Rates and Equilibria of the Michael-Type Addition of Benzenethiol to 2-Cyclopenten-1-ones

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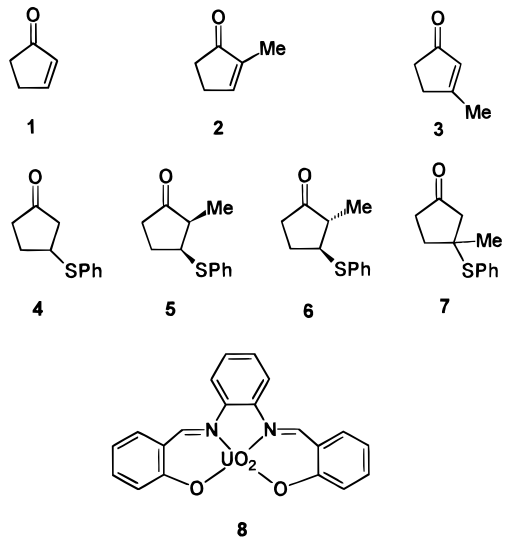
The triethylamine-catalyzed addition reactions of benzenethiol to 2-cyclopenten-1-one and its 2- and 3-methyl derivatives have been found to be appreciably reversible in chloroform solution. Rates and equilibria have been carefully measured at 25 °C in order to assess the negative influence on addition exerted by methyl groups substituted on the carbon−carbon double bond. 2-Methyl-2-cyclopenten-1-one has been found to react with benzenethiol under kinetic control to give the cis adduct as the sole detectable product in a highly stereoselective anti addition process. However, on prolonged reaction times the system slowly evolved toward a new state of equilibrium in which the more stable trans adduct, derived from a syn addition mode, was the predominant isomer.

Introduction

The Michael addition of thiols to activated olefins has been known for more than 50 years.[1] Its importance both in biochemical processes[2] and in synthesis[3] is well recognized. This class of reactions has been the object of a number of kinetic[4] and stereochemical[5] investigations, as well as of many theoretical studies.[6] However there are still many unexplored features in particular concerning the influence of substituents at the double bond on addition rates and equilibria,[7] and a real systematization of reaction mechanism and structural effects in Michael-type additions of thiols is lacking.

The Et_3N-catalyzed addition of benzenethiol to 2-cyclopenten-1-one (**1**) in chloroform solution, yielding quantitatively (3-phenylthio)cyclopentanone (**4**), was our target reaction in a recent work[8] aimed at developing supramolecular catalysts based on the salophen uranyl unit **8**. Early attempts at extending our studies to the methyl derivatives **2** and **3** were frustrated by very low conversions into the corresponding addition products. Multiple substitution of methyl (alkyl) groups on the enone double bond is known to decrease yields of addition products in general,[9] yet the strongly adverse effects of one methyl group on yields in our reaction system caused much surprise. A closer examination revealed that a major reason for these low yields was thermodynamic in nature, but to the best of our knowledge no equilibrium data for the addition of thiols to enones were available for comparison.



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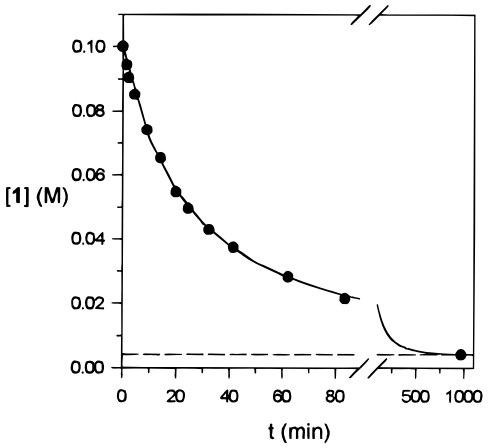
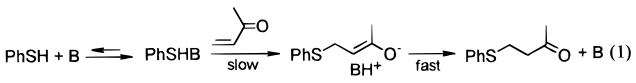


Figure 1. Time−concentration profile for the addition of benzenethiol to **1** (Table 1, entry 4). The points are experimental, and the curve is calculated from eq 5. The dashed line represents the calculated equilibrium concentration of **1**.

As a first part of a systematic investigation of the basic mechanistic features of the nucleophilic addition of thiols to enones, we now report on a quantitative study of rates and equilibria of the Et_3N-catalyzed addition of benzenethiol to enones **1**−**3** in chloroform solution at 25 °C.

Results and Discussion

The proposed mechanism[4a,d] of the base-catalyzed addition in apolar aprotic solvents involves the rate-limiting reaction of the activated olefin with a weak, rapidly formed complex between thiol and tertiary base B (eq 1), for the nature of which the question is open as to whether the structure of a simple hydrogen-bonded complex (PhSH···B) or a hydrogen-bonded ion pair salt ($PhS^-\cdots HB^+$) is more appropriate. In any case, since the concentration of the complex is negligibly low, clean third-order kinetics were observed[4a,d] (eq 2), first-order in the enone (E), thiol (T), and base.



$$\text{rate} = k[\mathrm{E}][\mathrm{T}][\mathrm{B}] \qquad (2)$$

Rates and equilibria of thiol addition were conveniently investigated by comparing the intensities of appropriate ^{1}H NMR signals of the enone and addition product to that of an internal standard. No extra peaks attributable to byproducts or reaction intermediates were observed. All experiments were carried out in $CDCl_3$ at 25.0 °C. For the sake of simplicity, we shall consider the results of each enone in turn.

2-Cyclopenten-1-one (1). In the presence of excess benzenethiol, **1** was transformed smoothly and quantitatively into **4** at room temperature.[8] However, in a series of kinetic experiments aimed at determining the order with respect to base catalyst, the initial concentration of both reactants was kept constant and equal to 0.100 M. A typical time−concentration profile is shown in Figure 1. The results are collected in Table 1. These experiments, while showing a clean first-order dependence on base

Table 1. Addition of Benzenethiol (0.100 M) to 2-Cyclopenten-1-one (0.100M) in the Presence of Et_3N[a] in Chloroform at 25.0 °C

entry	$[Et_3N]$, mM	$[E]_e$, mM	k_1[b] ($L^2\,mol^{-2}\,s^{-1}$)	k_{-1}[c] ($L\,mol^{-1}\,s^{-1}$)
1	1.08	5	1.70	4.4×10^{-4}
2	2.13	4	1.70	4.4×10^{-4}
3	2.15	3	1.64	4.2×10^{-4}
4	4.30	4	1.53	3.9×10^{-4}
		mean:	1.64 ± 0.04	$(4.2 \pm 0.2) \times 10^{-4}$

[a] In the absence of base catalyst no reaction (<5%) was observed after 10 days. [b] Errors are on the order of 3−5%. [c] Calculated as k_1/K, with $K = (3.9 \pm 0.2) \times 10^3\ M^{-1}$. Errors are in the order of 8−10%.

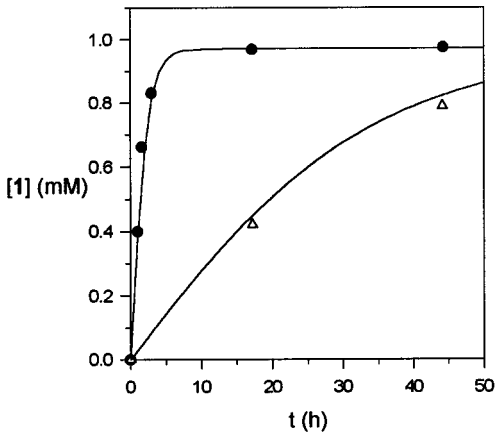


Figure 2. Kinetic profiles for the retrograde reaction of 4.62 mM **4** in the presence of 4.3 mM Et_3N (△) and in the presence of 4.3 mM Et_3N plus 1.0 mM **8** (●). The curves are calculated from eq 5. The rate constant of the metal catalyzed reaction is given in ref 8.

catalyst, revealed the unexpected occurrence of small, but clearly detectable amounts of unreacted enone at infinite time that were suggestive for the existence of the equilibrium of eq 3, where A represents the adduct, with K values in the range of $(3-5) \times 10^3\ M^{-1}$.

$$\mathrm{T} + \mathrm{E} \overset{K}{\rightleftharpoons} \mathrm{A} \qquad (3)$$

A definite confirmation of the appreciable reversibility of the reaction, together with a more precise determination of the equilibrium constant was obtained from experiments in which the equilibrium was approached from the adduct side. A diluite solution of **4** (4.62 mM) was treated with Et_3N (4.3 mM). As shown in Figure 2 the liberation of the corresponding enone **1** was significantly accelerated by the addition of 1.0 mM metal catalyst **8**. In the absence of metal catalyst the system was still far from equilibrium after 44 h. The K value of $3.9 \pm 0.2 \times 10^3\ M^{-1}$ calculated from the equilibrium enone concentration of 0.97 mM obtained in the presence of **8** compares very well with the range of K values estimated from the data in Table 1. Once the equilibrium constant was precisely known, treatment of rate data for the reaction system of eq 4 was straightforward. For this system the standard integrated equation[10] is given in eq 5, where the quantity $1/\tau$ is defined in eq 6 and the

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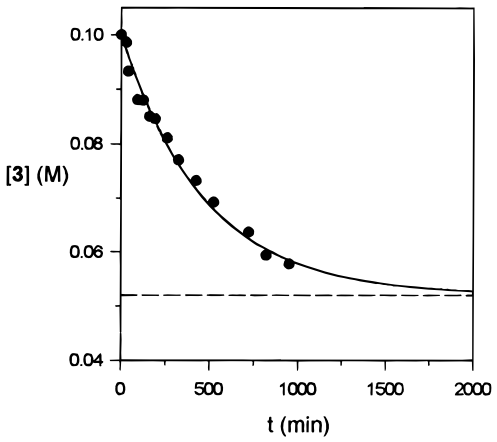

Figure 3. Time−concentration profile for the addition of benzenethiol to **3**. The points are experimental, and the curve is calculated from eq 8. The dashed line represents the calculated equilibrium concentration of **3**.

subscripts o and e refer to initial and equilibrium concentrations, respectively. Equation 5 contains k_1 as the only unknown quantity. The k_1 values listed in Table 1 were obtained by a conventional curve-fitting procedure. The corresponding k_{-1} values were calculated as k_1/K.

$$\mathrm{T} + \mathrm{E} \underset{k_{-1}[\mathrm{B}]}{\overset{k_1[\mathrm{B}]}{\rightleftharpoons}} \mathrm{A} \tag{4}$$

$$\frac{[\mathrm{E}] - [\mathrm{E}]_e}{[\mathrm{E}]_o - [\mathrm{E}]_e} = \frac{\exp(-t[\mathrm{B}]/\tau)}{1 + k_1\tau([\mathrm{E}]_o - [\mathrm{E}]_e)[1 - \exp(-t[\mathrm{B}]/\tau)]} \tag{5}$$

$$\frac{1}{\tau} = k_1([\mathrm{E}]_e + [\mathrm{T}]_e) + \frac{k_1}{K} \tag{6}$$

3-Methyl-2-cyclopenten-1-one (3). Transformation of **3** into the corresponding addition product **7** causes a change of the resonance of the methyl group from a narrow and unresolved multiplet at δ 2.05−2.06 to a sharp singlet at δ 1.44. Since very low reaction rates and conversions into **7** were observed in this case, a high concentration of benzenethiol was used to maximize both rate and yield of addition product. A solution of **3** (0.100 M), benzenethiol (1.01 M), and Et_3N (4.9 mM) was monitored at selected times over a period of 16 h (Figure 3). In the presence of excess benzenethiol, the system reduces to the simple case of eq 7, first order in both directions, for which a convenient form of the integrated rate equation[11] is given by eq 8. A nonlinear least-squares treatment of analytical data according to eq 8 afforded a best fit value of 0.052 M for $[E]_e$ and one of 3.5×10^{-5} s^{-1} for the quantity $k_1[B][T] + k_{-1}[B]$. From the above values, equilibrium and rate parameters were easily computed as $K = 0.88 \pm 0.08$ M^{-1}, $k_1 = (3.3 \pm 0.2) \times 10^{-3}$ L^2 mol^{-2} s^{-1}, and $k_{-1} = (3.8 \pm 0.6) \times 10^{-3}$ L mol^{-1} s^{-1}. An additional experiment gave $K = 0.90 \pm 0.05$ M^{-1}, $k_1 = (3.5 \pm 0.1) \times 10^{-3}$ L^2 mol^{-2} s^{-1}, and $k_{-1} = (3.9 \pm 0.4) \times 10^{-3}$ L mol^{-1} s^{-1}.

$$\mathrm{E} \underset{k_{-1}[\mathrm{B}]}{\overset{k_1[\mathrm{B}][\mathrm{T}]}{\rightleftharpoons}} \mathrm{A} \tag{7}$$

$$\frac{[\mathrm{E}] - [\mathrm{E}]_e}{[\mathrm{E}]_o - [\mathrm{E}]_e} = \exp[-(k_1[\mathrm{B}][\mathrm{T}] + k_{-1}[\mathrm{B}])t] \tag{8}$$

An independent determination of K was obtained from an experiment carried out in the presence of metal catalyst. A solution containing **3** (0.103 M), benzenethiol (0.487 M), Et_3N (4.9 mM), and **8** (2.0 mM) was monitored as a function of time. Relative intensities of the signals of the enone reactant and addition product reached constant values after about 30 h and remained constant over an extended period of time (120 h). The measured equilibrium concentrations $[\mathbf{3}]_e = 0.073$ M and $[\mathbf{7}]_e = 0.030$ M were translated into a K value of 0.91 ± 0.04 M^{-1}, which compares well with the values determined above.

2-Methyl-2-cyclopenten-1-one (2). The procedure adopted for analysis of the reaction system involving **2** followed exactly the same protocol as for **3**. In a first experiment, a mixture of **2** (0.100 M), benzenethiol (1.01 M), and Et_3N (4.9 mM) was monitored at selected times over a period of about 200 min (Figure 4). The gradual decrease in intensity of the multiplet at δ 1.73−1.71 due to the methyl group of **2** was accompanied by the buildup of a doublet centered at δ 1.13, $J = 7.2$ Hz, and a multiplet at δ 4.00−4.07. These two signals, whose intensities were consistently in a 3:1 ratio, were attributed to the methyl group and to the hydrogen on C_3, respectively, of an addition product. The latter was assigned the structure of the cis isomer **5** (vide infra). This finding was in keeping with stereochemical studies[5] showing that addition of sulfur nucleophiles to activated olefins are in general stereoselective with anti addition of the proton.

Analysis of the time−concentration profile of Figure 4, carried out as above on the basis of eq 8, afforded a value of 0.044 M for $[E]_e$ and one of 3.5×10^{-4} s^{-1} for the quantity $k_1[B][T] + k_{-1}[B]$, from which the following values were computed: $K = 1.28 \pm 0.11$ M^{-1}, $k_1 = (3.5 \pm 0.2) \times 10^{-2}$ L^2 mol^{-2} s^{-1}, and $k_{-1} = (2.7 \pm 0.4) \times 10^{-2}$ L mol^{-1} s^{-1}. In a second experiment, we obtained $K = 1.31 \pm 0.07$ M^{-1}, $k_1 = (3.4 \pm 0.2) \times 10^{-2}$ L^2 mol^{-2} s^{-1}, and $k_{-1} = (2.6 \pm 0.3) \times 10^{-2}$ L mol^{-1} s^{-1}.

An additional experiment in which benzenethiol (0.325 M) and **2** (0.094 M) were reacted in the presence of 4.9 mM Et_3N and 1.0 mM **8** gave the results shown in Figure 5. The disappearance of the enone reactant was accompanied by the formation of adduct **5** as the sole product only in the early stages of the reaction. However, after about 2 h the ^1H NMR spectra revealed the presence of appreciable amounts of a second product, whose buildup was complete after 140−160 h. Typical signals of this product are a sharp doublet at δ 1.12, $J = 7.2$ Hz, and a complex multiplet at δ 3.10−3.20, with relative intensities of 3:1. The multiplet at δ 3.10−3.20 was assigned to the methine proton α to the sulfur of the trans adduct **6**, based on the well-known shielding effect of a methyl substituent on cis and vicinal hydrogens in five-membered rings.[12] In the other isomer, the methine proton α to the sulfur resonates at much lower fields, consistent with the assigned structure **5**, where the methyl group is trans to the vicinal hydrogen.

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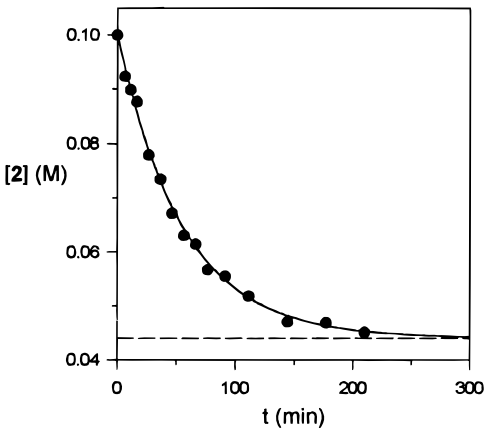


Figure 4. Time−concentration profile for the addition of benzenethiol to **2**. The points are experimental, and the curve is calculated from eq 8. The dashed line represents the calculated equilibrium concentration of **2**.

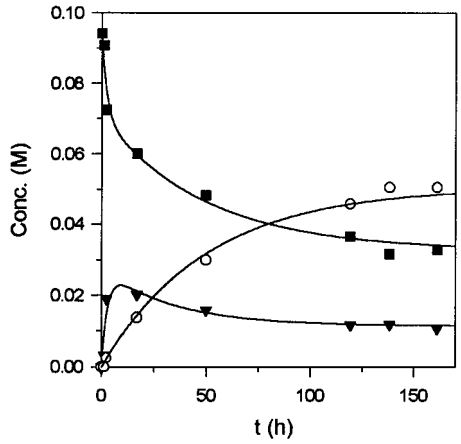
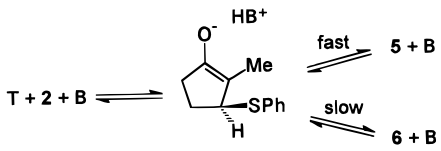


Figure 5. Time−concentration profiles for the addition of benzenethiol to **2**. ■, **2**; ▼, **5**; ○, **6**. The lines are guides for visual comparison.

Scheme 1



With the exception of the initial transient phase, all of the time−concentration data of the species involved in equilibrium T + **2** ⇌ **5** are consistent with a *K* value of 1.30 ± 0.10 M^{-1}. This is not only in excellent agreement with the estimate from the previous experiments but also shows that the above equilibrium is attained rapidly and maintained throughout the entire time-course of reaction, although the system is evolving toward a new state of equilibrium. From the final composition of the system, a *K* value of 6.1 ± 0.3 M^{-1} was calculated for the equilibrium T + **2** ⇌ **6**.

To sum up, the less stable cis isomer **5** is formed about 2 orders of magnitude more rapidly than the more stable trans adduct **6** because of the anti addition mode of the incoming proton. It seems likely that the overall process can be conveniently described by Scheme 1, in which a key role is played by a common enolate−ammonium ion-pair intermediate. Thus, the system under study provides an additional example of a situation in which the composition of a system under kinetic control differs markedly from that under thermodynamic control. A similar situation has been reported for addition of benzenethiolate ion to 4-*tert*-butyl-1-cyanocyclohexene in ethanol solution.[5c]

Table 2. Addition of Benzenethiol to Enones 1−3 in the Presence of Et_3N in Chloroform at 25.0 °C. Rate and Equilibrium Parameters

substrate	k_1 (L^2 mol^{-2} s^{-1})	k_{-1} (L mol^{-1} s^{-1})	*K* (L mol^{-1})
1	1.64 ± 0.04	(4.2 ± 0.2) × 10^{-4}	(3.9 ± 0.2) × 10^3
2[a]	(3.4 ± 0.2) × 10^{-2}	(2.6 ± 0.2) × 10^{-2}	(1.30 ± 0.05)
3	(3.4 ± 0.1) × 10^{-3}	(3.8 ± 0.3) × 10^{-3}	(0.90 ± 0.03)

[a] The data refer to the formation of the cis isomer (**5**). For the process **5** ⇌ **6** the equilibrium constant is 6.1/1.3 = 4.7.

Summary and Concluding Remarks

Rate and equilibrium constants for addition of benzenethiol to enones **1**−**3** are collected in Table 2. It is common knowledge that Michael additions are reversible reactions.[13] Yet we could trace in the literature very few investigations of equilibria for this kind of reactions.[14] Thus, the data in Table 2 not only provide for the first time an assessment of the influence of methyl substituents on rates and equilibria of nucleophilic addition to the double bond but also the first equilibrium data for addition of a sulfur nucleophile.

Given the well-known ability of methyl groups to stabilize a double bond by acting as electron donors to the π system, there seems to be little doubt that a major reason for the adverse influence of methyl substituents on both addition rates and equilibria is electronic in nature. However, steric effects are also likely to play a definite role in determining the low equilibrium constants for addition of benzenethiol to **2** and **3** because there is a substantial increase in bond eclipsing in the addition products. The steric situation in the rate-determining transition states leading to the enolate intermediates is clearly quite different for that found in the addition products. Consequently, failure of a rate−equilibrium relationship[15] was easily anticipated and actually confirmed by the observation that a plot of log k_1 against log *K* (not shown here) was decidedly nonlinear.

The very low *K* values measured for thiol additions to **2** and **3** have important implications from a preparative standpoint. Whereas in the case of the parent compound **1** a slight excess of benzenethiol is sufficient to drive addition to completion at synthetically useful reactant concentrations, benzenethiol concentrations in the order of several moles per liter would be required to convert significant fractions of **2** and **3** into the corresponding adducts.

We finally note that the reaction of benzenethiol with enone **2** is highly stereoselective with anti addition of the proton under kinetic control. This result is in keeping with literature reports on the stereochemistry of addition of heteronucleophiles both to cyclic[5a−c] and open-chain[5d,e] activated olefins.

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To gain a deeper insight into the mechanism of Michael additions of sulfur nucleophiles, we are carrying out a thorough computational study of the base-catalyzed thiol addition to 2-cyclopenten-1-ones based on density functional theory. The results of this investigation will be published in due time.

Experimental Section

Materials. Thiophenol was distilled under reduced pressure before use. Triethylamine was distilled over sodium metal. 2-Cyclopenten-1-one, 2-methyl-2-cyclopenten-1-one, and 3-methyl-2-cyclopenten-1-one were reagent-grade commercial samples and used as received. The salophen uranyl catalyst was available from a previous investigation.[8] Chloroform-*d* was stored over 4 Å molecular sieves for at least 24 h. (3-Phenylthio)cyclopentanone was prepared according to the literature.[16]

Rate and Equilibrium Measurements. NMR tubes were dried in an oven at 130 °C for at least 24 h and then stored in a desiccator. All sample manipulations were carried out under an argon athmosphere. Calculated amounts of triphenylmethane (internal standard) and of all of the reactants except triethylamine were introduced into an NMR tube, and a spectrum (either at 200 or 300 MHz) was recordered at time zero. Then a known amount of triethylamine was added, and spectra were recorded at selected time intervals. Nonlinear least-squares fit of experimental data to eq 5 or, whenever appropriate, to eq 8 gave the third-order rate constants. Errors were calculated as $\pm 2\sigma$ (95% confidence limit).

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