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Rispens, T; Engberts, JBFN

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Kinetic solvent effects on 1,3-dipolar cycloadditions of benzonitrile oxide

Theo Rispens and Jan B. F. N. Engberts*

Physical Organic Chemistry Unit, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

ABSTRACT: The kinetics of 1,3-dipolar cycloadditions of benzonitrile oxide with a series of *N*-substituted maleimides and with cyclopentene are reported for water, a wide range of organic solvents and binary solvent mixtures. The results indicate the importance of both solvent polarity and specific hydrogen-bond interactions in governing the rates of the reactions. The aforementioned reactions are examples for which these factors often counteract, leading to a complex dependence of rate constants on the nature of the solvent. For the reactions of *N*-ethylmaleimide and *N*-*n*-butylmaleimide with benzonitrile oxide, isobaric activation parameters have been determined in several organic solvents, water, and water–1-propanol mixtures. Interestingly, the activation parameters reveal significant differences in solvation in different solvents that are not clearly reflected in the rate constants. In highly aqueous mixtures, enforced hydrophobic interactions lead to an increase in rate constant, relative to organic solvents. However, the overall rate enhancement in water is modest, if present at all, because the solvent polarity diminishes the rate constant. This pattern contrasts with common Diels–Alder reactions, where polarity, hydrogen-bond donor capacity and enforced hydrophobic interactions work together, which can result in impressive rate accelerations in water. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: Diels–Alder reaction; cycloaddition; water; hydrophobic interactions; binary solvent mixtures; isobaric activation parameters

INTRODUCTION

Diels–Alder (DA) reactions are often described as relatively insensitive towards the nature of the solvent, although rate enhancements of the order of 10^2–10^3 on going from *n*-hexane to water are nevertheless commonly found.[1] Rate constants of 1,3-dipolar cycloadditions (DC) are even less dependent on the the solvent.[2–5] Even rate constants in water hardly differ from those in other solvents and, when accelerations are observed,[6–8] they are modest, compared with those for DA reactions. Notably, DC reactions sometimes show a reverse dependence of rate constant on the polarity of the medium, the reactions being slowed in polar media.[2,7,9,10] Intermediate cases are also known, leading to almost negligible changes in rate constants. For example, for the reaction between phenyldiazomethane and norbornene, rate constants vary only by a factor of 1.8 over a wide range of solvents (water not included).[2] The inverse dependence of rate constant on the polarity of the solvent is most pronounced for nitrones and nitrile oxides as dipolarophiles. These compounds possess relatively high dipole

moments, which are (partially) lost during the activation process. The latter accounts for the inverse dependence on polarity. Rate constants plotted against $E_T(30)$ (a measure of the solvent polarity, see below) usually show a fair correlation. However, rate constants in protic solvents sometimes deviate from this trend.[2] Lewis acids are also known to sometimes induce either accelerations or inhibitions of DC reactions.[11–13]

1,3-Dipolar cycloadditions of benzonitrile oxide

Benzonitrile oxide (**1**, Scheme 1), a very reactive 1,3-dipole, was first prepared in 1886 by Gabriel and Koppe.[14] Benzonitrile oxide is often generated *in situ*, because it dimerizes quickly. In fact, it dimerizes in solution so easily that its reactivity was at first not recognized,[15] but cycloadditions proceed smoothly even with completely unactivated dipolarophiles such as ethene under ordinary laboratory conditions.[16] Cycloadditions with **1** were explored in the 1950s (for an overview, see in Ref. 17); early mechanistic studies include Refs 18 and 19.

Solvent effects on DC reactions with **1** and derivatives are remarkably small.[2] Studies of solvent effects have often been brief and inconclusive about the different

*Correspondence to: J. B. F. N. Engberts, Physical Organic Chemistry Unit, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.
E-mail: j.b.f.n.engberts@rug.nl
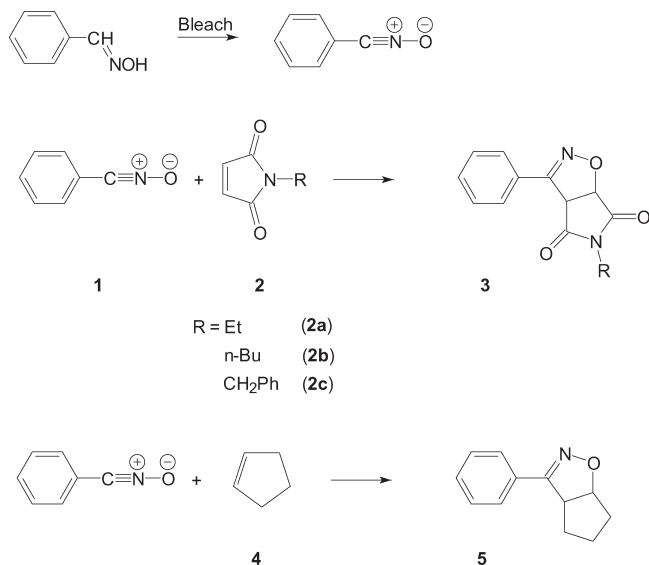
Scheme 1

factors that control rates.[8,20,21] In a detailed kinetic study, the DC reactions between **1** and several electron-rich and electron-poor dipolarophiles have been studied for a number of solvents, including water, and also for mixtures of ethanol and water.[9] The dipolarophiles include cyclopentene, methyl vinyl ketone and *N*-methylmaleimide. Whereas reactions involving an electron-rich dipolarophile are still 3–10 times faster in water than in most organic solvents, reactions involving electron-poor dipolarophiles are slightly decelerated. This difference was rationalized on the basis of FMO theory;[22] **1** is a good hydrogen-bond acceptor, and its FMOs are lowered in energy when dissolved in a protic solvent. On reacting with the electron-rich dipolarophile cyclopentene, the dominating interaction is $LUMO_1$–$HOMO_{cyclopentene}$. Consequently, the energy gap, and hence the Gibbs energy of activation, are smaller in a protic solvent. In the case of an electron-poor dipolarophile, the dominating interaction is $LUMO_{dipolarophile}$–$HOMO_1$. FMO energies of both reactants are lowered in a protic solvent (the electron-poor dipolarophiles studied are also susceptible to hydrogen-bond formation), but it was proposed that this occurs more effciently for **1**, leading to a rate retardation. (The relative energies of the FMOs of **1** and electron-poor dipolarophiles are such that both $LUMO_1$–$HOMO_{dipolarophile}$ and $HOMO_1$–$LUMO_{dipolarophile}$ interactions may contribute significantly. The focus on only one of these HOMO–LUMO interactions may therefore not be fully justified, although this simplification was sufficient to interpret the data presented in this paper.) However, this explanation does not account for the complicated dependence of the rate constants on the solvent; for instance, $k(n\text{-hexane}) \approx k(\text{ethanol}) \approx k(\text{water}) > k(1,4\text{-dioxane}) > k(\text{dichloromethane}) \approx k(2,2,2\text{-trifluoroeth-anol})$ for the reaction of **1** with *N*-ethylmaleimide (**2a**, Scheme 1). The fact that, for electron-poor dipolaro-

philes, rate constants in *n*-hexane, ethanol and water are nearly equal contradicts the explanation of the lowering of the rate constant due to the hydrogen-bond interactions with **1**. A larger destabilization of the hydrophobic initial state, relative to the less hydrophobic transition state (enforced hydrophobic interactions), may explain why in water the rate is not much lower than in organic solvents, but for ethanol such a counteracting effect on the rate is not possible. In summary, hydrogen bonding and hydrophobic interactions are important factors that influence rate constants in water, but in general, solvent effects on DC reactions of **1** are still only partially understood.

As mentioned, rate constants for the reaction of **1** with *N*-methylmaleimide in several solvents have been previously determined.[9] The complicated results prompted a more detailed study. Here, an extensive study is presented of the influence of the medium (pure solvents and mixtures of solvents) on rate constants of 1,3-dipolar cycloadditions of benzonitrile oxide (**1**) with *N*-alkyl-substituted maleimides (**2a–c**) and with cyclopentene (**4**) (Scheme 1). Emphasis is placed on the complex interplay of different factors that control the rate, in particular hydrogen bonding and polarity. In this regard, the reactions of **1** with **2a–c** are of particular interest, because both substrates are susceptible to hydrogen-bond formation. The reaction of **1** with **4** is a convenient reference, because **4** does not form significant hydrogen bonds.

RESULTS AND DISCUSSION

Solvent dependence of the rate constant

In Fig. 1, $\log k_2$ is plotted against $E_T(30)$[23] for a wide range of solvents for the reaction of **1** with **2a** and with **4** (Table 1). The solvents roughly form two groups: protic and aprotic solvents.

First, when considering the group of apolar solvents [with values of $E_T(30)$ below $\sim$40], $\log k_2$ decreases roughly linearly with $E_T(30)$. This pattern is indicative of a polar initial state (**1**) and a less polar activated complex, in which the charge separation of the 1,3-dipole has partly disappeared. Note that DA reactions are almost invariably faster in a more polar solvent. In the activated complex, some charge separation develops, that is stablilized by polar interactions. One reason why rates of DC reactions (proceeding via an analogous mechanism) are so weakly dependent on the solvent is that this charge separation is mediated by the partial disappearance of the 1,3-dipole, leading to only small accelerations, or even, as for the reactions of **1** with **2a** and **4**, to a decrease in rate on going to a more polar solvent.

For solvents where $E_T(30) > 40$, the medium effects are more complicated. A comparison of the reactions between **1** and **2a** and between **1** and **4** sheds some light on this phenomenon. The latter reaction is classified as
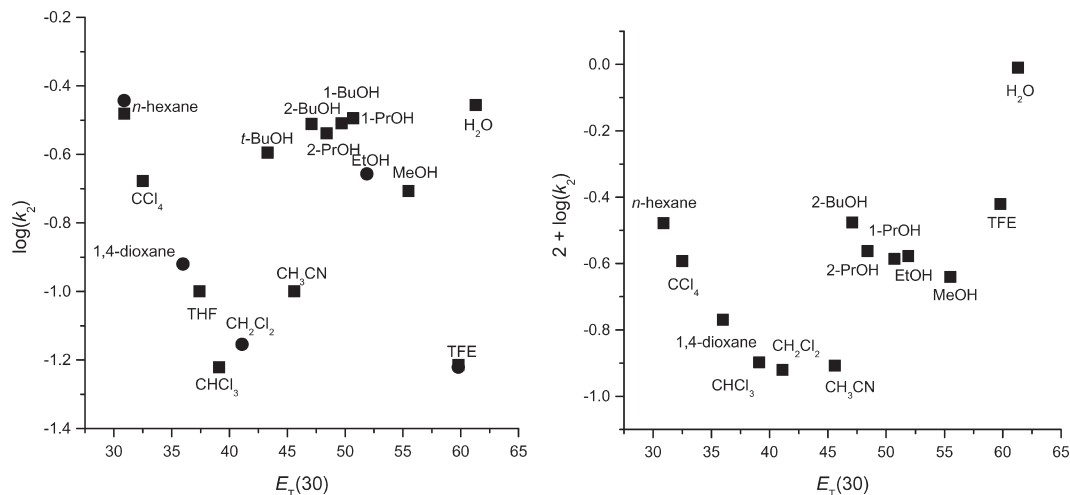
Figure 1. Values of $\log k_2$ ($M^{-1}\,s^{-1}$) for the reaction of **2a** (left) and of **4** (right) with **1** vs the $E_T(30)$ values[23] of various solvents at 25 °C. DMSO is left out, as side-reactions interfered with the cycloaddition; the choice of solvents is further limited by the requirement of being able to monitor the reaction at 273 nm (closed circles are values for N-methyl- rather than N-ethylmaleimide[9])

inverse electron demand (IED). Therefore, hydrogen bonding to **1** is favorable. Furthermore, **4** is not capable of forming hydrogen bonds. Compared with the aprotic solvents, alcohols show larger rate constants for the reaction of **1** with **4**. The more polar the alcohol, the smaller is the rate constant (except for TFE). This trend may be the continuation of the effect of the polarity (see below; Fig. 3). Two solvents stand out. 2,2,2-Trifluoro-ethanol (TFE), a very potent hydrogen-bond donor, causes a larger rate constant than the other alcohols. This is also true for water. In addition, a further acceleration may be ascribed to enforced hydrophobic interactions.[9] Hence *both* solvent polarity and the hydrogen bond-donating capacity of the solvent affect the reaction rates and, interestingly, in this particular case in *opposite* directions (the hydrogen bond-donating capacity, of course, also contributes to the solvent polarity). For most DA reactions, both factors increase the rate of the reaction. For DC reactions, it appears that usually these two factors either enhance or diminish the rate constants. The DC reaction of **4** with **1** is an example where these

factors are opposed, and therefore generate a much more complex dependence of rate constant on solvent.

For the reaction of **1** with **2a**, hydrogen bonding is also possible for the dipolarophile, which introduces further complexity. In the absence of hydrogen-bond donors, the same dependence of rate constant on solvent polarity is found as for the reaction of **1** with **4**. Again, hydrogen bond-donating solvents produce an additional rate increase, but now the rate constant in TFE is much *lower* than that in other alcohols.

The two simplest explanations for this pattern are: (i) the reaction is still mainly IED; hydrogen bonding occurs both to **1** and **2a**, affecting **1** more than **2a**; only in the case of TFE is hydrogen bonding more efficient to **2a**; (ii) the reaction is mainly NED, hydrogen bonding also occurs both to **1** and **2a**, but affects **2a** more than **1**. Only in the case of TFE does hydrogen bonding to **1** supersede hydrogen bonding to **2a**. The kinetic data can be understood using either explanation, but UV–visible spectra of **1** in different solvents support the latter explanation (Fig. 2). The maximum in the absorption

Table 1. Rate constants for the reaction of **1** with **2a** and **4** in various solvents at 25 °C

Solvent	$E_T(30)$[a]	$k_{2,2a}$[b]	$k_{2,4}$[c]	Solvent	$E_T(30)$[a]	$k_{2,2a}$[b]	$k_{2,4}$[c]
n-Hexane	30.9	0.330	0.333	2-BuOH	47.1	0.308	0.334
CCl$_4$	32.5	0.210	0.255	2-PrOH	48.4	0.289	0.274
1,4-Dioxane	36.0	0.12[d]	0.170	1-BuOH	49.7	0.310	n.d.
THF	37.4	0.100	n.d.	1-PrOH	50.7	0.320	0.259
Chloroform	39.1	0.059	0.127	EtOH	51.9	0.22[d]	0.265
CH$_2$Cl$_2$	41.1	0.07[d]	0.120	MeOH	55.5	0.196	0.229
t-BuOH	43.3	0.254	n.d.	TFE	59.8	0.061	0.380
CH$_3$CN	45.6	0.10	0.124	Water	61.3	0.350	0.978

[a]Values from Ref. 23.
[b]Units $M^{-1}\,s^{-1}$.
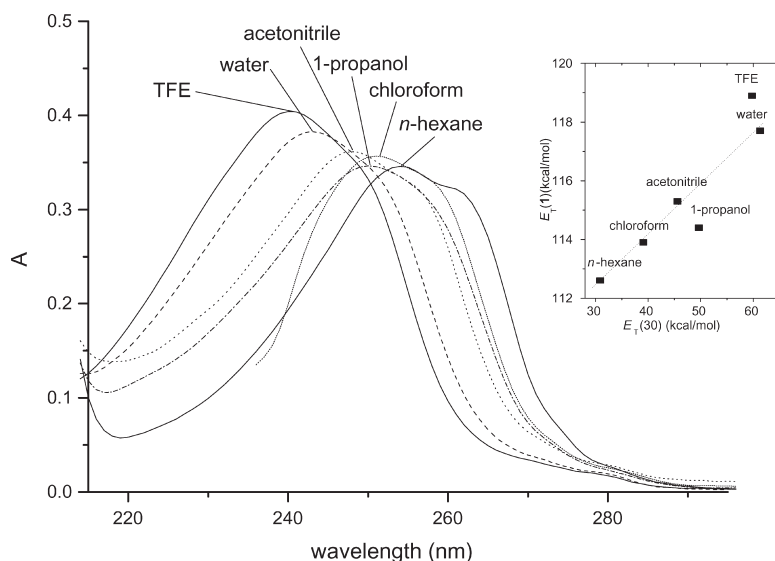[c]Units $10^{-2}\,M^{-1}\,s^{-1}$.
[d]Value for N-methylmaleimide.[9]

Figure 2. UV spectra of **1** in various solvents at 25 °C. The inset shows the corresponding transition energies [(E_T (**1**) plotted against E_T(30)]

band of **1** shifts from 252 nm in *n*-hexane to 248 nm in acetonitrile, 250 nm in 1-propanol, 243 nm in water and 240.5 nm in TFE, indicating both a relatively weak interaction with 1-propanol and an efficient interaction with TFE (even more efficient than with water). The energy of the transition [E_T(**1**)] plotted against E_T(30) clarifies this pattern. For **1** + **4**, the rate constant for TFE deviates positively from the trend found among the alcohols, whereas for **1** + **2a**, a negative deviation is found (Fig. 3). This pattern is also in line with a relatively efficient binding of TFE to **1**, and supports the NED mechanism for the reaction of **1** with **2a**.

A sharp deviation from a general trend in a plot of log*k* against solvent polarity (Fig. 3) may indicate a change in mechanism. In this case, one may perhaps regard the introduction of hydrogen bonds as a change in mechanism. A similar (but reversed) pattern was found for the reaction of phenylazide with norbornene, both experimentally[6] and theoretically.[24] Nevertheless, the deviation remains an unusual observation. An alternative explanation, based on a change from a concerted mechanism to a mechanism involving a zwitterionic intermediate, may be rejected on several grounds: (i) the dependence on the solvent polarity should be much larger for such a mechanism;[5] (ii) Hammett ρ values for the reaction of **1** with electron-poor styrenes (in CCl$_4$)[19] and with acrylonitrile (in water)[21] are small and similar, contradicting a (change to a) zwitterionic mechanism; (iii) activation entropies are large and negative over the full range of solvents (see below) and are characteristic of a concerted reaction mechanism.

The effect of solvent polarity is extrapolated from the range of solvents with E_T(30) values between 30 and 40 (Fig. 3), to illustrate the divergence from this trend for the more polar solvents [E_T(30) values > 40]. The E_T(30) scale is based on one parameter, that includes hydrogen-bond donor capacity, hydrogen-bond acceptor capacity

and polarizability–dipolar interactions. The contribution of the hydrogen bond-donating capacity of the solvent in just providing a more polar reaction environment could be smaller than indicated by E_T(30), as betaine-30 is rather sensitive to these interactions. In fact, the fair correlation of log*k* with E_T(30), *including* alcohols, found for many other DA and DC reactions,[2] may be the result
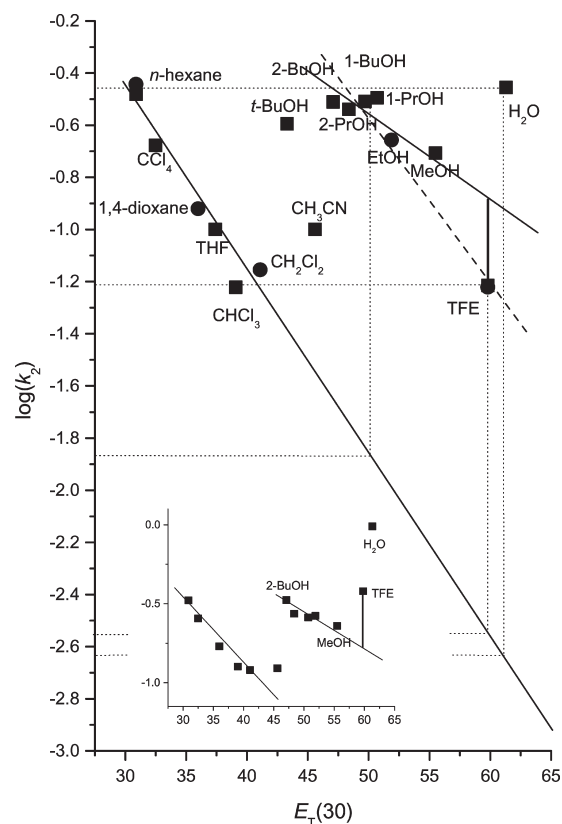

Figure 3. Data from Fig. 1, with various trends indicated. Main plot, **1** + **2a**; inset, **1** + **4**

of solvent polarity (including hydrogen bonds) playing a smaller role in determining the rate in alcohols than estimated on the basis of $E_T(30)$, together with hydrogen bonds inducing (catalyze/inhibit) additional effects, which work in the same direction as the solvent polarity. This is supported by many other cases, in which a difference in slope is found among the alcohols, and is consistent with the idea that in general both non-specific (polarity) and specific ('catalytic' hydrogen bonds) solvation is important.

Acetonitrile is the odd one out, in particular for the reaction of **1** with **2a**. A similar pattern was found for a related reaction.[8] A specific accelerating effect of aprotic dipolar solvents has been suggested,[25] but the effect is far from general (in the case of **1** + **4**, the rate constant for acetonitrile deviates only slightly. Examples where the effect is absent are given in Refs 2, 5 and 7).

Several multiparameter analyses have also been undertaken (results not shown), using the Abraham–Kamlett–Taft model, extended with the solvent parameter Sp. These models discern different aspects of polarity, e.g. the hydrogen-bond donor capacity (α). Usually, decent correlations are found for DA reactions, but for the DC reactions descibed in this paper no satisfactory fit was obtained.

Isobaric activation parameters

Isobaric activation parameters ($\Delta^\ddagger G^\ominus$, $\Delta^\ddagger H^\ominus$ and $\Delta^\ddagger S^\ominus$) for the reactions of **1** with **2a** and **2b** have been determined in different solvents (Table 2). On going from n-hexane to chloroform, the rate decreases, and the accompanying increase in activation enthalpy is in line with a stabilization of the polar initial state (with respect to the activated complex) by the more polar chloroform. Curiously, for the reactions in 1-propanol, $\Delta^\ddagger H^\ominus$ and $\Delta^\ddagger S^\ominus$ are the same as those in n-hexane. When compared with chloroform, the enthalpy of activation is decreased, as a result of hydrogen bonding (to the dipolarophiles), in such a way that the FMO interaction energy is lowered. Note that in both cases, the changes in $\Delta^\ddagger H^\ominus$ and $\Delta^\ddagger S^\ominus$ are much larger than the changes in $\Delta^\ddagger G^\ominus$, but strongly compensating. This indicates that differences in solvation

play an important role, although the overall rate constant need not be affected to a large extent, because of this compensating behavior.

In TFE, the rate constants of these reactions are low, which has been explained in terms of FMO theory.[9] The activation parameters reveal that the decrease in rate constant is entirely due to a more unfavorable entropy of activation, which seems hard to reconcile with a larger difference in energies between the HOMO and LUMO of the reactants. [Note that for ordinary Diels–Alder reactions, a larger hydrogen bond-donating capacity of a solvent leads to an increase in rate because of TS stabilization and that this is reflected in a decrease in the enthalpy of activation. In terms of FMO theory, the LUMO of the dienophile is lowered in energy because of (stronger) hydrogen bonding and the energy gap with the HOMO of the diene is decreased.] Instead, the high solvent polarity may be responsible for the low rate constant, but this is expected to lead to an increase in $\Delta^\ddagger H^\ominus$ also. Moreover, for the reaction of **1** with **4** no corresponding decrease in rate constant is found. Yet another explanation is that the activated complex is more strongly solvated by TFE than are the reactants, but that this enthalpic advantage is overcompensated by an unfavorable entropic effect, leading to an increase in the Gibbs energy of activation. This explanation is highly speculative, but in line with the large negative entropy of activation in TFE. Of course, this effect ultimately may be present together with the lowering of the HOMO of **1**. As mentioned, it is possible that the changes in desolvation cause (large) differences in $\Delta^\ddagger H^\ominus$ and $T\Delta^\ddagger S^\ominus$ that nearly compensate each other.

The activation parameters for the reactions in water are more in line with expectation, with relatively small negative entropies of activation and relatively large enthalpies of activation. Water and aqueous mixtures will be discussed later.

Isobaric activation parameters for the reactions of **1** with **2a** and **2b** follow the same pattern. Differences in solvation (hydration) due to the presence of a larger alkyl substituent apparently do not affect the activation process. The n-butyl tail is still too small to fold back or have any interaction with **1**.

Table 2. Isobaric activation parameters for **1** + **2a** and **2b** at 25 °C

Compounds	Solvent	$\Delta^\ddagger G^\ominus$ (kJ mol^{-1})[a]	$\Delta^\ddagger H^\ominus$ (kJ mol^{-1})[b]	$-T\Delta^\ddagger S^\ominus$ (kJ mol^{-1})[b]
1 + **2a**	n-Hexane	75.8	42.5	33.3
	Chloroform	80.0	51.8	28.2
	1-Propanol	75.9	42.7	33.1
	Trifluoroethanol	79.9	34.4	45.5
	Water	75.7	50.2	25.5
1 + **2b**	n-Hexane	75.5	40.8	34.7
	1-Propanol	75.2	40.5	34.8
	Trifluoroethanol	79.5	33.0	46.4
	Water	74.6	48.0	26.6

[a]Standard error < 0.1 kJ mol^{-1}.
[b]Standard error 1.5–2 kJ mol^{-1} for **2a**, 1 kJ mol^{-1} for **1b**.
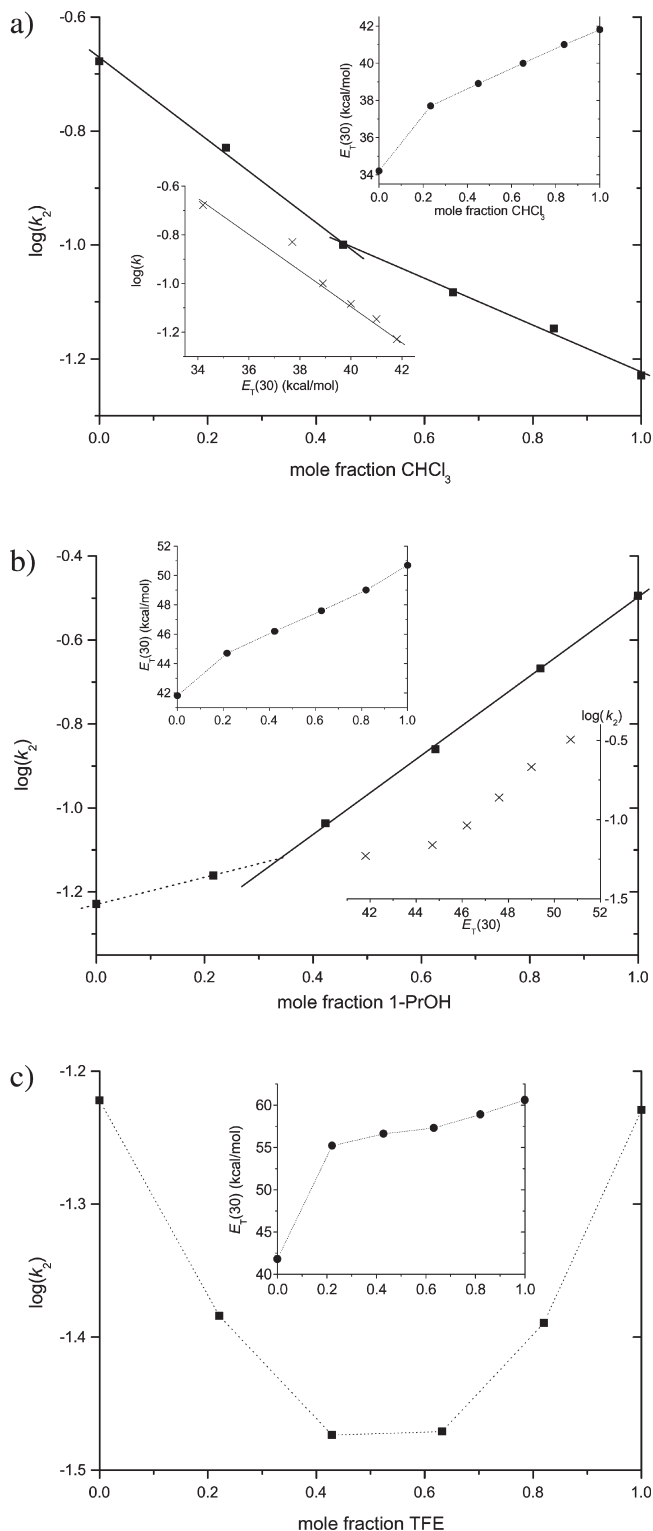
a)

b)

c)

Figure 4. Logarithms of the bimolecular rate constants ($M^{-1} s^{-1}$) of the reaction of **2a** with **1** in mixtures of chloroform with (a) CCl$_4$, (b) 1-propanol and (c) TFE at 25 °C. (In all cases, the plots hardly differ when converted to a molar scale, as in all cases the molar volumes of the solvents are similar and the extent of non-ideal mixing limited.) The insets show the corresponding $E_T(30)$ values and logk_2 vs $E_T(30)$

Binary solvent mixtures

To investigate further the complex kinetic behavior of the present reactions, rate constants for reaction of **1** with **2a** were determined in the solvent mixtures chloroform–CCl$_4$, chloroform–TFE, chloroform–1-propanol and 1-propanol–TFE (Figs 4 and 5). A comparison with $E_T(30)$ values in these mixtures provides information concerning the influence of the solvent polarity on the reaction. The $E_T(30)$ values already offer clues concerning the nature of the mixtures. In all cases, $E_T(30)$ shows a linear dependence on the composition, except for a small range of compositions (Figs 4 and 5). In case of chloroform–TFE, the formation of strong hydrogen bonds between TFE and betaine-30 is definitely responsible for the sharp increase in $E_T(30)$ at low mole fractions of TFE. In mixtures of acetonitrile with 1-propanol[26] or chloroform with ethanol[27] the same pattern was observed, with a dependence of $E_T(30)$ on the mole fraction resembling a binding curve at low mole fractions of 1-propanol or ethanol, and a more gradual, linear dependence once 'saturation' has been reached. Strong hydrogen bonds between the alcohol and the negatively charged phenolic oxygen of betaine-30 are responsible for this pattern. In the other mixtures, a strong preference for one of the solvents is not observed because (i) neither of the two solvents is a (strong) hydrogen bond donor or (ii) both solvents are (strong) hydrogen bond donors. The chloroform–CCl$_4$ mixture is an interesting case, because chloroform is a relatively weak hydrogen bond donor. Nevertheless, some kind of binding is observed.[28]

Analogously to betaine-30, **1** can be expected to form strong hydrogen bonds. Also **2a** is a good hydrogen bond acceptor, but probably to a lesser degree.

In chloroform–CCl$_4$ mixtures, two linear relationships are observed in a plot of logk_2 versus solvent composition, with slightly different slopes. No strong interactions
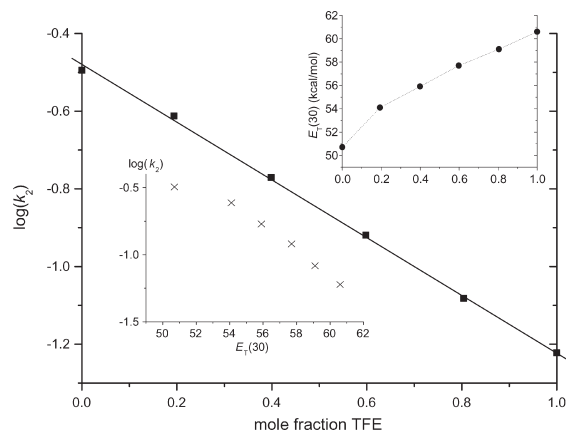

Figure 5. Logarithms of the bimolecular rate constants ($M^{-1} s^{-1}$) of the reaction of **2a** with **1** in mixtures of 1-propanol with TFE at 25 °C. The insets show the corresponding $E_T(30)$ values and logk_2 vs $E_T(30)$

(hydrogen bonds) between solvents (the hydrogen bond donor capacity α is 0.78 for 1-propanol, 0.93 for methanol, 1.17 for water and 0.44 for chloroform; this indicates that chloroform has an ability to form hydrogen bonds, but to a much lesser extent than the alcohols) and reactants are anticipated, and the rate constant is governed primarily by the polarity of the medium. As reactants and betaine-30 are preferentially solvated to different degrees, a linear correlation between $\log k_2$ and $E_T(30)$ over the full range of composition is not observed.

In chloroform–1-propanol mixtures, 1-propanol will be the better hydrogen-bond donor. The FMOs of both reactants will be affected by the formation of hydrogen bonds. In this case, a net accelerating effect results. A plot of $\log k_2$ versus composition reveals that no strong binding of 1-propanol to either reactant occurs, because $\log k_2$ gradually increases towards the value of $\log k_2$ in pure 1-propanol. The increased slope for $x_{1\text{-PrOH}} > 0.3$ may result from additional hydrogen bonding with **2a** starting to be significantly involved in the activation process. Solvent polarity also plays a role, but the 'catalytic' effect of 1-propanol is more prominent.

In mixtures of chloroform and TFE rate constants for reaction of **2a** with **1** [Fig. 4(c)] are *lower* than those in either pure solvent, passing through a minimum at $x_{TFE} = 0.5$. $E_T(30)$ values are indicative of preferential solvation of betaine-30 by TFE, and the same may well be the case for **1**. However, the changes in $E_T(1)$ indicate that although a significant degree of preferential solvation of **1** occurs, the preferential solvation is not as dramatic as for betaine-30 (Fig. 6). For the sake of comparison, the reaction of **1** with **4** was also studied using chloroform–TFE mixtures (Fig. 6). A nearly linear dependence of $\log k_2$ on the mole fraction of TFE was found, with only a small deviation in the chloroform-rich region. This pattern rules out any irregular effects of TFE on **1**. Perhaps the catalytic effect of TFE on **2a** is small initially, but gains importance at higher mole fractions of TFE, bearing in mind that a similar pattern is found for mixtures of chloroform with 1-propanol, albeit without a minimum.

These observations lead to the following explanation: the rate-accelerating effect induced by hydrogen bonding depends on the solvent and is different for the different reactants. TFE interacts efficiently with **1** and induces catalytic effects that enhance the reacion with **4** but reduce the rate constants for **2a**. The interactions are not so strong that extensive preferential solvation of **1** by TFE occurs in mixtures of chloroform and TFE. 1-Propanol interacts with **1** less efficiently, inducing smaller effects. By contrast, 1-propanol interacts efficiently with **2a**, and an overall accelerating effect is found for 1-propanol. In mixtures of chloroform with TFE, the rate initially drops $(\mathbf{1} + \mathbf{2a})$ because of hydrogen bonding of TFE to **1**. However, at higher mole fractions of TFE, the rate constant again increases, most likely because then (additional) hydrogen bonds between TFE and **2a** are involved.

Compared with 1-propanol, the rate inhibition in TFE due to hydrogen bonding to **1** seems to dominate. However, note that in the hypothetical case that only the polarity would affect the rate constant (as illustrated in Fig. 3) the rate constant would be (much) lower. The 'catalytic' effect (hydrogen bonding with **2a**) therefore still contributes more than inhibition due to hydrogen bonding to **1**. The inhibition is just more efficient with TFE than with other alcohols.

In mixtures of 1-propanol with TFE, the many possibilities for TFE to form hydrogen bonds to 1-propanol will reduce peculiarities in solvating **1** or **2a**, and a linear dependence of $\log k_2$ on x_{TFE} is found for the complete solvent composition range (Fig. 5).

Water and aqueous solvent mixtures

Rate constants for the reactions of **1** with **2a–c** in water and 1-propanol are given in Table 3. The rate constants show a slight increase with increasing tail length R (Et, *n*-Bu, Bz) in 1-propanol, and a more pronounced increase in water. In other words, the rate constants in water compared with 1-propanol ($k_w/k_{alcohol}$) increase with increasing hydrophobicity of the dipolarophile. This pattern has
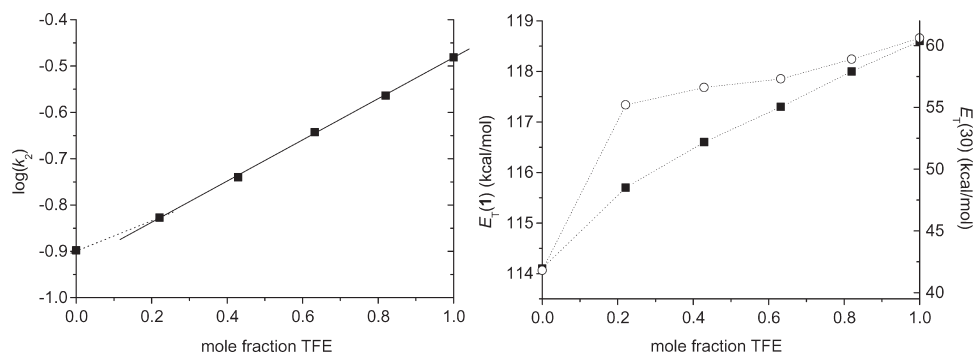

Figure 6. Left: values of $\log k_2$ ($\text{M}^{-1}\text{s}^{-1}$) for the reaction of **1** with **4** at 25 °C in mixtures of chloroform and TFE. Right: corresponding values of $E_T(1)$ (■) and $E_T(30)$ (○)

Table 3. Rate constants for the reaction of **1** with **2a–c** in water and in 1-propanol at 25 °C

Medium	2a		2b		2c	
	k_2 ($M^{-1} s^{-1}$)	k/k_w	k_2 ($M^{-1} s^{-1}$)	k/k_w	k_2 ($M^{-1} s^{-1}$)	k/k_w
Water	0.35	1	0.55	1	0.73	1
1-Propanol	0.30	0.86	0.37	0.67	0.45	0.59

also been observed for DA reactions of 2,3-dimethylbutadiene with *N*-alkylmaleimides,[29] and are possibly due to an additional hydrophobic interaction between the reactants, lowering the Gibbs energy of activation. Another, extreme example of this phenomenon is observed for the DC reactions of *C,N*-diphenylnitrone with dimethyl fumarate and dibutyl fumarate, for which $k_w/k_{alcohol}$ is 12 and 108, respectively.[7] Inspection of Fig. 3 reveals that, compared with the trend found among the alcohols, the rate constant in water shows a positive deviation. This minor effect may be attributed to enforced hydrophobic interactions.[9] Such a small contribution is to be expected for two polar reactants. From elaborate calculations on DA reactions involving the hydrophobic cyclopentadiene, the contribution of enforced hydrophobic interactions was estimated to be a factor of 5–6 in rate.[30] In this case, the contribution is estimated to be a factor of 2–3. For the reaction of **1** with **4**, the effect appears larger, which can be attributed to the fully apolar character of **4**.

Rate constants in aqueous alcohol mixtures

In mixtures of water and 1-propanol or 2-methyl-2-propanol, with [alcohol] 2 M, the reactions of **1** with **2a** and **2b** are slightly accelerated, compared with water (Fig. 7), leading to a maximum in rate constant, at around 45 M water. Similar maxima have been observed for many cycloadditions, although there are examples where the
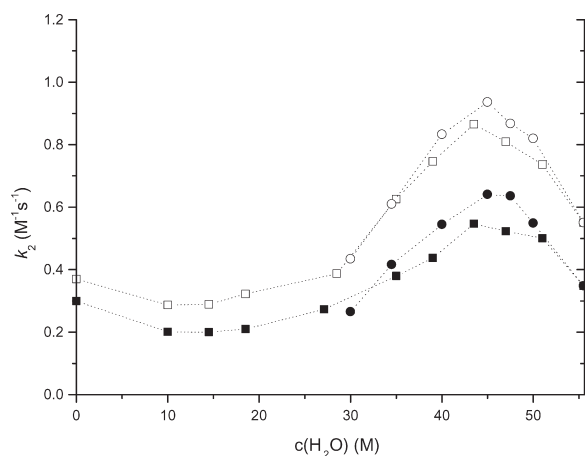

Figure 7. Rates in water–1-propanol mixtures (squares) and water–2-methyl-2-propanol mixtures (circles), for the reaction of **1a** with **2a** (closed symbols) and **2b** (open symbols)

effect is absent.[31] Plotted versus the mole fraction of water, the positions of the maxima seem to depend on the hydrophobicity of the alcohol. However, Fig. 7 reveals that the maximum appears at roughly equal *concentrations* of water. In other words, the positions of the maxima correlate with the size of the cosolvent molecules, if the mole fraction scale is used. The mole fraction scale may not be the best choice for discussing medium effects in aqueous solvent mixtures.

There is also a shallow minimum in rate constant around 15 M of water. In this concentration range, the hydrogen-bond network of water becomes completely disrupted and hydrophobic effects no longer play a role. Compared with 1-propanol, addition of a small amount of water increases the hydrogen bond-donating capacity of the solvent mixture, which for these reactions is both favorable (activation of the dipolarophile) and unfavorable (deactivation/stabilization of the 1,3-dipole), and a net unfavorable effect results.[9] In methanol–water mixtures, the minimum is absent, and the rate constant increases monotonically on adding water, up to 40 M. Once more, an unusually complex dependence of rate constant on the nature of the reaction medium is found.

Isobaric activation parameters in mixtures of water and 1-propanol

Isobaric activation parameters have also been determined for the reactions of **1** with **2a** and **2b** in water–1-propanol mixtures (Fig. 8). Up to 40 M water, the variation in activation parameters is small. $\Delta^\ddagger H^\ominus$ slightly decreases and $-T\Delta^\ddagger S^\ominus$ increases accordingly. In the water-rich mixtures, $-T\Delta^\ddagger S^\ominus$ suddenly drops significantly, accompanied by a largely compensating increase in $\Delta^\ddagger H^\ominus$. In the water-rich regime, hydrophobic effects come into play, and $-T\Delta^\ddagger S^\ominus$ drops (initial state destabilization by hydrophobic hydration). Whereas at around 40 M of water the solvent mixture behaves as a 'normal' polar solvent, at higher water concentrations the characteristic features of water at room temperature (i.e. hydration of apolar compounds accompanied by a large unfavorable entropy term) become apparent. The patterns in the activation parameters are in part similar for **2a** and **2b**, as was found among the pure solvents, but significant differences are observed for $\Delta^\ddagger H^\ominus$ and $\Delta^\ddagger S^\ominus$ in the concentration range where hydrophobic effects are important. The alkyl substituent in the dipolarophile clearly influences the activation process in these aqueous mixtures, most likely
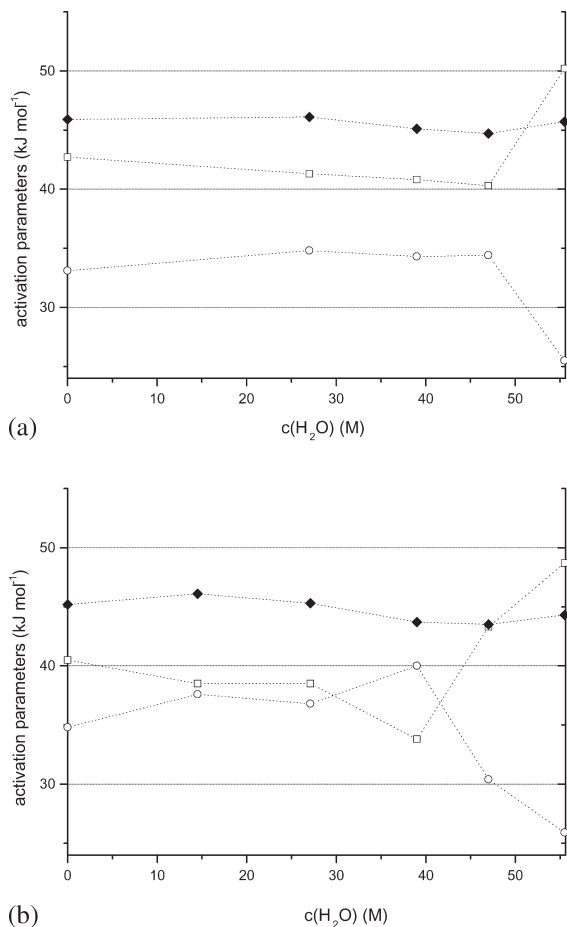
Figure 8. Activation parameters for the reaction of **1** with (a) **2a** and (b) **2b** in water–1-propanol mixtures at 25 °C: $\Delta^{\ddagger}G^{\ominus} -30$ (◆); $\Delta^{\ddagger}H^{\ominus}$ (□); $-T\Delta^{\ddagger}S^{\ominus}$

by inducing differences in solvation/hydration. The butyl group could, for example, induce a larger preference of the dipolarophile for being solvated by propanol. These differences in solvation are again 'innocent', i.e. not reflected in the rate constants. Nevertheless, these data show that despite the absence of large effects of water on the rate constants of these reactions, typical 'aqueous' behavior is occurring in water-rich mixtures.

CONCLUSIONS

A systematic study of solvent effects on the reactions of benzonitrile oxide (**1**) with *N*-alkylmaleimides (**2**) and cyclopentene (**4**) has provided additional insights into the factors that determine the rates of cycloadditions in different media. This study emphasizes the importance of both polarity and hydrogen-bond donating capacity: (i) differences in charge distributions for reactants and activated complex cause polar interactions with the solvent (including hydrogen bonds) to enlarge or reduce the energy gap between both states; (ii) a hydrogen bond formed between reactant and solvent (hydrogen-bond donor) affects the HOMO and LUMO of the reactant,

similarly to the impact of a Lewis acid catalyst, and this specific effect can either accelerate or inhibit the reaction. For the present reactions these two factors *oppose* each other, which partially explains the modest solvent effects on these reactions, and leads to the complex dependence of rate constants on solvent.

In the case of the reactions of the *N*-alkylmaleimides with benzonitrile oxide, hydrogen bonding (with corresponding changes in the FMOs) to both reactants occurs, with opposite effects: hydrogen bonding to the dipolarophiles is favorable, but hydrogen bonding to the benzonitrile oxide unfavorable. This pattern can be rationalized with FMO theory, assuming the reaction has normal electron demand (NED).

In mixtures of solvents, of which only one is a hydrogen-bond donor, log*k* varies gradually with the composition (often linearly), indicating the absence of significant preferential solvation of the reactants due to hydrogen-bond interactions. The specific, 'catalytic' effects of hydrogen bonds are not accompanied by strong binding or complexation of the hydrogen bond-donating solvent to the reactants.

Interestingly, isobaric activation parameters reveal significant differences in solvation in different solvents that are not reflected in the rate constants.

In (highly) aqueous mixtures, hydrophobic effects are important, but this does not lead to large increases in rate, because the contribution of these effects is modest, and these effects are counteracted by other factors. This pattern contrasts with common DA reactions, where polarity, hydrogen-bond donor capacity and enforced hydrophobic interactions work together, which can result in impressive rate accelerations in water.

EXPERIMENTAL

Materials

N-n-Butylmaleimide (**2b**)[29] has been synthesized previously. The $E_T(30)$ probe was kindly provided by Prof. Dr Chr. Reichardt (University of Marburg, Germany). 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 run over basic aluminium oxide prior to use. Cyclopentene (**4**) was distilled before use.

Kinetic experiments

The procedure, described in the literature,[9] where **1** is generated *in situ* in a CH$_2$Cl$_2$–bleach two-phase system, and small aliquots of the organic layer are transferred to the reaction mixture, was found to lead to poor kinetics for aqueous solutions because of solubility problems. Instead, the preparation of **1** was performed by dissolving

benzaldoxime in a bleach–1-propanol mixture in a test-tube and shaking this tube for a few seconds. After the addition of sodium chloride a two-phase system quickly emerged, and 0.5–1 µl of the organic layer was transferred to a quartz cuvet, which contained the reaction mixture with the dipolarophile. This method led to excellent kinetics and was used for most kinetic measurements. No differences in rate constants were found in aprotic solvents when using 1-propanol rather than dichloromethane for this method.

Kinetic measurements were performed using UV–visible spectroscopy (Perkin-Elmer $\lambda 5$ or $\lambda 12$ spectrophotometer). The dipolarophile was used in excess, and reactions were monitored at 273 nm. The reactions were followed for at least four half-lives and pseudo-first-order rate constants were obtained using a fitting program. Typical conditions were [dipolarophile] $= 1$–10 mM and [1,3-dipole] ≈ 0.025–0.05 mM. Activation parameters were calculated from 4–5 rate constants in the temperature range 20–40 °C.

UV–visible spectra of **1** and the $E_T(30)$ probe were recorded on a Perkin-Elmer $\lambda 5$ spectrophotometer at 25 °C. $E_T(30)$ values were calculated from the longest wavelength charge-transfer absorption band of the dye, $E_T(30)$ (kcal mol^{-1}) $= 28591/\lambda_{max}$ (nm);[23] $E_T(\mathbf{1})$ values were calculated accordingly from its longest wavelength absorption band. A few microliters of solvatochromic dye was injected into a known volume of solution or solvent mixture. In the case of betaine-30, stock solutions were prepared in ethanol. For **1**, the procedure described above was used.

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