Multiparameter correlation of the rate of a [2 + 2] cycloaddition reaction versus solvophobicity parameter and normalized polarity parameter in aqueous solutions

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ABSTRACT: The second-order rate constants of the [2 + 2] cycloaddition reaction between diethyl azodicarboxylate and ethyl vinyl ether were obtained spectrophotometrically in various solvents and aqueous solutions of 1,4-dioxane and methanol at $30 \pm 0.1\,°C$. In all media except aqueous solutions, a very good linear correlation of $\log k_2$ *vs* E_T^N (normalized polarity parameter) was obtained ($n = 11$, $r = 0.991$, $s = 0.086$). Because of the higher polarity of the activated complex relative to the reactants, the rate of the reaction increase with increasing solvent polarity parameter. Dual-parameter correlation of $\log k_2$ *vs* π^* (dipolarity/polarizability) and α (hydrogen bonding acidity) also gives good results in various solvents ($n = 11$, $r = 0.985$, $s = 0.118$). Both π^* and α have approximately equal effects on the reaction rate. In aqueous solutions of 1,4-dioxane and methanol, the second-order rate constants of the reaction increase dramatically with increasing mole fraction of water. A dual-parameter correlation of $\log k_2$ *vs* Sp (solvophobicity parameter) and E_T^N was found in aqueous solutions ($n = 13$, $r = 0.988$, $s = 0.165$), in which Sp plays an important role in determining the reaction relative to E_T^N. This model represents a significant improvement in regression coefficient with respect to the single parameter correlation *vs* Sp or E_T^N ($r = 0.954$ and 0.854, respectively). Similarly to aqueous solutions, a dual-parameter correlation of $\log k_2$ *vs* Sp and E_T^N was obtained in all media ($n = 21$, $r = 0.987$, $s = 0.177$). Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: solvophobicity parameter; cycloaddition reaction; solvent effects; polarity parameter; kinetics; multiparameter correlation; dipolarity; hydrogen bonding acidity

INTRODUCTION

Water is an unconventional solvent for organic reactions. However, in addition to obvious economical and environmental advantages, water has surprisingly beneficial effects on organic reactions, which has popularized water as a reaction medium.[1,2] Studies in the last decade have revealed that a number of organic reactions proceed more rapidly in aqueous solutions than in organic solvents.[3–7] Detailed kinetic studies and computer simulations suggest that hydrophobic interactions have an important role in the acceleration of organic reactions in aqueous solutions.[8,9] The development of various kinds of approaches to hydrophobic hydration is necessary for a better understanding of its key role in controlling biochemical processes in water.[10,11]

Modeling of solvent effects is one of the most useful methods to obtain information about the mechanism of organic reactions. In the last few years, special attention has been paid to Diels–Alder cycloadditions owing to the different solvation mechanisms involved in this process.[12–16] More recently, in the 1,3-dipolar cycloaddition reaction of *C,N*-diphenylnitrone with various dipolarophiles, hydrophobic interactions were considered to be a major factor in increasing of the reaction rate in aqueous media.[17,18]

After the success of the Diels–Alder and 1,3-dipolar cycloaddition reactions in aqueous solutions, we were interested in a [2 + 2] cycloaddition reaction in order to investigate the effects of aqueous solutions on these class of cycloadditions. Detailed kinetic studies of organic reactions in this field have been restricted to [2 + 4] and [2 + 3] cycloaddition reactions.[6,7] Therefore, we studied the [2 + 2] cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether in various solvents and aqueous solutions of 1,4-dioxane and methanol at 30 °C (Scheme 1).
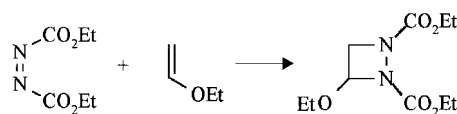
Scheme 1.

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Table 1. First-order rate constants of reduction and hydrolysis reaction of diethyl azodicarboxylate in various solvents at 30 °C[a]

Medium	k_0 (s^{-1})×10^5	Medium	k_0 (s^{-1})×10^5
MeOH	4.23 ± 0.11	MeOH (50:50)	102 ± 2
EtOH	1.21 ± 0.04	1,4-Dioxane (90:10)	0.272 ± 0.006
Propan-1-ol	1.69 ± 0.05	1,4-Dioxane (80:20)	2.02 ± 0.05
Propan-2-ol	2.68 ± 0.08	1,4-Dioxane (70:30)	5.06 ± 0.11
MeOH (90:10)	17.9 ± 0.5	1,4-Dioxane (60:40)	11.3 ± 0.2
MeOH (80:20)	33.2 ± 0.8	1,4-Dioxane (50:50)	21.3 ± 0.5
MeOH (70:30)	42.9 ± 0.9	1,4-Dioxane (40:60)	48.3 ± 0.9
MeOH (60:40)	64.9 ± 1.2		

[a] Errors are standard deviations; at least three runs were averaged. Solutions were prepared in water (ratios are v/v).

RESULTS AND DISCUSSION

The solvents were selected according to their Sp (solvophobicity parameter) and E_T^N (normalized polarity parameter) values in order to cover a broad range of solvents. Diethyl azodicarboxylate is reduced by alcohols[19] and is hydrolyzed in aqueous solutions[20,21] of 1,4-dioxane and methanol; therefore the second-order rate constants of the [2 + 2] cycloaddition reaction (k_2) of this compound with ethyl vinyl ethyl (EVE) in these media were obtained from the equation

$$k_{obs} - k_0 = k_2[\text{EVE}] \quad (1)$$

where k_0 is the first-order rate constant of hydrolysis and reduction reaction of diethyl azodicarboxylate and k_{obs} is observed pseudo-first-order rate constant of the overall reaction of diethyl azodicarboxylate. The values of k_0 were obtained in aqueous solutions and alcoholic media in separate experiments (Table 1).

The second-order rate constants of [2 + 2] cycloaddition were obtained in various solvents and aqueous solutions of 1,4-dioxane and methanol at 30 °C (Tables 2 and 3).

A very good linear correlation of logk_2 vs E_T^N was obtained in all solvents except aqueous solutions of methanol and 1,4-dioxane:

$$\log k_2 = -5.305(\pm0.051) + 2.553(\pm0.114)E_T^N \quad (2)$$
$$(n = 11, r = 0.991, s = 0.086, F_{1,9} = 498.2)$$

Figure 1 shows plot of logk_2 vs E_T^N. The second-order rate constants of this reaction increase with increasing solvent polarity parameter. This increase is attributed to a major interaction of polar solvents with the activated complex relative to the reactants; therefore, the polarity of the activated complex of the reaction is higher than those of the reactants. Changes in solute–solvent interactions during the activation process will influence the rate constant. Reactions which are accompanied by an increase in charge separation in their activation process are accelerated in solvents of increasing polarity. It is clear that solvent effects for the reaction are modest such that k_2 (in methanol)/k_2 (in toluene) is approximately 46. In contrast to strongly solvent-dependent [2 + 2] cycloaddition reactions (which proceed through a 1,4-dipolar zwitterionic intermediate by a two-step mechanism or through a dipolar activated complex by a one-step mechanism), [2 + 2] cycloadditions are also known which exhibit one-step, nearly synchronous bond formation without significant charge separation in the activated

Table 2. Rate constants of [2 + 2] cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether in various solvents at 30 °C[a]

Solvent	E_T^N	Sp	π^*	α	k_2 (l mol^{-1}s^{-1})×10^5	logk_2
Toluene	0.099	0.000	0.49	0.00	0.807 ± 0.026	−5.093
Benzene	0.111	0.000	0.59	0.00	1.19 ± 0.05	−4.924
1,4-Dioxane	0.164	0.079	0.55	0.00	1.33 ± 0.05	−4.876
THF	0.207	—	0.58	0.00	1.36 ± 0.06	−4.866
Ethyl acetate	0.228	0.064	0.55	0.00	1.94 ± 0.06	−4.712
DMF	0.404	0.138	0.88	0.00	3.72 ± 0.13	−4.429
DMSO	0.444	0.227	1.00	0.00	8.38 ± 0.18	−4.077
Propan-2-ol	0.546	0.100	0.49	0.76	14.6 ± 0.3	−3.836
Propan-1-ol	0.617	0.108	0.52	0.84	20.4 ± 0.4	−3.690
Ethanol	0.654	0.144	0.51	0.98	24.6 ± 0.5	−3.609
Methanol	0.762	0.200	0.58	1.14	36.8 ± 0.5	−3.434

[a] Errors are standard deviations; at least three runs were averaged.

Table 3. Rate constants of [2 + 2] cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether in various pure solvents and aqueous solutions at 30 °C[a]

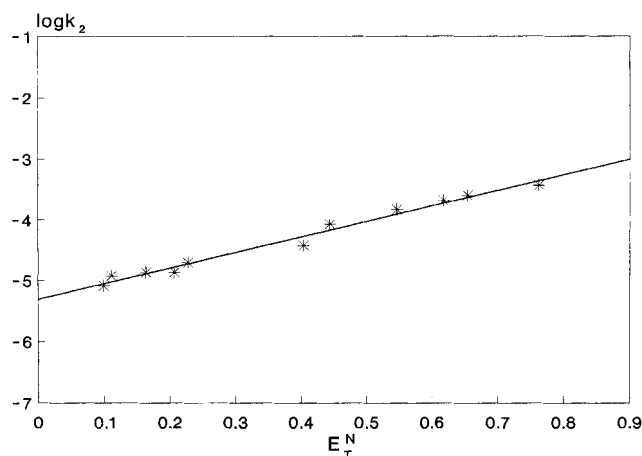| Medium	E_T^N	Sp	k_2 $(l\,mol^{-1}s^{-1}) \times 10^5$	$\log k_2$
1,4-Dioxane	0.164	0.079	1.33 ± 0.05	−4.876
1,4-Dioxane (90:10)	0.494	0.062	5.54 ± 0.05	−4.256
1,4-Dioxane (80:20)	0.565	0.139	16.4 ± 0.6	−3.785
1,4-Dioxane (70:30)	0.624	0.245	51.6 ± 1.7	−3.287
1,4-Dioxane (60:40)	0.667	0.390	120 ± 1.9	−2.921
1,4-Dioxane (50:50)	0.707	0.521	419 ± 14	−2.378
1,4-Dioxane (40:60)	0.750	0.646	858 ± 22	−2.066
MeOH	0.762	0.200	36.8 ± 0.5	−3.434
MeOH (90:10)	0.784	0.273	58.0 ± 2.1	−3.237
MeOH (80:20)	0.799	0.354	153 ± 8	−2.815
MeOH (70:30)	0.818	0.446	649 ± 16	−2.188
MeOH (60:40)	0.836	0.531	1148 ± 26	−1.940
MeOH (50:50)	0.852	0.631	3636 ± 74	−1.439

[a] Errors are standard deviations; at least three runs were averaged. Solutions were prepared in water (ratios are v/v).

complex.[22,23] Since this reaction shows modest solvent effects, we therefore suggest that the polarity of the activated complex of the reaction cannot be very different from those of the reactants. The unequal (non-synchronous) bond formation in the activated complex creates partial charges which are stabilized by polar solvents. As a result, the correlation of $\log k_2$ vs E_T^N is very good. The normalized polarity parameter (E_T^N) is a blend of pure polarity (dipolarity/polarizability) and hydrogen bonding interactions. In order to show the magnitude of these interactions in the reaction rate, a dual-parameter correlation of $\log k_2$ vs π^* and α was obtained:

$$\log k_2 = -5.767(\pm 0.165) + 1.606(\pm 0.241)\pi^* \\ + 1.361(\pm 0.084)\alpha \quad (3)$$
$$(n = 11, r = 0.985, s = 0.118, F_{2,8} = 129.7)$$

As can be seen, the coefficients of π^* and α are not very different. As a result, the dipolarity/polarizability and hydrogen bonding acidity of the medium have approximately equal effects on the reaction rate. A plot of experimental values of $\log k_2$ vs values calculated using Eqn. (3) shows that the interpretations are accurate (Fig. 2). The single-parameter correlation of $\log k_2$ vs π^* and α gives bad results ($r = 0.030$ and 0.897, respectively).

Because of solubility problems and strong hydrolysis of diethyl azodicarboxylate in water, the second-order rate constant of the reaction in this solvent was not obtained. In order to study effect of water on this reaction, rate constants of the reaction were obtained in aqueous solutions of 1,4-dioxane and methanol (Table 3).

Figure 3 shows a plot of second-order rate constants of the reaction vs mole fraction of water (X_w). It is clear that the rate constants of the reaction increase dramatically on addition of water. The increase in the reaction rate in aqueous solutions of methanol is higher than that in 1,4-dioxane. These observations are similar to those for Diels–Alder and 1,3-dipolar cycloaddition reactions in

Figure 1. Plot of $\log k_2$ vs E_T^N for the [2 + 2] cycloaddition reaction in various solvents at 30 °C
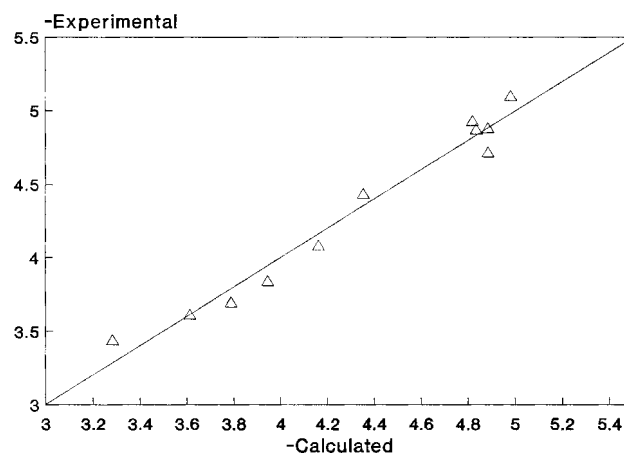
Figure 2. Plot of the experimental values of $\log k_2$ vs calculated values from Eqn. (2) (dual-parameter model of $\log k_2$ vs π^* and α) for the reaction in various solvents at 30 °C
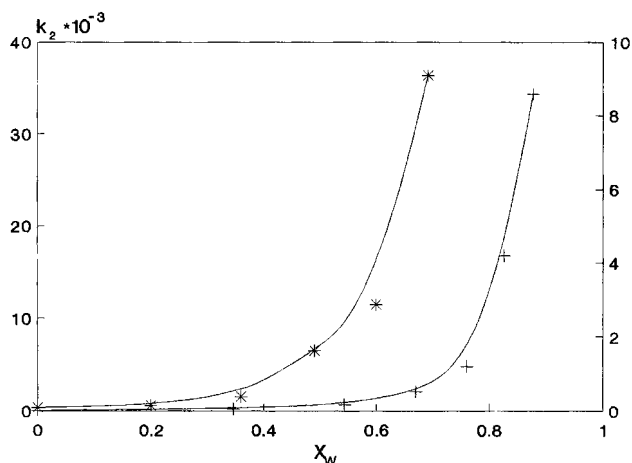
Figure 3. Plot of k_2 (l mol^{-1}s^{-1}) vs X_w for the [2 + 2] cycloaddition reaction in aqueous solutions of 1,4-dioxane (+ symbols and right-hand scale) and methanol (* symbols and left-hand scale) at 30 °C

Figure 4. Plot of the experimental values of logk_2 vs calculated values from Eqn. (4) (dual-parameter model of logk_2 vs Sp and E_T^N) for the reaction in aqueous solutions of 1,4-dioxane and methanol at 30 °C

aqueous solutions.[17,18] This increase in the reaction rate is not due to the polarity of the medium, because a good linear correlation of logk_2 vs E_T^N was not obtained in aqueous solutions of methanol and 1,4-dioxane ($n = 13$, $r = 0.854$). In order to analyze the effects of the medium on the reaction rate, a dual-parameter correlation of logk_2 vs E_T^N and Sp in aqueous solutions of 1,4-dioxane and methanol was found:

$$\log k_2 = -5.441(\pm 0.184) + 1.882(\pm 0.354)E_T^N$$
$$+ 3.432(\pm 0.334)Sp \quad (4)$$
$$(n = 13, r = 0.988, s = 0.165, F_{2,10} = 207.9)$$

It is obvious that Sp plays a more important role in determining the reaction rate relative to the normalized polarity parameter in aqueous solutions of 1,4-dioxane and methanol. This dual-parameter model represents a significant improvement in regression coefficient with respect to the single-parameter models ($r = 0.854$ only with E_T^N and $r = 0.954$ only with Sp) and the calculated results from Eqn. (4) are in good agreement with the experimental results. The values of logk_2 from experimental data were plotted against the values of logk_2 calculated by Eqn. (4) (Fig. 4). Similar studies on Diels–Alder reactions showed lower regression coefficients ($r = 0.961$ for the reaction of cyclopentadiene with acrylonitrile[12] and $r = 0.942$ for the reaction of cyclopentadiene with methyl acrylate[16]). In fact, Eqn. (4) implies that the activated complex of the reaction which has higher polarity relative to the reactants would be stabilized by the polarity of medium (dipolarity/polarizability and hydrogen bonding ineraction). Hydrogen bonding between water molecules and hydrogen-bond acceptor groups in the more polarizable activated complex stabilize the activated complex relative to the
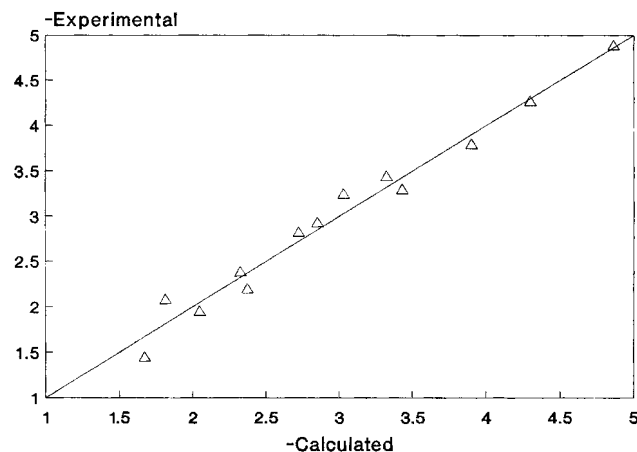
reactants and hence the reaction rate increases. Also, the solvent would destabilize the reactants through its solvophobicity factor,[24] because in the reaction of two apolar reactants, the unfavorable water contacts with reactants are reduced and then the apolar reactants have a tendency to stick together in aqueous solutions.[13] These factors increase the reaction rate dramatically so that the ratio of k_2 (in 50% aqueous methanol) to k_2 (in toluene) is approximately 4505. The second-order rate constant of the reaction in water calculated from Eqn. (4) is 0.75 l mol^{-1} s^{-1}, but the expected value from correlation of logk_2 vs E_T^N [Eqn. (2)] is 1.77×10^{-3} l mol^{-1} s^{-1}. The ratio of the calculated second-order rate constant of the reaction from Eqn. (4) to the expected value from Eqn. (2) is approximately 420. In fact, this ratio shows a contribution of hydrophobic interactions with increase in the reaction rate. In order to show the applicability of dual-parameter correlation of logk_2 vs E_T^N and Sp in the all solvents (various solvents and aqueous solutions), a similar equation was obtained in the all solvents (except for THF, the Sp value of which was not found in the literature):

$$\log k_2 = -5.359(\pm 0.106) + 1.892(\pm 0.255)E_T^N$$
$$+ 3.206(\pm 0.304)Sp \quad (5)$$
$$(n = 21, r = 0.987, s = 0.177, F_{2,18} = 349.7)$$

In this case also Sp plays a more important role in determining the reaction rate relative to E_T^N. Single-parameter correlations of logk_2 vs Sp and E_T^N do not give good results ($r = 0.948$ only with Sp and $r = 0.906$ with E_T^N). Figure 5 shows a plot of experimental values of logk_2 vs expected values calculated by Eqn. (5).

In 1,3-dipolar cycloaddition reactions of *C,N*-diphenylnitrone with various dipolarophiles, the polarity of the
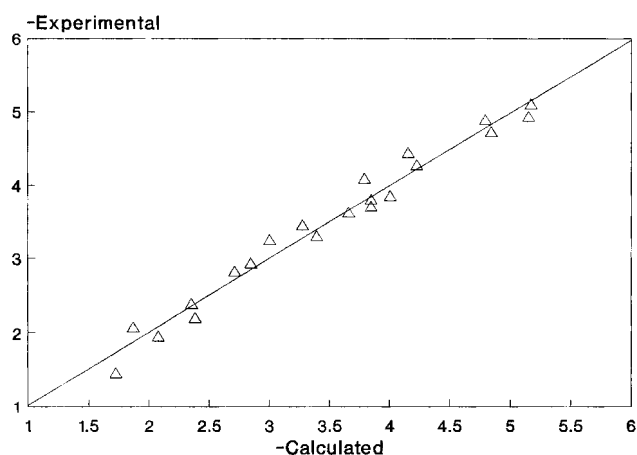
Figure 5. Plot of the experimental values of $\log k_2$ vs calculated values from Eqn. (5) (dual-parameter correlation of $\log k_2$ vs Sp and E_T^N) for the reaction in various solvents and aqueous solutions of 1,4-dioxane and methanol at 30 °C

reactants is higher than that of the activated complex and polar solvents stabilize reactants more than the activated complex.[17] Therefore, the normalized solvent polarity parameter (E_T^N) and the solvophobicity of the medium (Sp) have opposite effects on the reaction rate,[18] that is, with increase in E_T^N the reaction rate decreases whereas with increase in Sp it increases. In contrast, in the $[2 + 2]$ cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether, Sp and E_T^N have similar effects on in the reaction rate. As a result, we suggest that the acceleration of the reaction in aqueous solutions can be attributed to two factors: stabilization of the activated complex of the reaction relative to the reactants owing to a greater interaction of polar solvents with it, and a substantial decrease in the hydrophobic surface area of the reactants during the activation process or enforced hydrophobic interactions that destabilize the reactants relative to the activated complex so that the rate constants of the reaction increase.[24]

EXPERIMENTAL

Materials. Diethyl azodicarboxylate was synthesized according to the literature.[25] Ethyl vinyl ether was purchased from Merck and distilled before use. All solvents of high purity were distilled before use. Water was redistilled in a quartz distillation unit.

Kinetic measurements. The rate of the reaction was studied spectrophotometrically (the spectrophotometer being coupled to a PC by an interface) by monitoring the decrease in the diethyl azodicarboxylate absorbance at 405 nm. Thermostated water was circulated around the cell of the spectrophotometer and the temperature was maintained at $30 \pm 0.1\,°C$.

The concentrations of ethyl vinyl ether varied from 0.059 M (in aqueous solutions of methanol) to 0.562 M (in toluene) and those of diethyl azodicarboxylate from 0.005 M (in aqueous solutions of methanol) to 0.0368 M (in toluene).

In all cases pseudo-first-order kinetics were observed. Pseudo-first-order rate constants of the reaction rates were obtained by the initial rate method or from slopes of plots of $\ln(A_t - A_\infty)$ vs time t. At least three runs were averaged for each rate constant.

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