Diels–Alder Reaction of Fumaronitrile and Cyclopentadiene in Water: the Influence of Cosolutes

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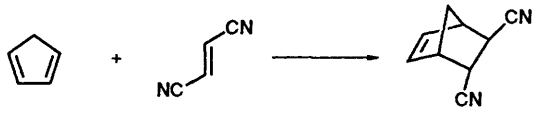
Rates of reaction are reported for the title compounds in aqueous solution. The influence of added salts on the rate of reaction is recorded: alkali-metal salts advance the rate, while tetraethylammonium chloride retards it. Sodium dodecyl sulphate and cetyltrimethylammonium bromide also retard the reaction, while the effect of cyclodextrins depends on their cavity size. The explanation of these phenomena in terms of the hydrophobic effect is considered and extended by measurement of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ parameters for the reaction.

The use of Diels–Alder reactions in water for organic synthesis has received much attention over the last decade.[1] Such processes are often, although not always, carried out in suspension,[1a] although it seems likely that even in these cases the reaction proceeds *via* the small amounts of dissolved reactants. In solution,[2] the acceleration observed over reactions in organic solvents has been attributed to the hydrophobic effect,[3] a factor which may also influence their selectivity.[2b,4] We have carried out an investigation of the aqueous Diels–Alder reaction of fumaronitrile (FN) and cyclopentadiene (CPD), Scheme 1, to seek further evidence for the hydrophobic effect in these types of bimolecular reaction.



Scheme 1

This particular reaction was chosen because it can be considered in many ways to constitute the quintessential normal 4 + 2 cycloaddition, particularly for study in aqueous solution. First, facilitating substituent effects exist in the components. The diene is activated by the methylene group at both C-1 and C-4, raising the HOMO energy, the methylene group further serving to hold it in the reactive *cisoid* configuration, while the dienophile is activated by the two electron-withdrawing cyano groups, lowering the LUMO. Secondly, both participants are sufficiently soluble to allow study by UV spectrometry, under pseudo-first-order conditions, with FN being in large excess. Thirdly, only one product, or, at least, a racemic mixture, is formed, which removes the complexity involved in consideration of the variation of *exo*/*endo* ratios, as well as reaction rate, as conditions are varied. For example, *exo*- and *endo*-transition states would have different $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values, as shown by the change in the *exo*/*endo* ratio as temperature is varied.[5]

Experimental

Dicyclopentadiene, FN, methyl vinyl ketone, sodium chloride, potassium chloride, sodium dodecyl sulphate and the cyclodextrins were obtained from Aldrich. Cetyltrimethylammonium bromide and lithium chloride were obtained from Fisons and tetraethylammonium chloride from BDH. The rate measurements and Beer's law studies were carried out on a Pye-Unicam PU8800 UV/VIS spectrophotometer equipped with a programmable cell changer and a thermostatically controlled cell chamber.

Preparation of Solutions.—FN solutions of 50 mmol dm^{-3} were obtained by weighing out the appropriate amount either directly into the volumetric flask or into a weighing bottle. After addition of the dienophile to the volumetric flask, it was made up to the mark with distilled water and shaken until all of the solid had dissolved. Solutions of methyl vinyl ketone were prepared in an analogous fashion. Stock solutions of CPD were prepared by dilution. Distilled CPD was stored in a freezer for a short while, prior to use. This retards the dimerisation reaction and makes the weighing process easier by reducing evaporation of the volatile liquid. Freshly distilled CPD (0.2644 g) was added to a 500 cm^3 volumetric flask and made up to the mark with distilled water. This was then diluted to the required concentration by pipetting out the required volume and diluting in a second volumetric flask. For example, 10 cm^3 of the 500 cm^3 solution into a 100 cm^3 flask gives a 0.8 mmol dm^{-3} stock solution.

Beer's Law Studies.—Stock solutions of FN (49.13 mmol dm^{-3}) and CPD (8.34 mmol dm^{-3}) were prepared in the normal manner. Various lower concentrations were obtained from these stock solutions by dilution. Water was used as the reference in the UV determinations.

For CPD, the absorbance at 239 nm was recorded for each concentration. For FN, absorbance was measured at 245 nm. This is not the λ_{max} because at the concentrations used in the study, the absorbance at this point is off scale. The concentrations used are of the same order as those used in the kinetic studies.

Kinetics.—FN was used as supplied and CPD was freshly distilled from the dimer each time it was required. Fresh solutions of each component were made up immediately before use and allowed to equilibrate to the operating temperature for at least 15 min before being mixed and dispensed into the cuvettes. By using the cell changer facility it was possible to run three samples simultaneously and follow the change in absorbance for various cycle times depending on the speed of the reaction.

The kinetic studies were carried out under pseudo-first-order conditions with the dienophile as the excess reagent. Rate data were analysed using pseudo-first-order kinetics with a correction term for the residual absorbance due to FN. Hence, a plot of $\ln (A - A_{\infty})$ *versus* time gives a line of gradient k, the pseudo-first-order rate constant, from which the second-order rate

Table 1 Effect of additives on the aqueous Diels–Alder reaction of CPD and FN

Entry	T/°C	Cosolute (c/mol dm^{-3})	$k_2/10^{-5}$ dm^3 mol^{-1} s^{-1}	r
1	25	—	9 510(167)	0.999
2	25	LiCl (1)	14 199(956)	0.999
3	25	KCl (1)	11 178(156)	0.999
4	25	NaCl (1)	13 432(90)	0.999
5	25	Et_4NCl (1)	7 320(154)	0.997
6	25	SDS (50×10^{-2})	8 154(133)	0.998
7	25	α-CD (5.04×10^{-3})	8 822(122)	1.000
8	25	β-CD (5.08×10^{-3})	19 113(450)	1.000
9	25	γ-CD (4.95×10^{-3})	11 696(423)	0.998
10	30	—	15 417(712)	0.998
11	30	CTAB (20×10^{-2})	14 629(366)	0.992

constant, k_2, is obtained according to $k = k_2$[dienophile]. Least-squares analysis of the rate data was performed on a Casio fx-3600P scientific calculator. Reported rate constants are the average of at least three runs with the standard deviation given in brackets. In general, a 50 mmol dm^{-3} stock solution of the dienophile was prepared, giving an in-cell concentration of 25 mmol dm^{-3}. The diene stock solution was prepared as 1.6 or 0.8 mmol dm^{-3} solution to give either 0.8 or 0.4 mmol dm^{-3} in-cell, depending on the speed of the reaction.

General Procedure.—The general method used was to pipette a known amount of the dienophile solution into a sample tube and place it into the water bath to equilibrate to the operating temperature. A sample of the CPD solution was allowed to equilibrate in the same manner. After equilibration, an equal volume of CPD solution was added to the dienophile solution and mixed in. A small quantity of the reaction mixture was used to wash the cuvettes out prior to filling them. When filling the cuvettes, care was taken to avoid the introduction of bubbles by keeping the end of the dropping pipette below the level of the solution within the cuvette. The cuvettes were then inverted to ensure mixing, wiped with tissue and inserted in the cell chamber of the preprogrammed spectrometer and measurement started.

After completion of reaction, the cuvettes were washed out with water, acetone and water again before the next run. Periodically the cuvettes were also washed out with aq. NaOH (5%) solution as it was found that any trace of acid gave erratic results.

Reactions in the Presence of Salts.—The required quantity of the cosolute was weighed into a sample tube and dienophile solution (10 cm^3) added. This solution was then used in the same manner as described above.

Activation Parameters.—Reactions in aqueous media were performed by preparing stock solutions in the same manner as described above. For the reactions in mixed solvents, the FN was prepared in the organic solvent component and CPD in water as above. Solutions in ethanol were prepared in an analogous manner to those in water. Reaction mixtures were prepared in the manner described above.

Cyclodextrin Catalysis.—Solutions of FN (100 mmol dm^{-3}) and CPD (1.6 mmol dm^{-3}) were prepared in the normal way. Solutions of various concentrations of the required cyclodextrin were obtained either by dilution of a 10 mmol dm^{-3} stock solution or by dissolving the required amount of cyclodextrin directly in distilled water (5 cm^3). Equal volumes (5 cm^3) of FN and CPD solutions were mixed. In order to obtain lower in-cell concentrations this solution was diluted by the addition of the required amount of distilled water. The reaction solution was obtained by taking 5 cm^3 of this mixture and adding it to the cyclodextrin solution (5 cm^3).

Syntheses

Cyclopenta-1,3-diene (CPD).—Dicyclopentadiene was heated in a distillation apparatus using a glass column and CPD distilled off at 41 °C to give CPD as a clear, volatile liquid. The initial drops of distillate were collected and later recycled. The collected CPD was stored in a freezer for a short while before use.

5,6-Dicyanobicyclo[2.2.1]hept-2-ene.—(*a*) FN (0.39 g, 5 mmol) was dissolved in distilled water (200 cm^3) and freshly distilled CPD (0.73 g, 11 mmol) added. The suspension was stirred rapidly at room temperature overnight. The resultant mixture was extracted with ether (3×50 cm^3) and the combined organic phase dried over anhydrous sodium sulphate. The ether was removed *in vacuo* and the crude product recrystallised from ethanol to give a white solid (0.66 g, 92%), m.p. 93 °C (lit.,[6] 95.5–96 °C); ν_{max}(Nujol)/cm^{-1} 2260m (CN) and 1620w (C=C); δ_H(60 MHz; $CDCl_3$) 1.7 (2 H, m), 2.5 (1 H, m), 3.1 (1 H, m), 3.4 (2 H, m) and 6.35 (2 H, m).

(*b*) FN (1.15 g, 14.7 mmol) was dissolved in dioxane (100 cm^3) and freshly distilled CPD (1.6 g, 24.3 mmol) added. After the reaction had been stirred at room temperature for 6 h, the solvent was removed *in vacuo* and the crude product recrystallised as above (1.97 g, 93%), m.p. 94 °C, ν_{max}(Nujol)/cm^{-1} 2260m (CN), 1620w (C=C); δ_H (60 MHz; $CDCl_3$) 1.7 (2 H, m), 2.5 (1 H, m), 3.1 (1 H, m), 3.4 (2 H, m) and 6.35 (2 H, m).

Results and Discussion

Scheme 1 shows a significant acceleration in aqueous conditions: the second-order rate constant in water at 20 °C being 6507(52), compared with 156(10) and 80.6 in ethanol and dioxane,[7] respectively, at the same temperature. It is important to note that in all these aqueous reactions discussed here, Beer's law has been found to apply consistently, indicating that aggregation of reactants does not occur, as other workers have likewise concluded.[8]

The influence of cosolutes added to the aqueous reaction are shown in Table 1. These results are consistent with known effects and provide evidence of hydrophobic influence. Lithium, sodium and potassium chlorides (entries 1–4 in Table 1) are found to increase the rate of reaction: alkali-metal chlorides are known to reduce the solubility of organic species[9] in water (salting-out), and they have been shown also to accelerate aqueous Diels–Alder reactions.[2a] In contrast, the ammonium salt (entry 5), where the positive charge is buried in the centre of the molecule, slows the reaction down, in keeping with the observation that such salts tend to increase the solubility of organic molecules in water (salting-in).[9]

Sodium dodecyl sulphate (SDS) and cetyltrimethylammonium bromide (CTAB) are both known to form micelles in aqueous media,[10] and comparison of entries 1 and 6, and 10 and 11, show that both species retard the reaction, a significant result which suggests that micellar catalysis is not the origin of the rate enhancement found in water, compared with organic solvents, in confirmation of the conclusion reached from the applicability of Beer's law, discussed above.

The cyclodextrin[11] effects (entries 7, 8 and 9 *cf.* 1) can be rationalised in terms of the cavity size,[2a,12] β- and γ-cyclodextrin have cavities sufficiently large to allow the reactants to form an inclusion complex, with a geometry which brings the

Table 2 Effect of dilution on the second-order rate constant, k_2, of Scheme 1 at 25 °C in aqueous media

Relative concn.[a]	$k_2/10^{-5}$ dm^3 mol^{-1} s^{-1}
1.00	9205(33)
0.91	9156(126)
0.83	9408(154)
0.77	9335(220)
0.66	9696(252)
0.50	9429(117)

[a] A value of 1.00 implies [FN] = 25 mmol dm^{-3} and [CPD] = 0.4 mmol dm^{-3} and a value of 0.50 implies 12.5 mmol dm^{-3} and 0.2 mmol dm^{-3}, respectively.

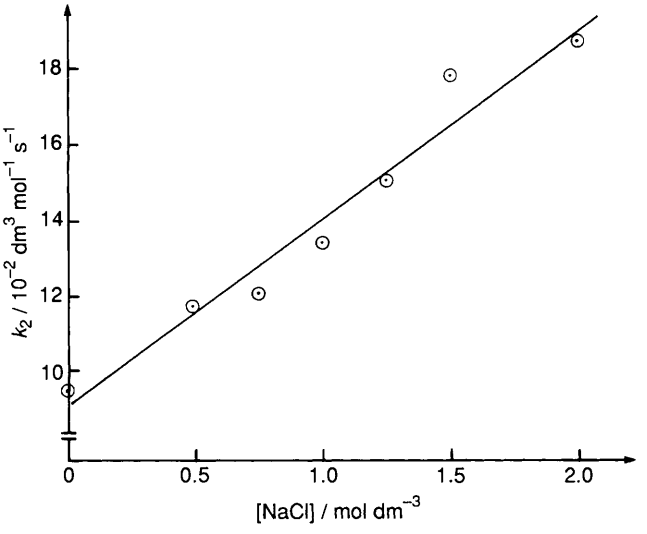


Fig. 1 Effect of added NaCl on the second-order rate constant, k_2, of Scheme 1

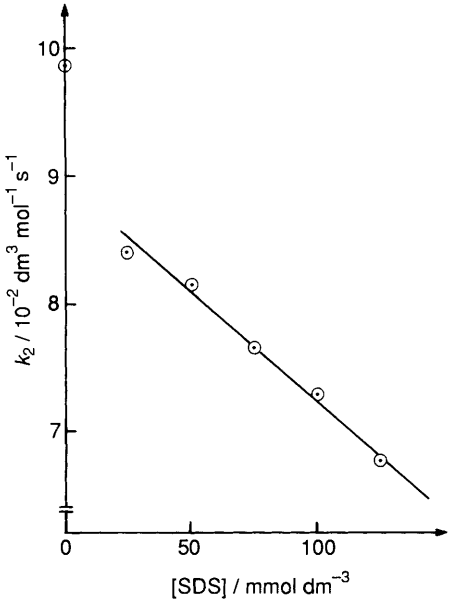


Fig. 2 Effect of added SDS on the second-order rate constant, k_2, of Scheme 1

reactive centres into a favourable orientation. The accelerative effect of the β-cyclodextrin (6.0–6.4 Å) over the γ-cyclodextrin (7.5–8.3 Å) is due to its smaller size—the reactants are drawn into closer proximity. In contrast, the even smaller cavity of the α-cyclodextrin (4.7–5.2 Å) results in inhibition. Complexation of the reactants reduces their concentration in the bulk aqueous solution, and thus lowers the rate of this reaction, but the

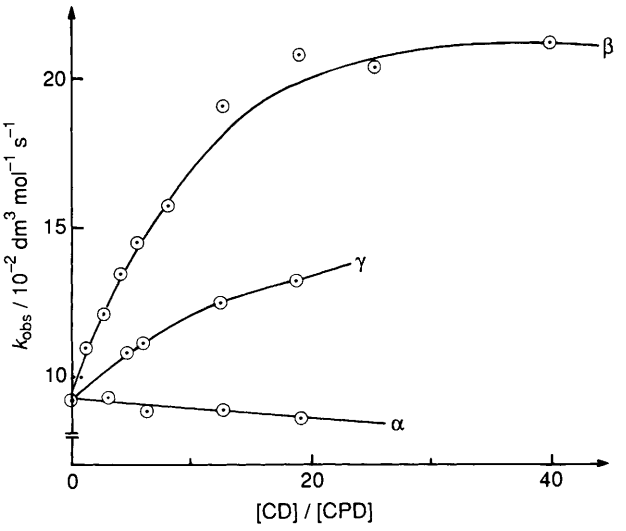


Fig. 3 Effect of added α-, β- and γ-CD on the observed second-order rate constant, k_{obs}

smaller cavity does not allow the reactants to enter into an orientation favourable for accommodating the transition state of the reaction.

Further elucidation of these various effects and influences can be afforded by variable-concentration studies.

Support for the hydrophobic effect, rather than micelle formation[13] by the reactants, providing the catalytic stimulus is given by the data in Table 2, in which the effect of varying the concentration of the reactants on the observed second-order rate constant is shown. If the reaction had been proceeding within organic molecular aggregates, rather than in the body of the aqueous phase, decreasing concentration should have produced a decrease in rate; in fact, the rate constants are, to within experimental error, the same as one another.

Fig. 1 shows the accelerative effect of increasing the concentration of a salting-out additive, due to the increasing lipophobicity of the solvent. The opposite effect is observed with the ampiphile SDS (Fig. 2). Increasing the concentration of the micelle-forming reagent increases the contribution of the reaction occurring in the essentially organic micelle environment, with an overall reduction in rate compared with the aqueous reaction. At the limit of the concentrations studied, there is no evidence for a levelling-off in the rate, which one would expect to see were all the reaction occurring in the micelle.

The plots for the cyclodextrins (Fig. 3) show enzyme-analogous kinetic saturation for the β-, and a similar profile, but one reflecting weaker catalysis, for the γ-cyclodextrin. The α-cyclodextrin plot shows essentially linear inhibition with increasing cyclodextrin concentration. These effects are an example of a non-covalent, conformational, catalytic process, as argued above. Enzyme kinetics are described using the Michaelis–Menten model, eqn. (1),[14a] and this type of approach

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} P + E \qquad (1)$$

can be used to analyse the kinetics for β-cyclodextrin.[14b] We base our analysis on the resultant Michaelis–Menten eqn. (2),

$$V = V_{max}[S]/([S] + K) \qquad (2)$$

correcting for the presence of an uncatalysed reaction component, rate constant k_o, which is the second-order rate constant of the uncatalysed reaction, and neglecting any contribution

de to non-productive inclusion complexes. It is thus possible to estimate the catalytic rate constant, k_{cat}, and also the apparent formation constant of the reactive inclusion complex K_m, for eqn. (3), using the expression given in eqn. (4) where V is the

$$\begin{array}{l} \text{diene} + \text{dienophile} + \text{CD} \overset{K'}{\rightleftharpoons} \text{complex} \xrightarrow{k'_{cat}} \\ \quad \downarrow k_o \qquad\qquad\qquad\qquad \text{adduct} + \text{CD} \\ \text{adduct} \end{array} \quad (3)$$

$$k_{obs} - k_o = \frac{k'_{cat}[CD]}{[CD] + K} \quad (4)$$

velocity at which the product P is formed, V_{max} is the velocity at saturation, $K = (k'_2 + k'_3)/k'_1$ and CD stands for the cyclodextrin.

Analysis of eqn. (4) in terms of a least-squares correlation of its reciprocal, *i.e.* a pseudo-Lineweaver–Burk plot,[14] gives a gradient equal to K_m/k_{cat} and intercept $1/k_{cat}$. This procedure has been tested on literature data,[8b] reproducing the reported values, obtained by computer model, in excellent agreement. The values obtained for catalysis by β-cyclodextrin are $k_{cat} = 14\,400 \times 10^{-5}$ dm^3 mol^{-1} s^{-1} and $K_m = 4.094$ mmol dm^{-3} ($K_{app} = k_m^{-1} = 244$ dm^3 mol^{-1}), reflecting a catalytic enhancement, (k_{cat}/k_o) of a factor of approximately 1.6.

A partial rationalisation of eqn. (4) follows from Laidler,[14b] utilizing the scheme of eqn. (3) modified as follows:

$$\text{diene} + \text{CD} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{CD}_A$$

$$\text{CD}_A + \text{dienophile} \xrightarrow{k_{cat}} \text{CD} + \text{adduct}$$

$$\text{diene} + \text{dienophile} \xrightarrow{k_o} \text{P}$$

whence[14b]

$$k_{obs} = \frac{k_{cat}[CD]_o}{([CD]_o + [\text{diene}]_o) + \dfrac{k_{-1} + k_{cat}[\text{dienophile}]_o}{k_{-1}}} + k_o$$

where k_{obs} is equal to the second-order rate constant k_2 as defined in the kinetics section of the Experimental section and $[CD]_o$ and $[\text{diene}]_o$ refer to total initial stoichiometric concentration. Writing

$$K_m = \frac{k_{-1} + k_{cat}[\text{dienophile}]_o}{k_1}$$

(the units of which will be mol dm^{-3})

$$k_{obs} = \frac{k_{cat}[CD]_o}{([CD]_o + [\text{diene}]_o) + k_m} + k_o$$

If $[CD]_o \gg [\text{diene}]_o$, which applies in our case, since $[CD]_o/[\text{diene}]_o = 5.5$ at worst, then

$$k_{obs} - k_o = \frac{k_{cat}[CD]_o}{[CD]_o + K_m}$$

Laidler's treatment applies only to initial rates of reaction. It is therefore surprising that we have obtained good linear plots for our kinetic runs overall. In view of this and other approximations involved in the Laidler treatment, these results must be regarded as preliminary. It would be interesting to investigate this and related systems in more detail, particularly in instances where the catalytic effect is greater (for monoethyl fumarate and diethyl fumarate the catalytic ratios k_{cat}/k_o are 40 and 100, respectively,[8b] compared with 1.6 for fumaronitrile, the partner in all cases being CPD). This in turn raises the question of the factors at work in the association of reactants and catalyst in this type of reaction, which are little understood.

Variable-temperature measurements may also furnish information on hydrophobic acceleration, and these we now consider.

The activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, of intermolecular Diels–Alder reactions in organic media are usually characteristic,[15] with a small endothermic enthalpic term (because bond-making and bond-breaking occur simultaneously), and a large negative entropic term (reflecting the loss of degrees of freedom during the formation of the cyclic transition state from the two reactants). The typical range of $\Delta S^{\ddagger}$ values for an intermolecular Diels–Alder reaction is -170 to -120 J K^{-1} mol^{-1}.[15]

This analysis does not include deductions for the aqueous Diels–Alder reaction. The accelerative and decelerative effects recorded in Table 2 are relatively small, involving only minor $\Delta G^{\ddagger}$ changes. Aggregation in aqueous media however is normally an entropically driven process[16] due to the release of water molecules from the highly ordered hydrophobic hydration spheres around the reactant molecules (the so-called 'flickering icebergs'[17]) as these molecules enter into reaction. This suggests that $\Delta S^{\ddagger}$ for a Diels–Alder reaction in water should be much less negative than in organic solvents, while the $\Delta H^{\ddagger}$ value should stay much the same. Only limited information is available to check this, so we undertook an investigation of the influence of temperature on the reaction in Scheme 1.

Table 3 gives the results we obtained, together with data from other workers for comparative purposes. Entries 1 and 9–12 bear out the notions outlined above. $\Delta S^{\ddagger}$ values for the reactions in ethanol and dioxane are consistent with values in less polar organic solvents, but $\Delta S^{\ddagger}$ for the aqueous reaction is strikingly different, being closer to the value associated with an intramolecular Diels–Alder reaction.[18] The activation parameters of Diels–Alder reactions are regarded as evidence for concerted reaction,[19] so the correct conclusion might be that the aqueous reaction is stepwise. The fact that the product of both reactions in water and dioxane are identical, and there is no evidence for di-*exo* or di-*endo* product, suggests however that a Michael addition is not involved, and implies that the observed $\Delta S^{\ddagger}$ value indeed reflects the hydrophobic aggregation of the reactants.

While this effect is marked for CPD with FN, it seems as if it is less so with CPD and acrylonitrile (entry 17), and not at all with CPD and methyl vinyl ketone (entries 13 and 14). Rideout[20] has attributed the acceleration by water on these latter reactions, to a combination of polarity and hydrophobic effects. These dienophiles have unsymmetrically polarised double bonds due to their substitution pattern, and will proceed *via* transition states that are more polar than that of the FN reaction,[21] and while bond-making may be concerted, so that the formal Michael pathway is avoided, it may be a long way from being synchronous. According to Jencks,[22] solutes of even moderate polarity tend to associate with either no change or at least only a moderate negative change in the entropy of the solvent. The trend towards less negative $\Delta S^{\ddagger}$ values seen with acrylonitrile, to a small extent, and with FN, in the presence of water, is paralleled by results for intramolecular [2 + 2] photocycloaddition.[23]

The effect of adding salts that have a salting-out influence (see above) is to shift the $\Delta S^{\ddagger}$ values towards the typical organic values (entries 2–4, *cf.* entry 1). The change in $\Delta S^{\ddagger}$ would tend to make such reactions slower if it were not for the reduction in the $\Delta H^{\ddagger}$ term. This can be rationalised in terms of the salts either breaking up the structure of the hydrophobic hydration shell, or

Table 3 Activation parameters[a] for the reaction of CPD with several dienophiles

Entry	Reactant	Solvent	$\log k_2$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	r	n	Ref.
1	(*E*)-NC–CH=CH–CN	H_2O	−1.187	78.4	62.2(4.0)	−55.3(13.5)	0.995	6	TW
2		Aq. (0.25 mol dm^{-3}) LiCl	−1.158	78.2	49.8(0.8)	−97.1(2.7)	1.000	5	TW
3		Aq. (0.5 mol dm^{-3}) LiCl	−1.083	77.8	41.9(3.6)	−122.2(11.9)	0.989	5	TW
4		Aq. (0.25 mol dm^{-3}) KCl	−1.164	78.3	57.1(2.8)	−72.0(9.5)	0.996	5	TW
5		Aq. (5 mmol dm^{-3}) SDS	−1.174	78.3	47.1(2.0)	−106.6(6.8)	0.998	6	TW
6		Aq. (50 mmol dm^{-3}) SDS	−1.234	78.7	45.1(1.6)	−115.2(5.2)	1.000	6	TW
7		Aq. (0.01 mol dm^{-3}) SDS	−2.958	79.0	49.4(3.0)	−101.1(10)	0.994	5	TW
8		Aq. (5 mmol dm^{-3}) CD	−0.864	76.6	34.7(2.7)	−142.2(8.5)	0.992	5	TW
9		MeOH–H_2O[b]	−1.437	79.8	40.5(6.0)	−134.1(2.1)	1.000	4	TW
10		EtOH–H_2O[b]	−1.424	79.8	50.7(1.7)	−99.0(5.8)	0.998	6	TW
11		EtOH	−2.808	87.5	52.2(1.5)	−120.5(4.8)	0.999	5	TW
12		Dioxane	−3.094	89.1	48.5	−138.1	—	—	7
13	H_2C=CHCOMe	H_2O	−1.353	79.3	34.9	−150.9	0.990	7	20
14		H_2O	−1.102	79.5	35.0(2.9)	−153.0(9.5)	0.990	6	TW
15		Dioxane	−4.044	94.5	55.2	−133.9	—	—	7
16	H_2C=CHCN	Aq. SDS	−3.602	92.0	51.0	−142.3	—	—	25
17		H_2O	−3.602	92.0	69.5	−80.7	1.000	2	20
18		Dioxane	−3.983	94.1	56.9	−146.4	—	—	31
19	H_2C=CHCO$_2$Me	Aq. SDS	−3.000	88.6	44.4	−150.6	—	—	25
20		Dioxane	−3.928	93.8	62.3	−133.9	—	—	7
21	CH_2=CHCO$_2$Bu	Aq. SDS	−2.897	88.0	58.6	−100.6	—	—	25

[a] Rate constants and $\Delta G^{\ddagger}$ at 20 °C. Units of $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are kJ mol^{-1} and $\Delta S^{\ddagger}$ J K^{-1} mol^{-1}. r is the correlation coefficient of the Eyring plot and n is the number of points on the plot (*i.e.* the number of temperatures used in the experiment). TW indicates 'This work'. [b] 1:1 by volume.

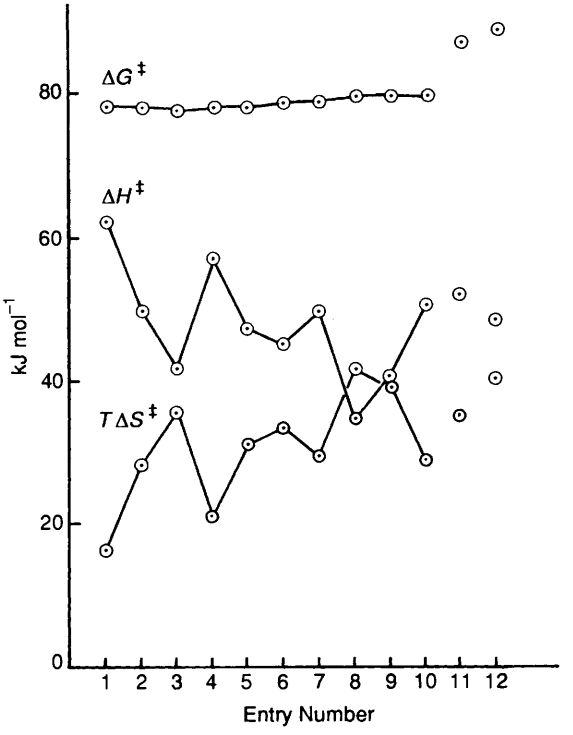


Fig. 4 Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ against entry number in Table 3 to illustrate the compensation effect

increasing the structure of the bulk solvent, or a combination of both factors. Since these salts are regarded as structure breakers[24] it would seem that it is the former effect that is more important.

Thermodynamic parameters for the influence of SDS (entries 5–7) tend to confirm the postulate given above, that the rate of aqueous Diels–Alder reactions are slowed down by micelle-forming species, because the reactants are concentrated within the organic environment of the micelle cavity, where the rate constant is lower than that in the aqueous phase. This is possibly why the $\Delta S^{\ddagger}$ values for the reactions reported by Sauer[25] (entries 16, 19–21) do not reveal the anomalous behaviour of water. Breslow[26] has interpreted the behaviour of such detergents as the result of an interaction with the hydrophobic solutes (the reactants), rather than with the solvent.

As noted above, cyclodextrins have been shown to affect the rate of Diels–Alder reactions by formation of hydrophobic inclusion complexes.[2a] β-Cyclodextrin catalyses the reaction of Scheme 1 by bringing the reactants into close proximity within its cavity, the formation of inclusion complexes being usually very rapid and reversible. It is interesting to note that the observed $\Delta S^{\ddagger}$ values for the reaction of Scheme 1 (entry 8) in the presence of β-cyclodextrin is almost identical with that observed for the reaction in dioxane.

The solvent effect on the rate of a reaction, and hence $\Delta G^{\ddagger}$, usually follows a predictable trend, at least in qualitative terms. For example, the $\Delta G^{\ddagger}$ values for the solvolysis of *tert*-butyl chloride in mixtures of ethanol and water decrease as the mole fraction of water is increased.[27] In contrast, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values vary considerably and in a less predictable manner, but compensate for each other. Here also for Scheme 1, the activation parameters change in opposite senses, with the lowered enthalpy term actually causing the reaction to be faster in spite of a more negative entropy term. This also applies to the β-cyclodextrin-catalysed reaction, where there is a massive reduction in $\Delta H^{\ddagger}$ which more than overcomes the unfavourable $\Delta S^{\ddagger}$ term. This particular example is slightly more complicated due to contribution to the activation parameters of the three-component pre-equilibrium that exists in the solution, eqn. (3). The general trends suggest however that overall there may be an approximate compensation or isokinetic relationship.[28] If the data shown in Table 3 for Scheme 1 is used to plot $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$, then such an approximate compensation effect is indeed revealed, which does not encompass the non-aqueous solvent systems (Figs. 4 and 5), but does include the cyclodextrin systems, although one must have some reservations about the exact implications of such a correlation. This type of behaviour is, however, well known for processes that involve the structural effects associated with hydrophobic hydration.[29] The compensation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, to produce relatively small changes in $\Delta G^{\ddagger}$, is due to the equilibrium of water molecules between different states within the system (highly ordered, bulky regions

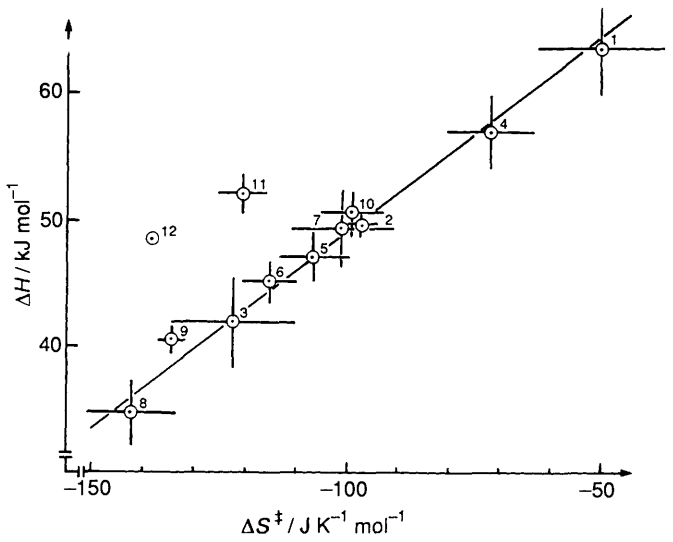


Fig. 5 Plot of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ to show the compensation effect. Numbers refer to the entries in Table 3

with monomeric, dense regions),[30] which allows water to accommodate changes in the reaction system by subtle changes in the water itself. The isokinetic temperature[28] may be evaluated as 37 °C, but this is very inaccurate: a plot of $\Delta G^{\ddagger}$ *vs.* $1/T$ reveals no trace of a common intersection point for 37 °C, indicative of the approximate nature of the compensation effect. Nevertheless, the notion does lead to some interesting and confusing speculations (as do all concepts of the isokinetic temperature), such as do salts that salt out at 20 °C salt in above the isokinetic temperature?

Conclusions

The accelerative effect of water as solvent on the Diels–Alder reaction of CPD with FN can be interpreted in terms of hydrophobic interactions between the addends. Approximate confirmation of this can be made by studying the influences of additives, particularly ionic salts, compounds capable of forming micelles, and cyclodextrins, together with the effect of temperature, on the rate of reaction.

In the debate,[2c,13] over hydrophobic catalysis *versus* micellar catalysis for the origin of aqueous acceleration in Diels–Alder reactions, it should be noted that generally small molecules have been used in the kinetic studies, while the molecules involved in synthetic work are often larger, a factor that could promote micelle formation, and reaction *via* such micelles in the latter case, unless water-solubilising groups are present. The concentration of reactants in the kinetic studies involving UV measurements is very low—millimolar—while synthetic work has been done on a molar scale in heterogeneous media, again conditions which are likely to promote micelle formation in the latter case. Nevertheless, the formation of micelles is a result of the hydrophobic effect, so the distinction between the two descriptions of the observed effects is minimal.

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