Cycloadditions in mixed aqueous solvents: the role of the water concentration[†]

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ABSTRACT: We examined the kinetics of a series of cycloaddition reactions in mixtures of water with methanol, acetonitrile and poly(ethylene glycol) (MW 1000). The reactions include the Diels–Alder (DA) reaction between cyclopentadiene and *N-n*-butylmaleimide or acridizinium bromide, the retro-Diels-Alder (RDA) reaction of 1,4,4a,9a-tetrahydro-4a-methyl-($1\alpha,4\alpha,4a\alpha,9a\alpha$)-1,4-methaneanthracene-9,10-dione and the 1,3-dipolar cycloaddition of benzonitrile oxide with *N-n*-butylmaleimide. Plots of log$k$ vs the molar concentration or volume fraction of water are approximately linear, but with a characteristic break around 40 M water. This break, absent for the RDA reaction, is ascribed to hydrophobic effects. Comparison with aqueous mixtures of the more hydrophobic 1-propanol shows that these mixtures induce qualitatively similar effects on the rate, but that preferential solvation effects cause the mixtures of 1-propanol to exhibit a more complex behavior of log$k$ on composition. The results are analyzed using the Abraham–Kamlett–Taft model. The solvent effects in aqueous mixtures are not satisfactorily described by this model. For some cycloadditions, small maxima in rate are observed in highly aqueous mixtures of alcohols. The origin of these maxima and the aforementioned breaks is most likely the same. Copyright © 2005 John Wiley & Sons, Ltd.

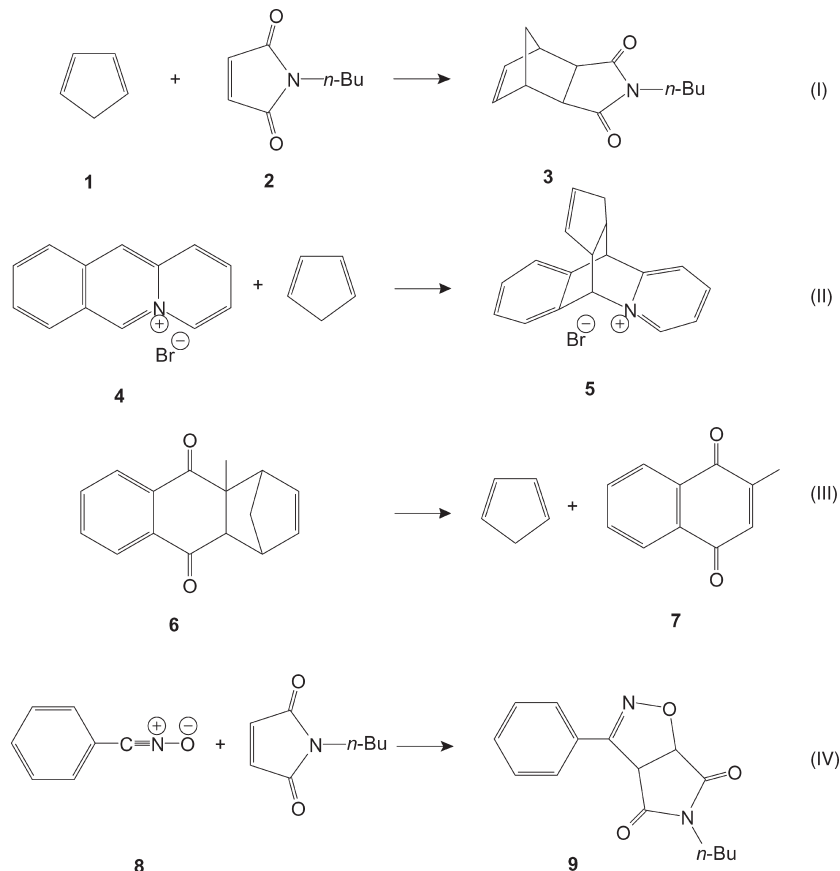KEYWORDS: cycloadditions; mixed aqueous solvents; water; Diels–Alder reaction

INTRODUCTION

Diels–Alder (DA) reactions in aqueous media have been studied thoroughly[1] since the pioneering work of Breslow's group in the early 1980s.[2] In particular, salt solutions of both salting-in and salting-out agents[3] and mixtures of water with alcohols (ethanol, propanol)[4,5] have been used frequently as the reaction medium. Nevertheless, aqueous Diels–Alder (DA) reactions have not revealed all their secrets yet. It has been well established that no single interaction mechanism is responsible for the dependence of the rate constants on the composition of (aqueous) solvent mixtures. Solvent polarity, hydrogen bonding and enforced hydrophobic interactions are important factors that may affect the rate constant. Aqueous mixtures with hydrophobic cosolvents such as 1-propanol are particularly complex, as preferential solvation effects may become significant, which hampers the search for correlations of reaction rates with composition. It is therefore surprising that little attention has been given to aqueous mixtures of, e.g., methanol, or other 'simpler' cosolvents.

To obtain a more complete picture of the reactivity in aqueous environments, we have studied a series of DA reactions in mixtures of water with several 'hydrophilic' cosolvents/cosolutes: polyethylene glycol (average mol. weight 1000) (PEG1000), methanol, and acetonitrile. Methanol and acetonitrile have a much smaller tendency to solvate molecules preferentially in an aqueous environment, compared with, e.g., 1-propanol. Methanol is, like water, both a good hydrogen-bond donor and acceptor. Acetonitrile, on the other hand, is a poor hydrogen-bond donor and only a relatively weak hydrogen-bond acceptor. This difference is nicely reflected, for instance, in the thermodynamics of mixing. Methanol mixes with water exothermically, whereas acetonitrile does so endothermically, because it ruptures the hydrogen-bond network of water without forming (strong) hydrogen bonds itself. PEG is a good hydrogen-bond acceptor, but is unable to donate hydrogen-bonds.

The reactions studied (I–IV) are shown in Scheme 1. They include the DA reaction between cyclopentadiene (**1**) and *N-n*-butylmaleimide (**2**) [reaction (I)], the DA reaction between **1** and acridizinium bromide (**4**) [reaction (II)], the retro-Diels–Alder (RDA) reaction of 1,4,4a,9a-tetrahydro-4a-methyl-($1\alpha,4\alpha,4a\alpha,9a\alpha$)-1,4-methaneanthracene-9,10-dione (**6**) [reaction (III)] and the 1,3-dipolar cycloaddition (DC) between benzonitrile oxide (**8**) and **2** [reaction (IV)]. Reaction (I) is an example

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Scheme 1

of a typical DA reaction, in which the dienophile is capable of accepting hydrogen bonds, which promotes the rate of the reaction. Reaction (II), on the other hand, involves two reactants that are not or only very weakly susceptible to hydrogen-bond formation. Comparison of reactions (I) and (II) may offer insight into the contribution of (direct) hydrogen bonding to changes in rate. The RDA reaction (III) reflects the reverse process of reaction (I). The activation process of this reaction can be influenced by hydrogen-bond formation, but association of two reactions (as part of the reaction) is absent. Therefore, hydrophobic effects play only a minor role in governing the rate of this reaction. Finally, reaction (IV) involves two relatively polar substrates, that are both susceptible to hydrogen bonding. A summary is provided in Table 1.

Table 1. Sensitivity of the rate constants of reactions I–IV

Reaction	Hydrogen bonding	Hydrophobic effects
(I)	+	+
(II)	0	+ + +
(III)	+	0
(IV)	± [a]	+

[a] Hydrogen bonding to both reactants influence rate in opposite ways.

RESULTS AND DISCUSSION

Aqueous mixtures of methanol, acetonitrile, 1-propanol and PEG1000

In Figs 1–4, the logarithms of the rate constants ($\log k$) are plotted against the concentration of water for reactions
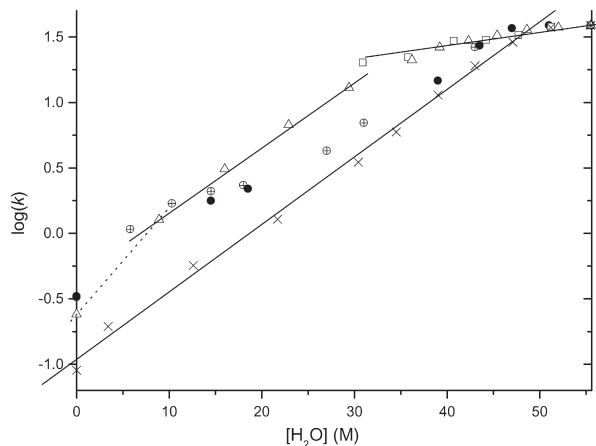

Figure 1. Log k vs the concentration of water for the reaction of **1** with **2** at 25 °C in mixtures of water with PEG1000 (□), methanol (△), acetonitrile (×) and 1-propanol (●; values for ethyl- rather than n-butylmaleimide are indicated with ⊕). k has units $M^{-1} s^{-1}$

Figure 2. Log k vs the concentration of water for the reaction of **1** with **4** at 25 °C in mixtures of water with PEG1000 (□), methanol (△), acetonitrile (×) and 1-propanol (●). k has units $M^{-1} s^{-1}$
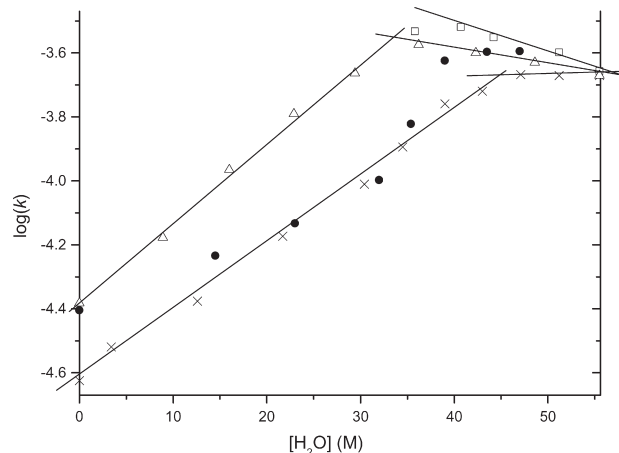

Figure 4. Log k vs the concentration of water for the reaction of **2** with **8** at 25 °C in mixtures of water with PEG1000 (□), methanol (△), acetonitrile (×) and 1-propanol (●). k has units $M^{-1} s^{-1}$

(I)–(IV) in mixtures of water with methanol, acetonitrile and PEG1000. We chose to plot the data against the molar concentration of water because the concentration is a measure of the amount of water present per unit volume, independent of the size of the cosolvent molecules, in contrast to the mole fraction scale. The volume fraction of water also scales with the (molar) concentration of water, although only insofar as the solvents mix ideally. The non-ideal part is only a minor contribution, although typically a few percent. Interestingly, linear dependences are found of log k on [H$_2$O] over large ranges of concentrations, with one (or two) relatively sharp bends.

For comparison, aqueous mixtures of 1-propanol were also examined. Although the data for 1-propanol roughly follow the same patterns found for methanol and acetonitrile, no linear dependence of log k on the concentration of water is observed. This behavior is attributed to preferential solvation effects. Nevertheless, one essential
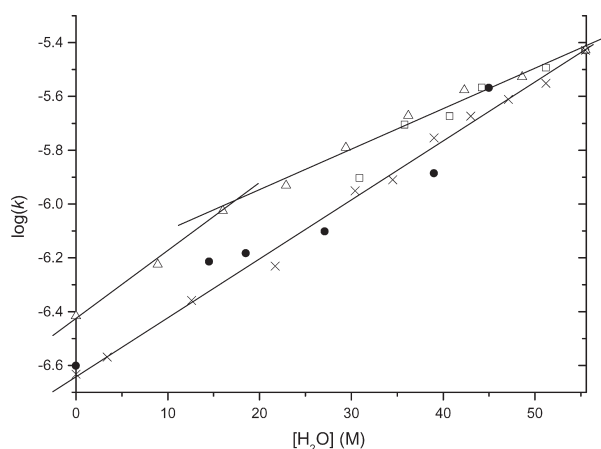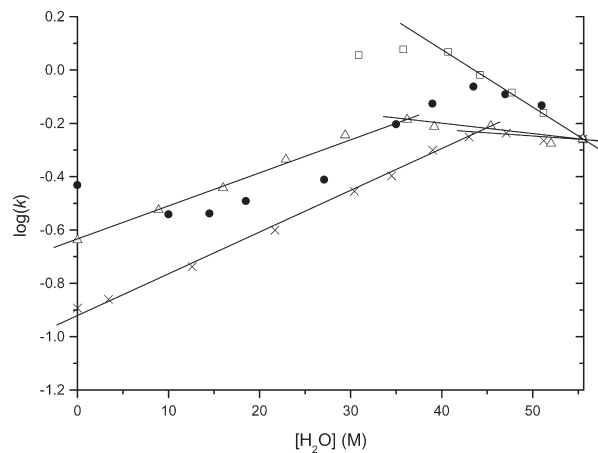

Figure 3. Log k vs the concentration of water for the unimolecular reaction of **6** at 40 °C in mixtures of water with PEG1000 (□), methanol (△), acetonitrile (×) and 1-propanol (●). k has units s^{-1}

feature is evident for all cosolvents: in the water-rich regime there is a sudden change in slope at around 40 M water (except for the RDA reaction; see below). Generally, the breaks occur at a somewhat higher concentration for acetonitrile than for methanol, with the break for 1-propanol in between. The breaks may reflect the ability of the water to maintain its hydrogen-bond network in the different mixtures (see below).

Disregarding reaction (III) for the moment, when comparing methanol and acetonitrile, the rate constants are invariably larger in methanol or aqueous mixtures of methanol than in acetonitrile or aqueous mixtures of acetonitrile. This is as expected, since methanol is more polar and capable of donating hydrogen bonds. Starting from either pure methanol or acetonitrile, log k increases linearly with the concentration of water over an extended range (up to 35–45 M), although for methanol a deviation is found at low concentrations of water in the case of reaction (I). The slopes are nearly identical for methanol and acetonitrile in each case. This is remarkable: one would expect the slope to be higher for acetonitrile, because the hydrogen-bond donating capacity varies more dramatically in aqueous mixtures of acetonitrile (based on α; see below).

In the water-rich regions, the slopes of log k vs [H$_2$O] become close to zero, and occasionally slightly negative. In the latter case, a maximum in rate constant is observed around 40 M water.

Solutions of PEG1000 were also studied, up to a concentration of 500 g l^{-1}. At still higher concentrations of PEG1000, the increased viscosity prohibited an accurate determination of rate constants. In cases, where maxima for the rate constants were found for alcohols [reactions (II) and (IV)], PEG1000 displays a similar pattern, and the maxima even exceed those found for 1-propanol. However, this is not a general observation: for the reaction of cyclopentadiene with naphthoquinone, a

maximum was found in mixtures of water with 2-methyl-2-propanol,[4] but not in aqueous solutions of PEG400.[6] In any case, the maxima are not just a peculiarity, caused only by hydrophobic cosolvents, such as propanol or butanol. Even methanol may induce an additional acceleration, albeit smaller than that found for 1-propanol.

For the RDA reaction, the characteristic changes in slope at around 40 M water are absent. For methanol, two linear areas are found, between 0 and 15 M and between 15 and 55 M. For acetonitrile, log$k$ is linear with [H$_2$O] over the entire range of composition. We suggest that the origin of the changes in slope of log$k$ vs [H$_2$O] around 40 M water for the other reactions lies in hydrophobic effects, as for the RDA reaction changes in hydrophobicity (during the activation process) are minor.[7]

Comparing reactions (I) and (II), the behavior of log$k$ in the various mixtures is qualitatively similar, despite the fact that reaction (II) is not directly influenced by hydrogen bonds. The magnitudes of the changes in rate constant are much larger for reaction (I) than for reaction (II), however. A similar behavior (large linear regions, particularly for acetonitrile, with changes in slope in the water-rich region) may result from the fact that the underlying mechanisms responsible for determining the rate variations are the same, and only the solvent sensitivities of the various reactions are different. This would rule out direct hydrogen bonding as an important contributor to changes in rate, which is not in line with previous results.[1] Alternatively, the other factors that influence the rate (in particular solvent polarity) and direct hydrogen-bond interactions vary with solvent composition in a similar manner, either coincidentally, or because of a more fundamental reason.

For the DC reaction (IV), the rate constants are hardly affected by changes in medium (k varies by a factor of < 2.5 in the case of methanol and < 4 in case of acetonitrile). For this reaction we found that the different types of interactions that affect the rate oppose each other, resulting in modest overall medium effects.[8] Despite this, the qualitative picture again is strikingly similar to that for reactions (I) and (II).

Correlations with the composition of the medium

In order to elucidate the origins of these solvent effects, we consider different approaches to rationalizing the data. In particular, attempts were made to fit the data to a multiparameter model, and comparisons are made with standard Gibbs energies of transfer in mixed aqueous solvents.

Linear multiparameter models. Properties of solvents, in particular solvent polarity, have been captured in a multitude of empirical scales, among them single-parameter scales such as $E_T(30)$,[9] and multiparameter scales, such as the Abraham–Kamlett–Taft (AKT) model (see below). Single-parameter scales try to avoid the difficult task of attributing complex trends in, for example, rate constants to variations in several 'fundamental' properties (e.g. electron-pair donating ability), by capturing them into a single, composite parameter. Such correlations naturally will be satisfactory only if the process under consideration bears some resemblance to the one on which the scale is based. Its main advantage is its simplicity. A major drawback is that correlations are still difficult to interpret. The multiparameter approach aims at more transparent correlations. Although usually empirical in nature, the individual parameters have a more fundamental flavor, capturing a single solvent property at a time. The AKT approach,[10] in its basic form, recognizes three aspects of solvation effects: dipolarity/polarizability (π^*), hydrogen-bond acidity (α) and hydrogen-bond basicity (β). The parameters are derived from spectral changes (UV–visible, NMR) for probe molecules that are sensitive to changes in these properties to various extents. Often, additional parameters that account for 'solvophobicity' are included, such as the Hildebrand solubility parameter (δ^2), based on the enthalpy of vaporization per unit volume of the solvent, or the solvophobicity parameter (Sp), based on transfer parameters of low molecular weight alkanes and noble gases from organic solvents to water.[11]

For a variety of DA reactions, rate constants were found to correlate with one or more properties of the solvents.[12–20] In most cases, the AKT model[10] was used to account for different aspects of solvent polarity. Usually, only pure solvents are taken into account, and often water is not included in the analyses. Desimoni *et al.*[12] analyzed solvent effects on a wide range of DA reactions and, based on that analysis, made a division into three types of DA reactions: type A, reactions that are mainly affected by the hydrogen-bond donor capacity α of the solvent, although significant contributions of π^* are sometimes also present; type B, reactions that mainly respond to changes in β; and type C, reactions that are insensitive to both α and β. In another study,[14] satisfactory fits were obtained with contributions of α, π and Sp. Upon inclusion of water, the contribution of Sp vastly increased. Mayoral and co-workers analyzed several DA reactions in a range of solvents, including aqueous mixtures.[15,17,18] Again, α and Sp were found to be important. Their relative contributions differed substantially when only aqueous mixtures or only (non-aqueous) solvents were taken into account.

The single-parameter $E_T(30)$ polarity scale does not account for the observed trends in log$k$ presented in the previous section. Instead, we have attempted to rationalize the observed trends in rate constants of the different reactions in terms of the AKT model, using the equation

$$\log k = \text{constant} + a\alpha + b\beta + p\pi^* + sSp \quad (1)$$

The coefficients a, b, p and s describe the relative contributions (they are not directly comparable with each other, as the scales for α, β, π^* and Sp are arbitrary and only have indirect physical meaning; to circumvent this, 'standardized coefficients' may be calculated[14]) of the different solvent properties, described by α, β, π^* and Sp. For mixtures of water with methanol, values are available for all parameters. For acetonitrile as the cosolvent, values of α, β and π^* are available, and values of Sp were estimated. Mixtures with 1-propanol were not taken into consideration, as preferential solvation effects are expected to interfere. The aqueous PEG mixtures will only be considered qualitatively, because no reasonable estimates for Sp could be made. In all cases, some parameters did not contribute significantly to the fit, and fits without these parameters were performed subsequently. A set of parameters used in a fit will be placed in braces, e.g. $\{\alpha, \pi^*\}$ means a fit only including α and π^*.

Although the aim was to study the contributions of the different properties in aqueous mixtures, pure solvents were also considered. The motivation was twofold. First, comparing results obtained for a series of solvents with those obtained for the mixures might be considered a consistency check. Alternatively, comparison may point out qualitative or quantitative differences between aqueous mixtures and non-aqueous solvents. Second, the parameters π^* and Sp, although poorly correlated for pure solvents ($r = 0.620$ for all solvents considered in this paper; $r = 0.495$ when water is omitted), turned out to be much better correlated in mixtures of water with methanol or acetonitrile ($r = 0.951$).

The results in Table 2 only include parameters that contribute significantly. In a few instances, alternative results are also presented, with smaller but still satisfactory regression coefficients. For a number of fits, calculated values of $\log k$ are shown in Fig. 5, together with the experimental values.

For reaction I, when only mixtures are considered, the best fit is obtained with $\{\alpha, \pi^*\}$, but with $\{\alpha, Sp\}$ a good fit is also obtained. Perhaps the most striking result is the close similarity in behavior of $\log k$ and π^* in water–methanol mixtures. For pure solvents, on the other hand, an acceptable fit is obtained only for $\{\alpha, Sp\}$. This result can be accounted for because water was included in the fit. Sp ranges from 0 to 0.35 for organic solvents, but for water $Sp = 1$. Therefore, a much larger rate in water than in organic solvents is conveniently captured by Sp. The inclusion of water usually amplifies the contribution of Sp.[14] Including the (other) pure solvents in the fits for the mixtures yields the best fit with $\{\alpha, Sp\}$ ($r = 0.979$; for $\{\alpha, \pi^*\}$, $r = 0.88$). The coefficients are within error margins consistent with each other. One interesting point to note is that although α contributes significantly, its characteristic pattern in mixtures of water and acetonitrile, with a drastic increase at low concentrations of water, is not reflected in the experimental $\log k$.

For reaction (II), the series of pure solvents did not give a proper fit. This result may be due in part to the limited number of points (8). Nevertheless, the dependence of $\log k$ on the solvent is complex and may not be fully captured by the AKT model. For aqueous mixtures, a strange result is obtained. Two mutually exclusive combinations of parameters give reasonable fits ($\{\alpha, \pi^*\}$, $r = 0.963$; $\{\beta, Sp\}$, $r = 0.979$). With $\{\beta, Sp\}$, unlike $\{\alpha, \pi^*\}$, the characteristic maxima in the plots of $\log k$ vs the concentration of water could be reproduced.

Table 2. Summary of fits using the AKT model[a]

Reaction	System	a	b	p	s	r
(I)	Mixtures[b]	1.42 (0.17)	—	4.16 (0.24)	—	0.991
		1.08 (0.30)	—	—	2.45 (0.23)	0.975
	Pure solvents (7)[c]	0.88 (0.22)	—	—	2.09 (0.34)	0.981
	All	0.92 (0.17)	—	—	2.33 (0.16)	0.979
(II)	Mixtures	—	1.86 (0.24)	—	1.34 (0.07)	0.979
		0.58 (0.13)	—	1.53 (0.19)	—	0.963
	Pure solvents (8)[d]	×[e]	×[e]	×[e]	×[e]	×[e]
	All	0.44 (0.11)	—	1.27 (0.19)	—	0.909
III	Mixtures	0.43 (0.11)	—	—	1.13 (0.09)	0.984
		0.65 (0.13)	—	1.77 (0.18)	—	0.975
	Pure solvents (10)[d]	0.80 (0.07)	—	1.01 (0.15)	—	0.986
		0.74 (0.13)	—	—	1.03 (0.32)	0.958
	All	0.82 (0.06)	—	1.09 (0.10)	—	0.975
		0.75 (0.07)	—	—	0.93 (0.10)	0.970
(IV)	Mixtures	—	1.46 (0.16)	—	0.88 (0.04)	0.977
	Pure solvents (13)[f]	×[e]	×[e]	×[e]	×[e]	×[e]
	All	—	0.37 (0.13)	—	0.635 (0.09)	0.775

[a] Error margins given in parentheses.
[b] Aqueous mixtures of methanol and acetonitrile.
[c] Some values taken from Ref. 21.
[d] Some values taken from Ref. 5.
[e] No acceptable fit with any combination of parameters could be obtained.
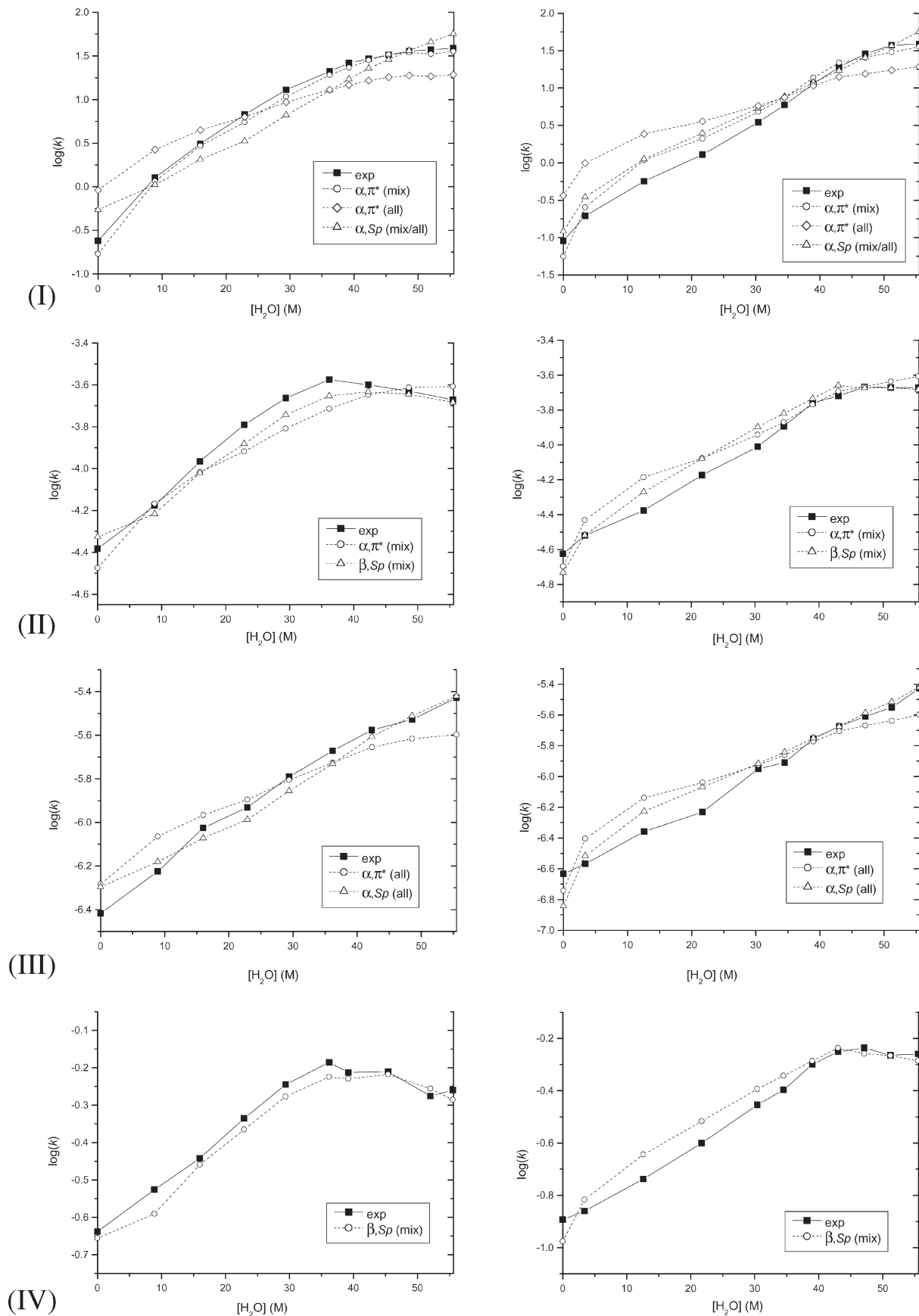[f] Values from Ref. 8.

Figure 5. Overview of log*k* values in mixtures of water with methanol (left) and acetonitrile (right) as determined from various fits (open symbols). Experimental values are indicated with closed squares

Mathematically, this pattern is caused by the fact that β increases on going from pure water to mixtures of water with either methanol or acetonitrile. This reaction falls into Desimoni *et al.*'s category B,[13] thus sensitive to β, in line with the result from our fit. On the other hand, $\log k$ also increases in mixtures of water with PEG, for which β was found to be constant up to 40 wt% of PEG.[22] Therefore, at least for mixtures of water and PEG, a sensitivity for β cannot explain a rate increase relative to water. When pure solvents and mixtures are combined, the most satisfactory fit is obtained with $\{\alpha, \pi^*\}$, but the correlation becomes much less satisfactory ($r = 0.909$), considering that the majority of data points (~ 20) included in the fit are those for the mixtures (for which $r = 0.963$).

For reaction (III), good fits were obtained with either $\{\alpha, \pi^*\}$ or $\{\alpha, Sp\}$. This is true for pure solvents (10), mixtures or a combination. For pure solvents, $\{\alpha, \pi^*\}$ produces the better fit. This result was expected because this reaction does not involve the association of two reactants during the activation process; solvophobic effects play only a minor role. It is therefore strange that (also) for pure solvents, for which π^* and Sp correlate poorly, a good fit is obtained with $\{\alpha, Sp\}$. This result confirms that results from multiparameter analyses should not be interpreted on a simple basis. Overall, the fits with $\{\alpha, \pi^*\}$ give the most consistent results. The relative contributions of α and π^* are both larger than those found by Desimoni *et al.*[13] for this reaction at 90 °C, but the ratio α/π^* is the same (note that they did not include water in the fit). Therefore, at higher temperatures, the reaction rate is less dependent on the solvent (the values of α and π^* have, in fact, been determined at 25 °C, and may not be applicable to systems at temperatures as high as 90 °C).

For reaction (IV), the results loosely resemble those for reaction II. Trends in $\log k$ among pure solvents are not satisfactorily described by the AKT model, as expected for a reaction with a particularly complicated dependence of $\log k$ on the solvent.[8] For aqueous mixtures of methanol or acetonitrile, on the other hand, a good fit is obtained with β and Sp. Again, only the rate profiles for mixtures of water with methanol or acetonitrile are properly described; the higher maxima in aqueous mixtures of 1-propanol, 2-methyl-2-propanol or PEG1000 cannot be explained by a dependence on β.

In summary, for reactions (I) and (III), the AKT model does a fair job and $\{\alpha, \pi^*\}$ or $\{\alpha, Sp\}$ suffice to describe trends in $\log k$, both in pure solvents and in aqueous mixtures. For reactions (II) and (IV), $\log k$ cannot be correlated accurately for pure solvents. In aqueous mixtures of methanol or acetonitrile, $\{\beta, Sp\}$ can account for the observed trends, including the small rate maxima, but as the same observations for aqueous PEG solutions cannot be described in this manner, this result may not have physical significance. In mixtures of water with acetonitrile, α varies considerably, and strongly nonlinearly with the concentration of water. In mixtures of

water with methanol, α is nearly constant. Therefore, the similar trends observed for $\log k$ in both types of mixtures point towards a weak dependence on the hydrogen-bond donating capacity. This conclusion is not fully confirmed by the fits, which reveal significant contributions of α, but the deviation of the calculated values of $\log k$ from the experimental values in acetonitrile-rich water–acetonitrile mixtures [especially for reaction (III)] shows that the contribution of α may be overestimated. In any case, the model at best only partially reproduced the characteristic trends in $\log k$ observed in these aqueous mixtures.

Transfer parameters and the log-linear model.
Another method for rationalizing trends in rate constants considers initial state (IS) and transition state (TS) effects separately (within the framework of transition state theory). This method requires that transfer parameters of the reactants are known. Those of the activated complex (AC) can be derived subsequently from those of the reactants in combination with the activation parameters. We did not determine transfer parameters for the reactants. Nevertheless, a qualitative discussion is worthwhile.

For the DA reaction between cyclopentadiene (**1**) and methyl vinyl ketone (MVK), resembling reaction (I), transfer parameters have been determined for aqueous mixtures of 1-propanol (Fig. 6).[4] They reveal a minor dependence of $\Delta_{tr}G°$(TS) on the solvent composition; especially for [H_2O] > 30 M, $\Delta_{tr}G°$(TS) is nearly constant, and increases slightly. For several other DA reactions, $\Delta_{tr}G°$(TS) from water to organic solvents was very small[21,23] and the small dependence of $\Delta_{tr}G°$(TS) on the nature of the reaction medium may be a general phenomenon.

For both **1** and MVK, two approximately linear regions are observed, with a bend, which for **1** occurs in the same region as found for $\log k$. The dependence of $\Delta_{tr}G°$(**1**) is particularly noteworthy. Inspection of Gibbs energies of transfer from water to aqueous solvent mixtures [data
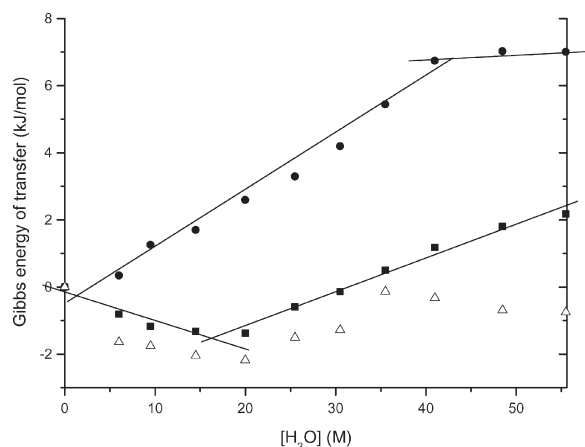

Figure 6. Gibbs energies of transfer ($\Delta_{tr}G°$) for **1** (●), MVK (■) and the AC (△), for the reaction of **1** with MVK in mixtures of water with 1-propanol (relative to 1-propanol)[4]

were collected from the literature, as cited in the text, in many cases, only solubilities were reported, which were converted to $\Delta_{tr}G$, all data were converted to the molar concentration scale (Ben-Naïm standard state), according to the procedures described in Ref. 24, to allow comparison] reveals that for a multitude of organic compounds, a similar pattern is found, with a small initial decrease in $\Delta_{tr}G°$ down to $[H_2O] \approx 40$ M and a sharper decrease for $[H_2O] \lesssim 40$ M.[25–38] Especially small, purely hydrophobic solutes such as (gaseous) alkanes and benzene show this behavior; the effect becomes more prominent for the more hydrophobic cosolutes, in particular 2-methyl-2-propanol, and at lower temperatures. For the alkanes, at elevated temperatures $\Delta_{tr}G°$ initially slightly decreases; at room temperature $\Delta_{tr}G°$ is essentially constant up to $[H_2O] \approx 40$ M, and at lower temperatures initially even a small increase in $\Delta_{tr}G°$ is found, resulting in a small maximum around 40 M water. The origin of this effect undoubtedly follows from the characteristic way in which water hydrates apolar substrates. In 'pure' water, hydrophobic hydration shells form around apolar solutes upon dissolution. This is a cooperative process involving many water molecules and is a special feature of water. However, mixing water with more and more cosolvent ultimately leads to the remaining water acting as 'normal' solvent molecules. Or, looking at it another way, when adding water to, for example, ethanol, the solution becomes more polar, as more and more water molecules are present, which will form hydrogen bonds with a solute if possible. When the mixture contains more and more water, at a certain point (at ~40 M water), water starts to form three-dimensional hydrogen-bonded clusters of 'bulk-like' water. Now, hydrophobic hydration becomes increasingly important. Compared with pure ethanol, an apolar substrate will be increasingly less comfortable with increasing amounts of water (the Gibbs energy increases). This trend continues when hydrophobic hydration sets in, but to a lesser extent, as hydrophobic hydration is less strenuous than the (at this point hypothetical) alternative, 'normal' mode of solvation. Widely varying values for $\Delta_{tr}H°$ and $\Delta_{tr}S°$ in this regime accompany this transition.

For many other organic compounds, usually bearing (several) polar groups, $\Delta_{tr}G°$ is almost a linear function of the volume fraction of water (linear with $[H_2O]$).[29,33,39–51] This pattern is expressed by the so-called log-linear model,[46] which simply states that $\log S_m = f \log S_x + (1-f)\log S_w$, where S_m, S_x and S_w are the solubilities in the mixture, the cosolvent and water, respectively, and f is the volume fraction. We note that $\Delta_{tr}G$ is the Gibbs energy of transfer of a solute from solvent 1 to solvent 2 at 1 M, under the assumption the conditions resemble those at infinite dilution. This is approximately the same as $-RT\ln(S_2/S_1)$, the main difference being possible contributions of solute-solute interactions to the solubility, especially when the solubility is high. In cases where correction factors (activity coefficients) have been determined, they usually turn out
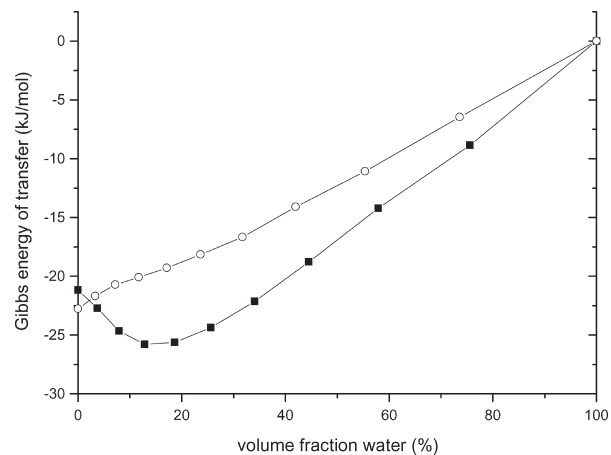

Figure 7. Gibbs energies of transfer ($\Delta_{tr}G°$) for betaine-30 from water to mixtures of water with acetonitrile (■) or ethanol (○), calculated from solubility data[39]

to be small. Plots consisting of two linear parts are also sometimes encountered.[33,49,51–54] However, when a solute has a more complex structure, with polar and apolar parts combined in a single molecule, different parts of the solute molecule may become preferentially solvated by either of the solvents in mixed solvents, and $\Delta_{tr}G°$ becomes a more complex function of the composition.[36,42,53,55–63] Indeed, $\Delta_{tr}G°$ can even pass through a minimum. A good example of both types of behavior is shown by betaine-30, for which $\Delta_{tr}G°$ is nearly a linear function of the volume fraction in water–ethanol mixtures, but passes through a minimum in water–acetonitrile mixtures (Fig. 7).

That $\Delta_{tr}G°$ is often a linear function of the volume fraction over all or parts of the composition range in aqueous solvent mixtures is in line with the kinetic data for DA reactions: if $\Delta_{tr}G°$ is a linear function of volume fraction for both IS and TS, $\Delta^{\ddagger}G°$ (or $\log k$) will also form a linear plot. We note that if a particular functional group in one of the reactants causes a deviation from linearity in $\Delta_{tr}G°(IS)$, and if this group is not involved in the activation process, because its position is remote from the reaction center, it will do so for $\Delta_{tr}G°(TS)$ likewise, and this non-linearity cancels in $\Delta^{\ddagger}G°$. Recently, we found a nearly linear dependence of $\log k$ on the concentration of water for the hydrolysis of p-methoxyphenyl-2,2-dichloroacetate in binary aqueous mixtures of acetonitrile, tetrahydrofuran and PEG400.[64]

One phenomenon that may in part be rationalized in terms of transfer parameters is the small rate enhancement, sometimes found in highly aqueous mixtures. Suppose the Gibbs energy of the AC, a species that is apparently not very sensitive to changes in medium, decreases slightly with decreasing water content (on going from water to aqueous solvent mixtures). If the IS follows the pattern in $\Delta_{tr}G°$ found for, e.g., **1**, the resulting $\Delta^{\ddagger}G°$ will also reflect this pattern (in reverse), and in some cases a minimum in $\Delta^{\ddagger}G°$ (maximum in rate constant) is observed. This pattern is illustrated in Fig. 8.
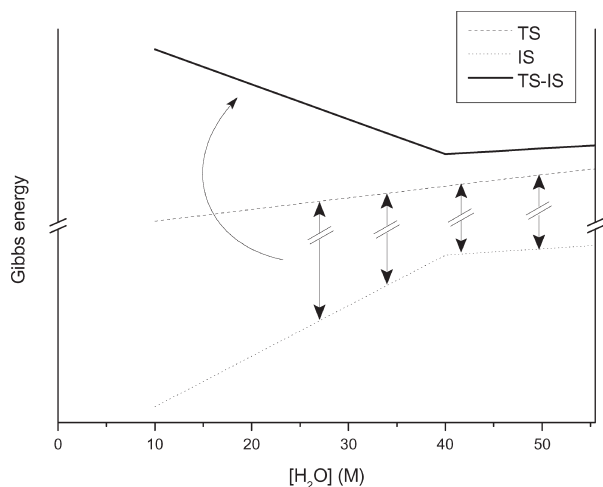
Figure 8. Illustration of a combination of Gibbs energies of transfer for an IS and a TS that will lead to a minimum in $\Delta^{\ddagger}G^{\circ}$ (maximum in rate) at $[H_2O] \approx 40$ M

In line with the temperature dependence of $\Delta_{tr}G^{\circ}$ of alkanes in aqueous mixtures (see above), k_{max}/k_w was found to decrease with temperature for reaction (IV). Regardless of whether a maximum is observed or not, a sudden change in slope of $\log k$ vs the concentration of water is observed almost invariably for any DA reaction. In most cases, this can be explained by assuming that $\Delta_{tr}G^{\circ}(IS)$ resembles the pattern found for **1**, and that $\Delta_{tr}G^{\circ}$ of the (less hydrophobic) TS varies little (and linearly) with composition. The 'reduction in hydrophobicity' as an integral part of the activation process is reflected in the activation Gibbs energy, with a characteristic bend at $[H_2O] \approx 40$ M. Only for RDA reactions, for which the hydrophobicity hardly changes on going from the IS to the TS, is this phenomenon absent.

That $\Delta_{tr}G^{\circ}$ is related to the volume fraction is most likely due to the fact that the probability of finding solvent 1 or 2 at a particular position in the solvation shell around a solute (in the condensed phase) depends on the volume fraction. Hence, in the absence of widely differing strengths of interactions, the solute–solvent interactions constituting the total solvation (and $\Delta_{tr}G^{\circ}$) are the average with respect to the volume fraction. We note that in a thermodynamic approach, often the mole fraction scale is used, as chemical potentials are usually described referring to partial vapor pressures, which are related to mole fractions. Although this is formally a correct approach, it neglects the structure of a condensed liquid phase, where any molecule is necessarily surrounded by (solvated by) other molecules. Although the volume fraction scale also has its drawbacks, it does recognize this fact and accounts for differences in size between solvent molecules.

When one solvent strongly interacts with the solute, this interaction can be regarded as binding, and a binding curve will be observed instead. However, if the two solvents have comparable, strong interactions, this effect is strongly moderated (for specific interactions, such as hydrogen bonds, the ratio of the number densities will describe the average solvation; if one or both solvents bear several functional groups that are able to act as 'binding sites', the number densities of these groups, rather than of the solvent molecules, will be the determining factor).

In many cases, the mode of solvation is intermediate between these two extremes; commonly referred to as preferential solvation. Because Sp is derived from Gibbs energies of transfer, it is not surprising that Sp also correlates approximately linearly with the volume fraction in mixed solvents. (One could argue that Sp contains
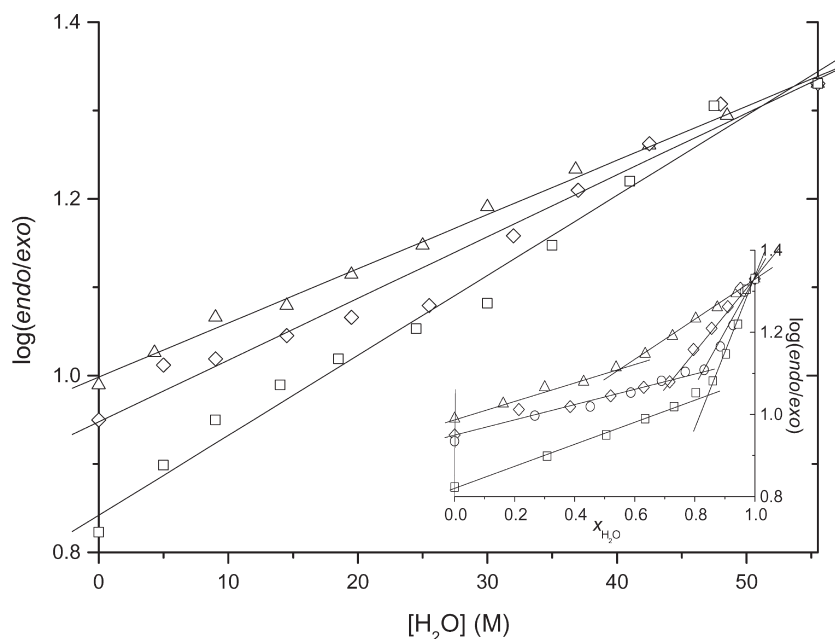

Figure 9. Values of $\log(endo/exo)$ for **1** + MVK in mixtures of water with methanol ($\triangle$), ethanol ($\diamond$), 1-propanol ($\bigcirc$), and 2-methyl-2-propanol ($\triangledown$), re-plotted versus the molar concentration of water. Inset: plotted versus the mole fraction of water[4]

information about only part of the 'solvophobicity'. A function $\Delta G_{tr} = ax + b$, with x a constant for a given solute, was fitted for compilation of several hydrophobic compounds.[11] Values of a were normalized to give Sp; but also b varies considerably and that information is just not used.)

In Fig. 9, $\log(endo/exo)$ is plotted for the reaction of **1** with MVK in aqueous mixtures of alcohols. Except for 1-propanol, $\log(endo/exo)$ is linear with $[H_2O]$ over the entire range of composition, albeit with some scattering. Because $\log(endo/exo)$ is determined solely by the difference in Gibbs energy of the TS, this is not an unexpected result. The more complicated trends in $\log k$ are due (at least in part) to IS effects. As the TS is thought not to be very hydrophobic, this pattern shows that in the absence of hydrophobic effects, (and in the absence of preferential solvation effects), trends in transfer Gibbs energies in water–alcohol mixtures are linear with the volume fraction.

In conclusion, the solvent dependence of $\Delta^{\ddagger}G^{\circ}$ may be understood in terms of $\Delta_{tr}G^{\circ}$ of IS and TS. The linear trends in $\Delta^{\ddagger}G^{\circ}$ over large parts of the volume fraction (or molar concentration) of water reflect the often found linear dependence of $\Delta_{tr}G^{\circ}$ on the volume fraction. Moreover, the breaks around 40 M water reflect $\Delta_{tr}G^{\circ}$ for many hydrophobic compounds, including **1**. A weak composition dependence of $\Delta_{tr}G^{\circ}$ for the hydrophobic IS before the break, combined with an also weak yet slightly larger decrease in $\Delta_{tr}G^{\circ}$ of the more polar TS, may even turn the break into a maximum. A drawback of this thermodynamic approach is that it provides less insight at the mechanistic level than the AKT approach.

CONCLUSIONS

For a number of different types of cycloadditions, mixtures of water with hydrophilic cosolvents and hydrophobic cosolvents affect reaction rates in a qualitatively similar manner. The interesting pattern of $\log k$, that changes little in highly aqueous mixtures but (much) more strongly at lower concentrations of water, is observed for different kinds of cosolvents, regardless of their nature.

For the more hydrophilic cosolvents, extensive linear dependences of $\log k$ on either the concentration or the volume fraction of water are found. This pattern reflects the thermodynamics of transfer of solutes from one solvent (mixture) to another. In cases where no peculiarities resulting from hydrophobic effects are expected, linear dependences on the concentration or volume fraction of water over the entire range of composition are found, e.g. for $\log k$ (reaction III) or $\log(endo/exo)$ (reaction of cyclopentadiene with MVK[4]). For more hydrophobic cosolvents such as 1-propanol, preferential solvation effects result in deviations from the linear trends.

For reactions (I) and (III), a multiparameter analysis using the AKT model reproduces solvent effects for pure organic solvents and aqueous mixtures reasonably well,

with consistent sets of parameters (important contributions of $\{\alpha, Sp\}$ and $\{\alpha, \pi^*\}$, respectively). Overall, solvent effects in aqueous mixtures were not satisfactorily described. The results call for a further study of the role of the hydrogen-bond donor capacity.

Small maxima in the rate constant are sometimes observed for cycloadditions in highly aqueous media, at around 40 M water. The maxima seem to be the outcome of the different dependences of the Gibbs energies of transfer of the initial state and the transition state. The former follow a pattern, characteristic for many hydrophobic compounds, where $\Delta_{tr}G^{\circ}$ changes little down to about 40 M water, after which it decreases considerably. The latter are characteristic for a more polar compound, with a more gradual decrease in $\Delta_{tr}G^{\circ}$.

EXPERIMENTAL

Materials

N-n-Butylmaleimide (**2**)[21] and 1,4,4a,9a-tetrahydro-4a-methyl-($1\alpha,4\alpha,4a\alpha,9a\alpha$)-1,4-methaneanthracene-9,10-dione (**6**)[5] have been synthesized previously. All other materials were obtained from commercial suppliers, and were of the highest purity available. Solvents were either of analytical grade or distilled; acetonitrile was purified over basic aluminium oxide prior to use. Acridizinium bromide (**4**) was prepared by a literature procedure;[65,66] H-NMR (D$_2$O): δ 9.92 (s, 1H), 9.02 (d, $J = 7.5$ Hz, 1H), 8.84 (s, 1H), 8.36 (d, $J = 9.3$ Hz, 1H), 8.29 (d, $J = 8.6$ Hz, 1H), 8.18 (d, $J = 8.6$ Hz, 1H), 7.80–8.06 (m, 4H).

Kinetic experiments

Cyclopentadiene (1) + N-n-butylmaleimide (2) or acridizinium bromide (4). Kinetic measurements were performed using UV–visible spectroscopy (Perkin-Elmer Lambda 5 spectrophotometer). Cuvets containing the reaction mixture together with **2** or **4** were thermostated at 25.0 °C. After the addition of cyclopentadiene (concentrated solution in acetonitrile), the reaction was monitored at 298 or 376 nm, respectively. Rate constants for **2** were obtained by conventional pseudo-first-order kinetics, and rate constants were reproducible to within 3%. For **4**, rate constants were determined using initial rate kinetics, and rate constants were reproducible to within 4%. Rate constants are the average of at least three independent experiments. Stock solutions of **2** and **4** were made in acetonitrile and methanol, respectively. In all cases, cyclopentadiene was used in excess. Typical conditions were [**1**] = 0.5–4 mM for **2** and 2–60 mM for **4**; [**2**] = 0.05 mM; [**4**] = 0.05–0.1 mM.

Benzonitrile oxide (8) + N-n-butylmaleimide (2). Kinetic measurements were performed as described previously.[67] Rate constants are the average of at least

three independent experiments and were reproducible to within 3%. Typical conditions were $[2] = 1\text{--}10\,\text{mM}$; $[8] \approx 0.025\text{--}0.05\,\text{mM}$.

RDA. Kinetic measurements were performed using UV–visible spectroscopy (Perkin-Elmer Lambda 5 spectrophotometer). The reaction was monitored at 340 nm and rate constants were determined using initial rate kinetics. A few microliters of a stock solution of **6** in 1-propanol were added to the cuvets. Initial concentrations of **6** were $0.2\text{--}2\,\text{mM}$. Rate constants were determined at least three times and were reproducible to within 5%.

Multiparameter fits

Values for α, β, and π^* for pure solvents were taken from Ref. 10 and for mixtures of water with methanol or acetonitrile values were taken from Ref. 68; for mole fractions between those listed, values were linearly interpolated. Values for Sp were taken from Refs 11 and 14. For volume fractions between those listed for mixtures of water and methanol, values were linearly interpolated. For mixtures of water with acetonitrile, no values of Sp have been determined. However, values of Sp for water–methanol give a fair linear correlation with the volume fraction; this is true to a lesser extent also for ethanol and 1,4-dioxane. Therefore, we estimated values of Sp in these mixtures by $Sp = f_a Sp_a + (1 - f_a) Sp_w$, were f_a is the volume fraction of acetonitrile and Sp_a and Sp_w are values in pure acetonitrile and water, respectively. No value of Sp for pure PEGs are known, hence PEG solutions were not included in the fits.

Least-squares fits were performed using the solver tool of Microsoft Excel, and Microcal Origin, using its multivariance tool to calculate errors and to perform null hypothesis tests (Student's t, $\alpha = 0.05$). Correlation coefficients were calculated as described in Ref. 69.

Acknowledgment

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