(*E*)-**3e**: yellow oil; NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3 H), 1.20–1.60 (m, 6 H), 3.15 (3 H, J = 7 Hz, 2 H), 7.44 (s, 1 H), 7.58–8.04 (m, 5 H); MS, m/e (M^+) calcd for $C_{13}H_{17}NO_4S$ 237.0948, found 237.0942.

(*Z*)-**3e**: yellow oil; NMR ($CDCl_3$) δ 0.82 (t, J = 8 Hz, 3 H), 1.20–1.60 (m, 6 H), 2.56 (t, J = 8 Hz, 2 H), 6.22 (s, 1 H), 7.56–8.04 (m, 5 H). Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 55.03; H, 5.88; N, 4.92.

Diels–Alder Reaction of 1a with Cyclopentadiene. A mixture of **1a** (0.37 g, 2.04 mmol) and cyclopentadiene (1.0 g, 15 mmol) in toluene was heated at 110 °C for 1 h. The solvent was evaporated, and the residue was subjected to column chromatography (silica gel/benzene–hexane) to give **4** 0.38 g (75%): NMR ($CDCl_3$) δ 1.5–2.1 (m, 1 H), 3.80 (t, J = 2 Hz, 1 H), 4.78 (d,d, J = 4,2 Hz, 1 H, H-6), 5.82 (d,d, J = 3, 6 Hz, 1 H), 6.28 (d,d, J = 3, 6 Hz, 1 H), 7.3 (m, 5 H). Minor isomer: NMR δ 4.20 (t, H-6). Compound 4 was converted into the corresponding sulfone on treatment with *m*-CPBA (2 equiv) in $CHCl_3$, and the structure was confirmed by comparison with spectral data of **6**, which was prepared by the Diels–Alder reaction of **3a**.

Diels–Alder Reaction of 2a with Cyclopentadiene. A mixture of **2a** (0.30 g, 1.55 mmol) and cyclopentadiene (0.90 g, 13.6 mmol) in 1 mL of methylene chloride was stirred at 20 °C for 3 h. Column chromatography (silica gel/benzene–hexane) gave **5**, 0.39 g (97%): NMR ($CDCl_3$) δ 1.5–2.4 (m, 2 H), 3.2–4.1 (m, 3 H), 5.18 (t, J = 4 Hz), 5.30 (d,d, J = 4, 3 Hz), 6.1–6.6 (m, 2 H), 7.5 (m, 5 H). NMR spectra of **5** were very complicated due to the presence of chiral center of the sulfoxide. The structure was further confirmed by conversion to the sulfone by oxidation with *m*-CPBA (1 equiv).

Diels–Alder Reaction of 3a with Cyclopentadiene. A mixture of **3a** (0.26 g, 1.22 mmol) and cyclopentadiene (0.49 g, 7.42 mmol) in 7 mL of methylene chloride was stirred at 20 °C for 30 min. Pentane (30 mL) was poured into the reaction mixture, and the mixture was cooled at −70 °C. The precipitated solid was collected, 0.28 g (82%), mp 145–152 °C, which was pure **6**. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H. 4.69: N, 5.01. Found C, 55.61; H, 4.74; N, 4.94. NMR ($CDCl_3$) δ [of endo-nitro isomer] 1.73 (d, J = 10 Hz, 1 H), 2.29 (d, J = 10 Hz, 1 H), 3.52 (d, J = 4 Hz, 1 H), 3.69 (d, J = 4 Hz, 1 H), 3.70 (d, J = 4 Hz, 1 H), 5.33 (t, J = 4 Hz, 1 H), 6.13 (d,d, J = 2.8, 5.6 Hz), 6.47 (d,d, J = 3.4, 3.5 Hz), 7.4–8.1 (m, 5 H), [of exo-nitro isomer] 1.76 (d, J = 10 Hz, 1 H), 1.88 (d, J = 10 Hz, 1 H), 3.37–3.60 (m, 2 H), 4.37 (t, J = 4 Hz, 1 H), 4.71 (d,d, J = 1.5, 4.3 Hz), 6.53 (d,d, 1 H, J = 3, 4 Hz), 7.4–8.1 (m, 5 H).

Diels–Alder Reaction of 2a with (*E*)-1,3-Pentadiene. A mixture of **2a** (0.60 g, 3.04 mmol) and (*E*)-1,3-pentadiene (1.38 g, 30 mmol) in 4 mL of toluene was heated at 100 °C for 4 h. Column chromatography (silica gel/benzene–hexane) gave **7** (oil), 0.21 g (54%): NMR ($CDCl_3$) δ 1.20 (d, J = 8 Hz, 3 H), 2.90–3.20 (m, 2 H), 3.40–3.80 (m, 1 H), 6.78 (m, 2 H), 7.28 (m, 1 H). The structure of this compound was confirmed by conversion into *o*-nitrotoluene. A mixture of **7** (0.10 g, 0.72 mmol) and DDQ (0.24 g, 1.06 mmol) in 2 mL of toluene was refluxed for 2 h. Column chromatography (silica gel/benzene–hexane) gave 0.08 g (81%) of *o*-nitrotoluene. GLC analyses showed that the product consisted of 90% of *o*-nitrotoluene and 10% of *m*-nitrotoluene.

Diels–Alder Reaction of 3a with (*E*)-1,3-Pentadiene. A mixture of **3a** (0.43 g, 2.02 mmol) and (*E*)-1,3-pentadiene (0.40 g, 6 mmol) in 10 mL of toluene was heated at 100 °C for 4 h. Column chromatography (silica gel/benzene–hexane) gave two products, **9a**, 0.26 g (46%), mp 61.5–62.5 °C, and **9b**, 0.28 g (49%), mp 83–84 °C.

9a: NMR ($CDCl_3$) δ 1.01 (d, J = 8 Hz, 3 H), 2.60–2.63 (m, 2 H), 3.05 (m, 1 H), 4.04 (m, 1 H), 5.21 (d,d, J = 6, 8 Hz, 1 H), 5.62–5.73 (m, 2 H), 7.58–7.90 (m, 5 H). Anal. Calcd for $C_{13}H_{15}NSO_4$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.37; H, 5.30; N, 4.89.

9b: NMR ($CDCl_3$) δ 1.11 (d, J = 7 Hz, 3 H), 2.45–2.63 (m, 2 H), 2.83 (m, 1 H), 4.02 (q, 1 H), 4.52 (d,d, J = 10, 12 Hz, 1 H), 5.63 (m, 2 H), 7.58–7.91 (m, 5 H). Anal. Calcd for $C_{13}H_{15}NSO_4$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.47; H, 5.39; N, 4.73.

Michael Addition of 1a, 2a, and 3a. A mixture of **1a** (0.22 g, 12 mmol) and pyrrolidine (0.10 g, 14 mmol) in 5 mL of methanol was stirred at 20 °C for 2 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel/benzene–hexane–ethyl acetate) to give **10**, 0.14 g (81%): mp 78 °C (lit.[8] mp 77–78 °C); NMR ($CDCl_3$) δ 1.9–2.2 (m, 4 H), 3.1–3.3 (m, 2 H), 3.6–3.8 (m, 2 H), 6.62 (d, J = 12 Hz, 1 H), 8.38 (d, J = 12 Hz, 1 H). The reaction of other olefins was carried out in the same way and the same product, **10**, was obtained in 89% and 71% yields from **2a** and **3a**, respectively.

---

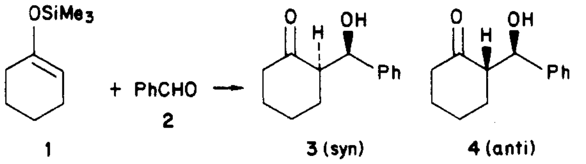
[8] Marchetti, L.; Passalacqua, V. *Ann. Chim. (Rome)* **1967**, *57*, 1266; *Chem. Abstr.* **1968**, *68*, 95420.

Communications

Water-Promoted Organic Reactions: Aldol Reaction under Neutral Conditions

Summary: The trimethylsilyl enol ether of cyclohexanone adds to benzaldehyde in aqueous solution at room temperature and atmospheric pressure without a catalyst to give good yields of condensation products with a selectivity that is the reverse in comparison with the acid-catalyzed reaction.

Sir: The Mukaiyama variant[1] of the aldol reaction, that is, the condensation of silyl enol ethers with aldehydes (eq 1), has become a popular tool in organic synthesis as it is relatively easily carried out, with readily available starting materials. However, acid-sensitive substrates may raise a problem, because stoichiometric amounts of $TiCl_4$ must be used. More recently,[2] it has been shown that the reaction could be conducted without catalyst, but under high pressure (10 kbars), to give good yields of products, with a selectivity that is the reverse in comparison with the acid-catalyzed reaction (Table I, entries 1 and 2). While these experiments gave some insight into mechanistic problems, their preparative developments may suffer at present from the scarcity of high-pressure equipment.



(1)

As part of a program of using water-soluble glyco-organic substrates[3] for aqueous organic reactions, we were led naturally to address the following questions:

---

[1] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

[2] Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* **1983**, *105*, 6963.

0022-3263/86/1951-2142$01.50/0

Table I. Reaction of 1 with 2 under Varying Conditions[a]

entry	1:2	solvent[d]	temp, °C	time	conditions	yields,[b] %	syn:anti[b]	ref
1	1:1	CH_2Cl_2	20	2 h	$TiCl_4$	82	25:75	1
2	1:1	CH_2Cl_2	60	9 days[c]	10 kbars	90	75:25	2
3	1:2	A	20	5 days	ST[e]	45 (43)[f]	74:26	
4	1:2	H_2O	20	5 days	ST	23	85:15	
5	1:2	A	55	2 days	US[g]	68	73:27	
6	1:5	A	55	2 days	US	61	72:28	
7	1:12	A	20	5 days	ST	40	67:33	
8	2:1	A	20	5 days	ST	37	78:22	
9	2:1	A	60	2 days	ST	47	73:27	
10	2:1	A	55	2 days	US	72	74:26	

[a] All reactions in this work were carried out under atmospheric pressure at a concentration of 0.4 M of the limiting component. [b] As determined by NMR spectroscopy ($CDCl_3$, 90 MHz) using the following signals of methylene protons: δ 4.83 (d, J = 9 Hz, 1 H, anti), 5.40 (d, J = 2.5 Hz, 1 H, syn). Compounds **3** and **4** have been found identical in every respect with those prepared under the $TiCl_4$-catalyzed aldol reaction.[1] [c] It may be significant that the time of reaction in water under an estimated 22 kbars (cohesive energy density of water) is smaller, at least of the same order as that of the reaction conducted under 10 kbars. [d] A refers to a mixture of oxolane–water (1:1). [e] Vigorous magnetic stirring or violent shaking. [f] Isolated yield after silica gel chromatography (1:1 ether–hexane). [g] In a Bransonic 220, 50-kHz cleaning bath.

(1) What are the requirements for such water-promoted reactions between two small hydrophobic molecules?

(2) Could water promote reactions otherwise impossible? We may note, for instance, that the increased endo selectivity observed in the very rapid aqueous cycloaddition[3-5] is probably not a consequence of the relatively high polarity of water. Truly, such an effect has been reported with nonpolar substrates in some solvents,[6] but in water, and other hydroxylated solvents, no correlation was observed with any function of the dielectric constant: methyl acrylate and cyclopentadiene gave less endo adduct in formamide (ϵ 109) and *N*-methylacetamide (ϵ 183) than in water (ϵ 80).[7] Furthermore, the lack of effect of water in the selectivity of the addition to the polar dienophile, $PhSOCH{=}CHCO_2H$,[8] suggested that hydrophobic interactions are involved with the nonpolar substrates.

The entropy-driven aggregation of two nonpolar molecules dissolved in water, the well-known hydrophobic effect, has been extensively reviewed in the literature.[9,10] In fact, it was suggested[11] that the effects of water on rate and selectivity could be related to its high cohesive energy E, and to the high energy necessary to create a cavity in it, because of its high interfacial energy. In this respect, water is unique among solvents, with the highest known value ($\delta = 23.53\ \mathrm{cal}^{1/2}\cdot\mathrm{mL}^{-3/2}$) of the Hildebrand parameter,[12] $\delta = (E/V)^{1/2}$, where V is the molal volume of the liquid. Then a reaction under kinetic control between two nonpolar molecules for which $\Delta V^{\ddagger}$ is negative must be accelerated in water *as it is under pressure*, to occupy the smallest possible volume of cavity, and when several transition states are possible, the more compact should be favored. The prediction[13] that the Diels–Alder reaction in structured solvents would show such features was borne out by experiments in water.[3-5]

We expected parallel behavior for the aldol reaction. The contribution of the building of a C–C bond to the activation volume is about −10 to −15 mL/mol. The pressure studies of the Mukaiyama reaction show unambiguously that $\Delta V^{\ddagger}$ is smaller for the syn isomer transition state, since the syn/anti ratio increases with the pressure.[2]

We now report that the reaction as shown in eq 1 occurs readily in water, at room temperature and atmospheric pressure, without a catalyst. *The stereoselectivity is the same as under pressure*; that is, it is the reverse of the selectivity observed under conditions of acidic catalysis. The results are summarized in Table I (entries 3–10).

In each case, the reaction went to completion (i.e., total disparition of the silyl enol ether) and the limitation on yield resulted from the simultaneous hydrolysis of **1** to cyclohexanone. Fairly good yields were achieved in water–oxolane (1:1) mixtures, but with concurrent loss of stereoselectivity with respect to the pure water (entry 4). In fact, in these conditions (with or without added oxolane), the mixture is heterogeneous, and the outcome depends upon the way of mixing: vigorous stirring or shaking was necessary to promote the reaction, and in the case of oxolane–water mixtures, the dispersion of organic material in the water phase was actually best achieved by sonication (entry 10), whereas in the case of pure water no significant improvement was found.

On the other hand, no reaction was observed at room temperature and atmospheric pressure, even after 15 days in the solvents toluene, oxolane, CH_2Cl_2, and CH_3CN in the absence of a catalyst.

As far as we know, except for Diels–Alder reaction and probably the coordination of hydrophobic ligands to Ni^{II},[14] no organic reactions between two small nonpolar molecules have been related to the hydrophobic effect. While we shall postpone theoretical implications to a further paper, we want to stress already at this stage the difference between such reactions where the role of water is essential and other ones, which display intriguing features in water, but work as well in other solvents.[15]

We are currently investigating other reactions with $\Delta V^{\ddagger} < 0$.

Acknowledgment. I thank Professor S. David for his

---

(3) Lubineau, A.; Queneau, Y. *Tetrahedron Lett.* **1985**, 2653.

(4) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, 1239 and references therein.

(5) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137 and references therein.

(6) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

(7) Samii, A. A.; de Savignac, A.; Rico, I.; Lattes, A. *Tetrahedron* **1985**, 2683.

(8) Proust, S. M.; Ridley, D. D. *Aust. J. Chem.* **1984**, *37*, 1677.

(9) Franks, F. In *Water, A Comprehensive Treatise*; Franks, F., Ed.; Plenum: New York, 1975.

(10) Tanford, C. In *The Hydrophobic Effect*; Wiley: New York, 1980.

(11) Dack, M. R. J. *Chem. Soc. Rev.* **1975**, *4*, 211.

(12) Hildebrandt, J. H.; Prausnitz, J. M.; Scott, R. L. In *Regular and Related Solutions*; Van Nostrand-Reinhold: Princeton, 1970.

(13) Dack, M. R. J. *J. Chem. Educ.* **1974**, *51*, 231.

(14) Cayley, G. R.; Margerum, D. W. *J. Chem. Soc., Chem. Commun.* **1974**, 1002.

(15) See, for example: Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, 1449 and references therein.

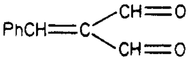
interest and C.N.R.S. for financial support.

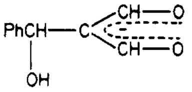
André Lubineau
Institut de Chimie Moléculaire d'Orsay
Laboratoire de Chimie Organique
Multifonctionnelle, Bat. 420
Université Paris-Sud, 91405 Orsay Cedex, France
Received November 21, 1985

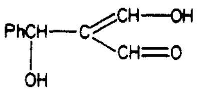
Reaction of Benzylidenemalonaldehyde with Water and Hydroxide Ion[1]

Summary: A stopped-flow kinetic study of the title reaction is reported from which rate and equilibrium constants of various elementary processes are deduced.

Sir: Alkylidene and arylidenemalonaldehydes are not only of interest to the theoretician because of their cross-conjugated π-system but also to the synthetic chemist because of their high bifunctional reactivity. Benzylidenemalonaldehyde (1), a prototype compound and hence of particular interest, has only recently been synthesized,[2] and its chemistry is just beginning to be explored.[3] We report here its kinetic and thermodynamic behavior in aqueous solution which indicates very high reactivity.


1


2


3

Arnold et al.[3a] have already shown that in water, even in the absence of added base, 1 is essentially completely converted to its hydroxide ion adduct 2. In strongly acidic solution UV data suggested that 1 is present in equilibrium with 3, which is the oxygen protonated (enol) form of 2; this suggestion was based on the fact that in acidic aqueous solution the absorbance at 302 nm (λ_{max} of 1) is substantially lower than in acetonitrile.[3a]

Our kinetic results which were obtained in a stopped-flow spectrophotometer confirm these preliminary observations[3a] and put them on a more quantitative basis. In a first set of experiments (pH 4.0 to 13.5) we approached the equilibrium from the reactant side, by adding a dilute buffer or a KOH solution to an acidic solution (0.002 M HCl) of 1 (in equilibrium with 3). The buffers used were acetate, cacodylate and borate, at total buffer concentrations of about 0.05 M or less. In a second set of experiments (pH 1.3 to 4.5), 2 was first generated in a 0.005 M KOH solution which subsequently was mixed with an acidic buffer (acetate and 3-chloropropionate, total buffer concentration $\leq$0.05 M) or an HCl solution in the stopped-flow apparatus. In both types of experiments we measured the rates at 302 nm (λ_{max} of 1) as well as at 270 nm (λ_{max} of 2), with equal results. Since the data obtained at 302 nm had less scatter we used those to construct the pH–rate profile shown in Figure 1. Tests for buffer dependence showed that, at the buffer concentrations used, buffer catalysis is negligible.

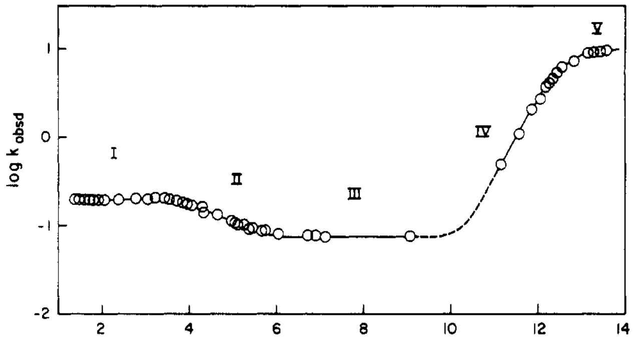


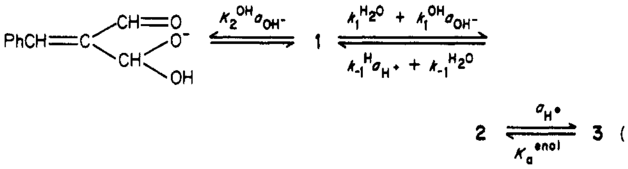
Figure 1. pH–rate profile for the reaction of benzylidenemalonaldehyde with water and OH⁻ at 25 °C, μ = 0.5 M (KCl).

Table I. Rate and Equilibrium Constants for the Reactions of Equation 1 in Water at 25 °C[a]

constant	benzylidene-malonaldehyde	benzylidene Meldrum's acid[b]
$k_1^{H_2O}$, s^{-1}	0.068	0.55
k_{-1}^{H}, M^{-1} s^{-1}	4.20×10^3	1.47×10^5
$K_1^{H_2O}$, M (p$K_1^{H_2O}$)	1.62×10^{-5} (4.79)	3.75×10^{-6} (5.43)
k_1^{OH}, M^{-1} s^{-1}	223	745
$k_{-1}^{H_2O}$, s^{-1}	2.57×10^{-7}	3.73×10^{-6}
$K_1^{OH} = K_1^{H_2O}/K_w$[c]	8.66×10^8	2.00×10^8
pK_a^{enol}	4.49	
$K_1^{H_2O}/K_a^{enol}$	0.50	
K_2^{OH}, M^{-1}	22	

[a] At μ = 0.5 M (KCl). [b] Reference 4. [c] $K_w = 1.87 \times 10^{-14}$ M^2.

The pH–rate profile is consistent with the following equation:


(1)

Phases III and IV of the profile correspond to water and OH⁻ attack on carbon, respectively, with

$$k_{obsd} = k_1^{H_2O} + k_1^{OH}a_{OH^-} \tag{2}$$

In phase V rapid equilibrium OH⁻ attack on one of the carbonyl carbons (K_2^{OH}) starts to become significant, with k_{obsd} given by

$$k_{obsd} = \frac{k_1^{OH}a_{OH^-}}{1 + K_2^{OH}a_{OH^-}} \tag{3}$$

Phase II is associated with acid-catalyzed loss of OH⁻ from 2 ($k_{-1}^{H}a_{H^+}$) with rapid oxygen protonation of 2 acting as preequilibrium in phase I. Thus for phases I and II k_{obsd} is given by

$$k_{obsd} = k_{-1}a_{H^+}\frac{K_a^{enol}}{K_a^{enol} + a_{H^+}} \tag{4}$$

which becomes

$$k_{obsd} = k_{-1}K_a^{enol} \tag{5}$$

for pH $\ll$ pK_a^{enol}.

The rate and equilibrium constants calculated from our results are summarized in Table I, along with corresponding parameters for benzylidene Meldrum's acid (5),[4]

---

(1) This is part 17 in the series "Nucleophilic Addition of Olefins". Part 16: Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.*, in press.

(2) (a) Reichardt, C.; Yun, K.-Y. *Tetrahedron Lett.* **1982**, *31*, 3163. (b) Reichardt, C.; Yun, K.-Y.; Massa, W.; Schmidt, R. E. *Liebigs Ann. Chem.* **1985**, 1987.

(3) (a) Arnold, Z.; Král, V.; Dvořák, D. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2602. (b) Král, V.; Laatikainen, R.; Arnold, Z. *Tetrahedron* **1985**, *41*, 4919.

(4) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1984**, *104*, 5133; **1980**, *102*, 1361.

0022-3263/86/1951-2144$01.50/0