) for the neutral hydrolysis as well as second-order rate constants (k_H) for the acid-catalyzed hydrolysis of a series of 1-acyl-1,2,4-triazoles (1a–j) are given in Table I. The data show that both k and k_H vary considerably upon variation of R_1. In Figures 1 and 2, ln $[k(m_c)/k(m_c=0)]$ is plotted as a function of the molality of ethanol and 1-propanol, respectively. In all cases linear plots were obtained with quite different slopes. The derived values of G(EtOH) and G(n-PrOH) are also recorded in Table I, together with calculated values for G(CH) and G(OH). It is clear that the decrease of the rate constants upon increasing alcohol concentration is caused by a dominant rate-decreasing contribution of the CH groups. These effects are only partly compensated by a positive contribution of G(OH). For example, for ethanol $|5G(CH)| > |G(OH)|$. The overall picture is consistent with a loss of hydrophobicity during the activation process.

Table II compares rate constants for the neutral hydrolysis (k) and for the acid-catalyzed hydrolysis (k_H) of a series of 1-acyl-(3-substituted)-1,2,4-triazoles. Substantial substituent effects are observed. Medium effects on k are analyzed in terms of plots of ln $[k(m_c)/k(m_c=0)]$ vs mo-

Table II. Rate Constants and Medium Effects for the Neutral and Acid-Catalyzed Hydrolysis of 1-Acyl-(3-substituted)-1,2,4-triazoles Showing the Effect of the 3-Substituent in the Triazole Ring (25 °C)

	R_1	R_2	$k \times 10^5$, s^{-1}	k_{H_2O}/k_{D_2O}	G(EtOH), J·kg·mol^{-2}	G(*n*-PrOH), J·kg·mol^{-2}	G(CH), J·kg·mol^{-2}	G(OH), J·kg·mol^{-2}	$k_H \times 10^2$, kg·mol^{-1}·s^{-1}
1a	Me	H	216	3.00	−52 (2)	−97 (2)	−22 (2)	59	20
2a	Me	*t*-Bu	59.7	3.06	−83 (2)	−157 (2)	−37 (2)	103	56
2b	Me	Cl	692	2.92					
1b	Et	H	290	3.13	−103 (2)	−158 (3)	−28 (3)	37	29
3a	Et	Me	132	3.19	−105 (3)	−190 (2)	−42 (3)	106	67
3b	Et	*t*-Bu	82.8	3.15	−146 (3)	−272 (4)	−63 (4)	167	80
3c	Et	Ph	212	3.24	−110 (3)	−159 (3)	−41 (3)	95	9.5
1g	*t*-Bu	H	341	3.09	−185 (1)	−289 (2)	−52 (2)	76	68
4a	*t*-Bu	Me	168	3.04	−208 (3)	−355 (3)	−74 (3)	160	213
4b	*t*-Bu	*t*-Bu	106	—[a]	−268 (10)	−555 (10)	−134 (10)	387	241
1j	Ph	H	203	2.62	−83 (2)	−172 (3)	−45 (3)	140	9.4
5	Ph	Ph	127	2.95	−119 (2)	−254 (3)	−68 (3)	219	2.8

[a] Because of the high sensitivity for acid catalysis, and accurate value of k_{H_2O}/k_{D_2O} for the neutral hydrolysis is difficult to obtain.

Table III. Spectroscopic Data for 1-Acyl-1,2,4-triazoles

	R_1	R_2	$\nu_{C=O}$,[a] cm^{-1}	UV λ_{max},[b] nm	^{13}C chemical shift,[c] δ C=O	C3	C5
1a	Me	H	1754	218	167.9	152.8	143.1
2a	Me	*t*-Bu	1749	226	173.6	168.2	143.2
2b[d]	Me	Cl	1765	225			
1b	Et	H	1752	221	171.4	152.6	143.2
3a	Et	Me	1747	226	171.3	162.6	143.5
3b	Et	*t*-Bu	1749	226	173.4	171.7	143.2
3c	Et	Ph	1746	258, 270[f]	171.7	163.5	143.8
1c	*n*-Pr	H	1751	217			
1d	*i*-Pr	H	1751	218	174.5	152.8	143.5
1e	*i*-Bu	H	1750	218			
1f[e]	*s*-Bu	H	1750	219			
1g	*t*-Bu	H	1735	220	175.1	152.1	145.0
4a	*t*-Bu	Me	1729	227	175.1	162.0	145.4
4b	*t*-Bu	*t*-Bu	1726	229	175.3	172.7	145.0
1h	*n*-Pent	H	1748	219			
1i	3-Pent	H	1748	219	173.5	152.6	143.2
1j	Ph	H	1716	250	164.2	152.8	145.7
5	Ph	Ph	1706	273	164.3	163.8	146.3

[a] In CCl_4. [b] In water. [c] In $CDCl_3$. [d] From ref 25. [e] From ref 8. [f] Wavelength used for monitoring the kinetics of hydrolysis.

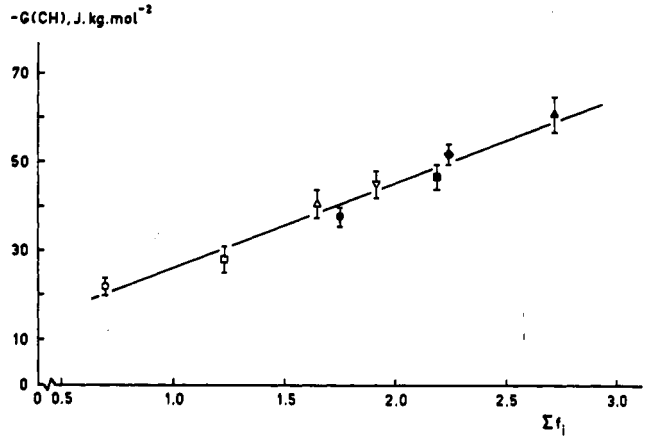

Figure 3. Plot of G(CH) vs the sum the Rekker hydrophobic fragmental constants ($\sum f_i$). The substrates are the 1-acyl-1,2,4-triazoles (R_1COTr): R_1 = Me (○); R_1 = Et (□); R_1 = *i*-Pr (△); R_1 = *n*-Pr (●); R_1 = Ph (▽); R_1 = *i*-Bu (■); R_1 = *t*-Bu (◆); R_1 = 3-Pent (▲).

lality of EtOH or *n*-PrOH, which show perfect linear correlation. Table II lists values for G(EtOH) and G(*n*-PrOH) as well as calculated values for G(CH) and G(OH). The alcohol-induced decrease of k is again the result of a dominant contribution of the CH groups in the cosolvent.

Interestingly, not only the solvation of R_1 but also that of the alkyl group R_2, which is quite far removed from the

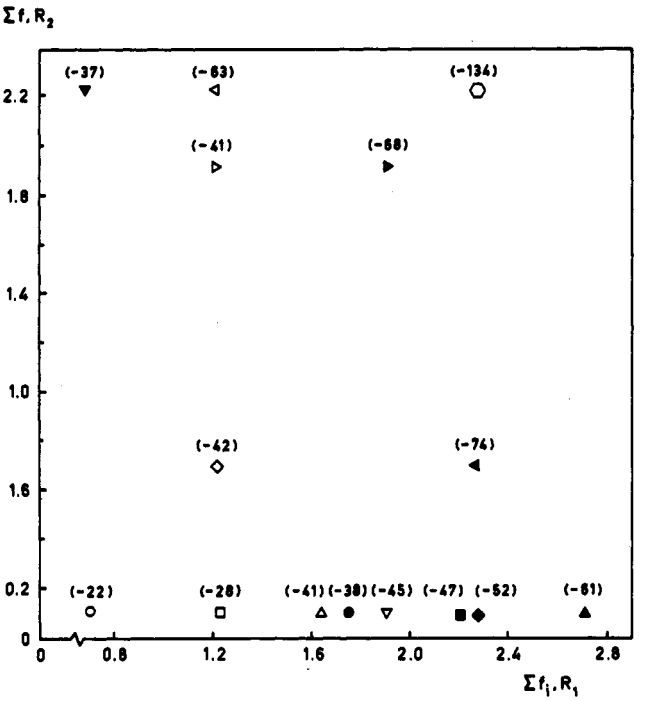

Figure 4. Diagram showing $\sum f_i$ (see text) for R_1 (horizontal axis) and $\sum f_i$ for R_2 (vertical axis). The numbers indicated for the different 1-acyl-(3-substituted)-1,2,4-triazoles are the G(CH) values at 25 °C: ○, R_1 = Me, R_2 = H; □, R_1 = Et, R_2 = H; △, R_1 = *i*-Pr, R_2 = H; ●, R_1 = *n*-Pr, R_2 = H; ▽, R_1 = Ph, R_2 = H; ■, R_1 = *i*-Bu, R_2 = H; ◆, R_1 = *t*-Bu, R_2 = H; ▲, R_1 = 3-Pent, R_2 = H; ◇, R_1 = Et, R_2 = Me; ◀, R_1 = *t*-Bu, R_2 = Me; ▷, R_1 = Et, R_2 = Ph; ▶, R_1 = R_2 = Ph; ▼, R_1 = Me, R_2 = *t*-Bu; ◁, R_1 = Et, R_2 = *t*-Bu; ○, R_1 = R_2 = *t*-Bu.

carbonyl reaction center, exerts a pronounced influence on the observed kinetic medium effect.

Carbonyl stretching frequencies, wavelengths of UV maxima, and ^{13}C NMR chemical shifts of the carbonyl carbon and the triazole carbons are reported in Table III for all substrates examined in this work.

Analysis of Substituent Effects. The general feature emerging from the data in Table I–III is the considerable sensitivity of rate constants, medium effects, and spectroscopic data toward variation of R_1 and R_2. According to the mechanism in Scheme I, the transition state for the neutral hydrolysis is less hydrophobic than the initial state. Now the assumption is made, based on previous results,[5-7] that solvation cosphere overlap between groups having similar solvation characteristics is a stabilizing influence and between groups having different solvation characteristics is a destabilizing effect. For EtOH and *n*-PrOH as the cosolvents, the effect of the hydrophobic groups is

dominant (vide supra). In fact, the contribution of G(CH) correlates well with the hydrophobicity of the substituents R_1 and R_2 in the substrates. Figure 3 shows an almost linear relationship between the sum of Rekker's hydrophobic fragmental constants ($\sum f_i$)[30] of the alkyl substituent R_1 (R_2 = H) and the G(CH) term. There is also a clear trend between the hydrophobicity of R_2 and G(CH). In Figure 4 we have constructed a plot using as the horizontal axis the value of $\sum f_i$ for R_1 and as the vertical axis the value of $\sum f_i$ for R_2. The contribution of the CH groups of the cosolvent to the overall medium effect is indicated for the particular substrates. The least hydrophobic substrates are found in the lower left corner of the diagram, whereas the most hydrophobic substrates are in the upper right corner. Between these two regions there is a large increase in the magnitude of G(CH). The diagram also reveals that G(CH) is much more sensitive to changes in hydrophobicity of R_1 than to similar changes of R_2. We note that the kinetic medium effect is not correlated with the overall hydrophobicity of the substrate. Presumably, the effects of R_1 and R_2 on G(CH) are not additive. For example, the sensitivity of G(CH) to changes in the hydrophobicity of R_1 increases as the substituent R_2 is made more hydrophobic. It is evident that changes in G(OH) follow the same trends that are observed for G(CH). However, some important features emerge from a comparison of the medium effects of EtOH and n-PrOH on the k values of isomeric substrates, e.g. **1e** and **1g** vs **1c** and **1d**. It is found that the medium effects are significantly smaller for the substrates in which branching is present at the β-carbon of R_1 than for the substrates with branching at the α-carbon (Figures 1 and 2). This effect finds its origin in the larger contribution of G(OH). Furthermore, it is noticeable that the contribution of G(OH) is more important for substrates where R_1 is phenyl rather than alkyl.

The dependence of the pseudo-first-order rate constants for neutral hydrolysis on R_1 and R_2 is complex. The substituent effects of R_1 do not correlate with known sets of polar or steric alkyl substituent constants.[8] Polarisability constants (e.g., P)[20] do not account for the substituent effects either. Steric effects will play a role since the coordination of the carbonyl carbon atom increases during the activation process. Surprisingly, however, the rate constant increases upon α-branching: Me < Et < i-Pr ≤ t-Bu. By contrast, a decrease in rate constant is observed in the series Et > n-Pr > i-Bu > n-Pent and i-Pr > s-Bu > 3-Pent. Thus, steric inhibition is only revealed by branching at the β-carbon atom. Previously, these effects have been correlated by a branching equation.[8]

It will be noted that for R_1 = t-Bu there is a significant decrease of the carbonyl stretching vibration and a remarkable downfield shift of the C-5 ^{13}C NMR resonance of the triazole ring (Table III). Following suggestions made by Pinkus et al.[31] for a comparable effect in methyl alkyl ketones, we submit that out-of-plane twisting of the t-Bu group occurs as a result of steric interference with the triazole moiety. This leads to decreased double-bond character in the carbonyl group, an effect not present for R_1 = Me, Et, or i-Pr. Presumably, this effect reduces the hydrolytic reactivity of **1g** and may explain why **1d** and **1g** exhibit similar k values. But, interestingly, the kinetic effect in the series R_1 = Me, Et, i-Pr, t-Bu appears to depend on the hydration change involved in the activation process. This is particularly well illustrated for hydrolysis reactions in aqueous solutions containing 5 M i-PrOH. Under these conditions no alcoholysis occurs. Keeping R_2 = H, we find the following k values for neutral hydrolysis: R_1 = Me, 112 × 10^{-5} s^{-1}; Et, 124 × 10^{-5} s^{-1}; i-Pr, 107 × 10^{-5} s^{-1}; t-Bu, 84.3 × 10^{-5} s^{-1}. Now the sequence of rate constants is about the reverse of that found in water. In the binary i-PrOH–H_2O solution, the hydrophobic hydration shells of the R_1 alkyl groups will be largely broken down and, apparently, under these conditions a normal steric effect (including out-of-plane twisting for R_1 = t-Bu) for α-branching is observed.

The rate constants for the acid-catalyzed hydrolysis (k_H; Tables I and II) are equally sensitive to substituent effects of the alkyl group R_1. Increasing hydrophobicity of R_1 is accompanied by larger k_H values (Tables I and II). In fact, for **4a,b** the acid catalysis is so effective that the pH range for the water-catalyzed reaction is very narrow. Just as for the neutral hydrolysis reaction, branching at the α-carbon atom has an incremental effect whereas β-branching strongly decreases the rate of acid-catalyzed hydrolysis. Small rate constants are found for substrates with R_1 = Ph.

Turning now to the effects of the substituents at C-3 in the triazole ring, the first point to note is that these effects are substantial. By contrast, the solvent deuterium isotope effects and the carbonyl stretching vibrations hardly respond to substituent variation at C-3. An increase in hydrophobicity of the group at C-3 leads to enhanced sensitivity toward acid catalysis as evidenced by the k_H values for R_2 = Me, t-Bu. The smallest rate constants are observed for R_2 = Ph. We contend that the substituent effects of R_2 on both k and k_H are not steric in nature. The substituent R_2 also hardly affects the ^{13}C NMR chemical shifts in the triazole ring, apart from that at C-3, as anticipated. It appears that the factor dominating the substituent effect of R_2 is an effect on the leaving ability of the triazole moiety. For 3-substituted 1,2,4-triazoles, the following pK_a's have been found:[32] 10.73 (R_2 = Me), 10.69 (R_2 = Et), 10.26 (R = H), 9.59 (R = Ph), 8.13 (R = Cl). During the activation process for the neutral hydrolysis, there will be an increase of the negative charge at N-1, and this may explain the finding that log k exhibits an inverse correlation with pK_a. For the acid-catalyzed hydrolysis, there is a correlation between log k_H and the pK_a of the corresponding 3-substituted triazolium ion: 3.28 (R_2 = Me), 3.20 (R_2 = Et), 2.27 (R = H), 2.05 (R_2 = Ph).[32] Thus, it seems that the simplest way to explain the alkyl substituent effect of R_2 is in terms of a rate-decreasing effect on the leaving ability of the triazole ring (neutral hydrolysis) and a rate-enhancing effect as a result of an increase in basicity (acid-catalyzed hydrolysis). The exact molecular basis of these effects yet remains obscure.

Conclusion

The present study shows that a quantitative treatment of medium effects on simple hydrolytic reactions in highly aqueous reaction media in terms of pairwise Gibbs energy interaction parameters and group contributions constitutes a highly useful procedure to understand substituent effects and reaction mechanisms in water and water-rich binary solvents. The data presented here show that alkyl substituent effects on the neutral and acid-catalyzed hydrolysis of a large series of 1-acyl-(3-substituted)-1,2,4-triazoles can be analyzed in terms of steric and solvation effects. But the most important conclusion is that the

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steric alkyl substituent effects themselves are strongly modulated by solvation changes during the activation process. In highly aqueous solutions the rate constants increase with increasing hydrophobicity of the alkyl substituents due to solvation effects, but the effect depends critically on the presence of an alcoholic cosolvent.[33] In water, alkyl substituent effects reflect the loss of hydrophobic surface of the substrate during the activation process. This reduction of hydrophobic hydration is larger if more hydrophobic substituents are present as indicated by the increased medium effect of relatively hydrophobic cosolvents. As anticipated, alkyl groups near the reaction center exert a more pronounced solvation effect than more remote alkyl groups. The overall substituent effects of large alkyl groups that decrease the rate constant for hydrolysis because of steric hindrance are, in fact, reduced because of a counteracting rate-increasing contribution due to the solvation effect as the alkyl moiety becomes more hydrophobic. This situation implies that any set of steric alkyl substituent constants, derived from kinetic data for reactions in water or highly aqueous reaction media, will contain a substantial contribution of solvation effects.

Experimental Section

Materials. Ethanol (p.a.) and 1-propanol (p.a.) were supplied by Merck and were used without further purification. Demineralized water was distilled twice in an all-quartz distillation unit. All solutions were made up by weight and contained 4×10^{-5} mol·dm^{-3} HCl (to suppress catalysis by hydroxide ions) for the measurement of rate constants for neutral hydrolysis and appropriate concentrations of HCl for the measurement of rate constants of acid-catalyzed hydrolysis. Solvent deuterium isotope effects were measured with D_2O solutions that contained 4×10^{-5} mol·dm^{-3} DCl. Generally, the pH range in which the reaction rate constant is independent of the actual pH is very small for compounds that undergo very effective acid catalysis. Therefore, measurements were performed between pH 4 and 4.5. The 1-acyl-(3-substituted)-1,2,4-triazoles **1a–j**, **2b**, and **5** have been reported previously.[8,25] The new substrates (vide infra) were prepared from the corresponding acyl chloride and 3-substituted 1,2,4-triazole according to a standard procedure.[8,25] Solid 1-acyl-1,2,4-triazoles were recrystalized twice from *n*-hexane, and the liquid substrates were distilled in vacuo. The 3-*tert*-butyl-1,2,4-triazoles,[34] 3-methyl-1,2,4-triazole,[35] and 3-phenyl-1,2,4-triazole[35] were prepared with use of standard procedures. NMR spectra were recorded on a Varian VXR-300 instrument with TMS as an internal standard.

1-Methanoyl-3-*tert*-butyl-1,2,4-triazole (2a): bp 100–101 °C (1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.64 (s, 3 H), 8.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.99 (p), 28.78 (p), 32.82 (q), 143.15 (q), 173.63 (q).

1-Ethanoyl-3-methyl-1,2,4-triazole (3a): mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.38 (s, 3 H), 3.10 (q, 2 H), 8.81 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.66 (p), 13.73 (p), 28.01 (s), 143.46 (t), 162.58 (q), 171.29 (q).

1-Ethanoyl-3-*tert*-butyl-1,2,4-triazole (3b): bp 75–77 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H), 1.32 (s, 9 H), 3.05 (q, 2 H), 8.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.65 (p), 27.96 (s), 28.73 (p), 32.81 (q), 143.23 (t), 171.67 (q), 173.41 (q).

1-Ethanoyl-3-phenyl-1,2,4-triazole (3c): mp 60–62 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 3.18 (q, 2 H), 7.45 (m, 5 H), 8.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.77 (p), 28.11 (s), 126.79, 128.56, 129.37, 130.2, 143.84 (t), 163.46 (q), 171.70 (q).

1-(2-Methylpropionyl)-3-methyl-1,2,4-triazole (4a): bp 50–51 °C (0.7 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 2.34 (s, 3 H), 8.72 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.83 (p), 26.68 (p), 41.08 (q), 145.37 (t), 161.99 (q), 175.14 (q).

1-(2-Methylpropionyl)-3-*tert*-butyl-1,2,4-triazole (4b): bp 180–182 °C (8 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9 H), 1.40 (s, 9 H), 8.70 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.71 (p), 28.75 (p), 32.70 (q), 41.06 (q), 145.04 (t), 172.66 (q), 175.29 (q).

Product Analysis. The reaction products of the solvolysis of compounds **1a,b,g,j**, **4a**, and **5** were analyzed quantitatively. Hereto, reactions were performed in the presence of 0.5, 1.0, and 1.5 mol·kg^{-1} ethanol and 1-propanol, respectively. The substrate concentration in these experiments was always about 5×10^{-3} mol·dm^{-3}, the HCl concentration was 4×10^{-5} mol·dm^{-3}, and the pH was checked before and after the reactions. After completion of the reaction, the products were analyzed by gas chromatography (Hewlett-Packard 5890 instrument, equipped with a 15-m wide-bore HP1 fused silica column) and, if necessary, by GC–MS (Ribermag R-10-10c) with the authentic triazoles, acids, and esters. The relative amounts of alcoholysis were determined by calibration. In every case, traces of ethyl and propyl ester could be determined. Independent experiments showed that the esters were not formed by esterification of the acid, formed after hydrolysis. The yield of the ester depended linearly on the molality of alcohol present. Although slight differences were found between the amounts of ester for the different substrates studied, the amount of ethyl ester formed at 1.5 mol·kg^{-1} ethanol never exceeded $3 \pm 1\%$ and the amount of propyl ester was even smaller, that is $2 \pm 1\%$. Kinetic analysis showed that this small amount of alcoholysis does not hamper our quantitative analysis of medium effects.

Kinetic Measurements. The pseudo-first-order rate constants were determined by following the change of absorbance at appropriate wavelengths; see Table III. About 3 μL of a concentrated stock solution in acetonitrile (5×10^{-2} mol·dm^{-3}) was added to the reaction medium (2.5 cm^3) in a quartz UV cell (1 cm) that was placed in a thermostated cell compartment of a spectrophotometer (Perkin-Elmer λ5, equipped with a data station or a Perkin-Elmer λ2 connected to a standard PC). The reactions were followed for about 10 half-lives, and excellent first-order kinetics was observed in all cases. For compound **4b**, some solubility problems occurred and some delay time was applied after injection of the probe solution before data points were collected. For every measurement about 100–150 data points were used. For the fast reactions, the PE λ2 was used and rate constants were calculated by a commercially available fitting program. Slower reactions were measured on both the λ5 and the λ2 with an end value approach as well as a fitting program. Rate constants at each molality of cosolvent were measured at least three times and were reproducible to within 1%. For the calculations of the value of $G(C)$ from data, obtained at at least six molalities, a least-squares procedure was used. The rate constants for the acid-catalyzed hydrolysis were calculated from pseudo-first-order rate constants obtained at six different pH values, by a least-squares analysis.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of the novel compounds **2a**, **3a–c**, and **4a,b** (13 pages). Ordering information is given on any current masthead page.

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