New Insight into the Mechanism of the Conjugate Addition of Benzenethiol to Cyclic and Acyclic Enones and of the Corresponding Uranyl−Salophen-Catalysed Version

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A thorough kinetic investigation of the triethylamine-catalysed addition of benzenethiol to 2-cyclopenten-1-one in chloroform shows that the highest energy transition state is a complex of thiol, enone, and base in a 1:1:1 ratio, but whether formation or disruption of the enolate–triethylammonium ion-pair intermediate is rate-limiting is uncertain. Intervention of a second thiol molecule in the assembly of the transition-state complex is ruled out, at least at thiol concentrations not exceeding 0.1–0.2 M. Thiol addition is accelerated significantly by uranyl–salophen complex **1** and its diphenyl derivative **2**. The complicated kinetics are described to high precision by means of ad hoc integrated rate equations in which associations to the metal catalyst of the enone reactant and addition product are taken into account. The kinetics are consistent with a four-body transition-state complex, whose formation results from the reaction of a (weak) thiol–base complex with a (strong) enone–uranyl–salophen complex. Open-chain and cyclic enones react at similar rates and respond to the presence of metal catalyst in much the same way. The relative catalytic efficiencies of ethyldimethylamine, triethylamine, and quinuclidine are determined essentially by differences in base strength, rather than steric bulk, in both the presence and absence of a metal complex. Only with the use of the relatively bulky Hünig's base is an adverse steric influence apparent, which is particularly severe in the reaction catalysed by the sterically demanding **2**.

Introduction

The base-catalysed addition of thiols to activated double bonds, which has been known for more than half a century,[1] is an important reaction not only because of its biological relevance,[2−5] but also in view of its extensive use in synthesis,[6−10] particularly in the field of enantioselective reactions.[11−16]

There is a large body of evidence that the reactive species in protic, polar solvents is the thiolate anion, which leads consistently to simple second-order kinetics (i.e., first order in both thiolate and substrate).[17−20] Much less information of kinetic nature is available, however, for reactions carried out in the aprotic, nonpolar solvents used commonly in synthetic procedures and, consequently, there are still many unexplored or poorly understood features of these transformations.

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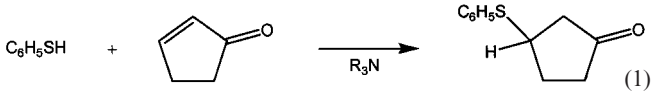
As a part of a research programme aimed at exploiting the Lewis acid character of uranyl derivatives in catalysis,[21] we have found that complexes **1** and **2** catalyse the addition of benzenethiol to cyclic enones remarkably well, and have reported in preliminary form some of the relevant kinetic features of the reaction.[22,23] In this paper, we report the results of a detailed study of the kinetics of the triethylamine-assisted addition of benzenethiol to 2-cyclopenten-1-one in chloroform solution [Equation (1)] aimed at defining the rate expressions precisely, both in the absence and presence of uranyl catalysts **1** and **2**. Also, we compare the rates of reaction of cyclic and open-chain enones, and report on the influence of the steric bulk of the tertiary base.



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Results and Discussion

The progress of reactions was monitored conveniently using ^{1}H NMR spectroscopy by comparing the relative intensities of signals of the enone reactants and addition

products with those of an internal standard (triphenylmethane) as a function of time. In all cases, the amounts of enone that disappeared and adduct that formed at any time t were identical to within the precision of the integrated signals' intensities. Extra peaks attributable to by-products or reaction intermediates were absent in all experiments.

The Background Reaction

Table 1 displays the results of a number of kinetic runs carried out at 25.0 °C in which the initial concentrations of reactant and bases were varied over wide ranges.

Table 1. Kinetic data for the addition of benzenethiol (T) to 2-cyclopenten-1-one (E) in the presence of Et_3N (B) in chloroform at 25.0 °C

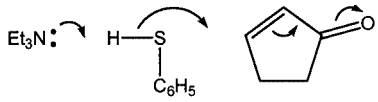
Entry	T [M]	E [M]	B [mM]	k_o [$M^{-2}s^{-1}$]
1	0.050	0.010	1.00	1.51
2	0.050	0.010	1.00	1.62
3	0.102	0.026	2.15	1.87
4	0.202	0.026	2.18	1.84
5	0.200	0.100	1.00	1.78
6[a]	0.102	0.102	1.08	1.70
7[a]	0.102	0.102	2.15	1.64
8[a]	0.102	0.102	2.13	1.70
9[a]	0.102	0.102	4.30	1.53
				mean 1.69 ± 0.13

[a] From ref.[24]

Addition of benzenethiol to 2-cyclopenten-1-one is reversible, with a value of the equilibrium constant K determined to be $(3.9 \pm 0.2) \times 10^3\ M^{-1}$ under the conditions of the kinetic experiments.[24] In runs 1−5, use of an excess of benzenethiol ensured the quantitative conversion of enone into product, whereas runs 6−9 reflect conditions where $4 \pm 1\%$ of the enone reactant was still detectable at infinite time. In all cases, time/concentration profiles showed strict second-order time dependence up to high conversions, with observed second-order specific rates ($k_{obsd.}$) strictly proportional to the base concentration. The last column in Table 1 lists the third-order rate constants k_o (calculated as $k_{obsd.}/[Et_3N]$). The remarkable constancy of the k_o values to within a reasonable range of experimental uncertainty, shows clearly that the rate law for the addition of benzenethiol (T) to 2-cyclopenten-1-one (E) catalysed by triethylamine (B) is that for an uncomplicated third-order reaction [Equation (2).]

$$\text{rate} = k_o[E][T][B] \quad (2)$$

It is of interest to compare the present results with those from the earlier literature. Dmuchowsky et al.[25] reported third-order kinetics − first-order in each reactant and in the base catalyst − for the tertiary amine catalysed addition of thiols to maleic anhydride in xylene. Fourth-order kinetics − second-order in benzenethiol − were reported, however, by Klimenko et al.[26] for a similar system. This observation indicates that a second molecule of benzenethiol might either activate the substrate through hydrogen bonding to the carbonyl group, or is involved in protonation of the enolate intermediate if its transformation into product is rate-limiting. Overall third-order kinetics in toluene were reported by Hiemstra and Wynberg[27] in an important paper on the asymmetric addition of aromatic thiols to cyclic enones catalysed by chiral β-hydroxy amines (cinchona and ephedra alkaloids). The catalyst's β-hydroxy group was argued convincingly to have an important catalytic function through hydrogen bonding to the carbonyl oxygen atom. Our present results show that there is no trace of a second-order contribution in benzenethiol, at least up to 0.1 M concentrations,[28] which definitely rules out the possibility that hydrogen bonding between the sulfhydryl and enone carbonyl units plays an important role in the activation of the enone function, even when the base catalyst lacks the neighbouring β-hydroxy groups of the cinchona and ephedra alkaloids.



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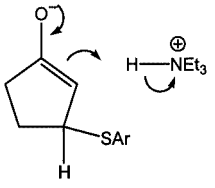
The overall third-order rate equation is consistent with the termolecular mechanism depicted in **3**, in which formation of the C−S bond is rate-limiting, as proposed by previous authors.[25,27] A termolecular complex does not necessarily require a three-body collision, but can instead be accomplished by having the enone react with a weak complex of thiol and base [Equation (3)].[25,27]

$$C_6H_5SH + NEt_3 \leftrightharpoons C_6H_5SH{\cdot}NEt_3 \quad (3)$$

The question is still open as to whether the structure of the complex above is better described as a simple hydrogen-bonded adduct ($Et_3N\cdots HSC_6H_5$), an ion pair salt ($Et_3N^+\ ^-SC_6H_5$), or an equilibrium mixture of these two forms.[29] We could not find any evidence by FT-IR and ^1H NMR spectroscopy for the appreciable formation of a complex between benzenethiol and Et_3N under conditions similar to those of the kinetic experiment. Hence, no conclusion can be drawn about its structure, although, frankly, it is of limited relevance, if any, in the present context. The important conclusion is that the concentration of the presumed complex is so low as to have a negligible influence on the kinetics of thiol addition.



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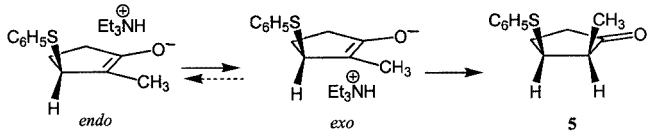
Also consistent with a third-order rate equation is a mechanism in which an enolate−ammonium ion-pair intermediate decomposes with rate-limiting proton transfer to the enolate α-carbon atom in **4**. In an investigation of the triethylamine-catalysed thiol addition to 2-methyl-2-cyclo-

penten-1-one,[24] we found that under kinetic control the *cis* adduct **5** was the sole detectable product formed in a highly stereoselective *anti* addition process. Thus, independent of whether the formation or disruption of the thiolate−ammonium ion-pair intermediate is rate-determining, the enolate intermediate must be sufficiently long-lived to permit the *endo* ion pair to be transformed into the *exo* ion pair required for the observed *anti* addition of the proton [Equation (4)].



(4)

In conclusion, the tertiary base catalysed thiol addition to 2-cyclopenten-1-one is a complex, multistep process most likely involving the intermediacy of an enolate. A proton is first transferred from the sulfur atom to the nitrogen atom and then to the α-carbon atom in a stereoselective *anti* fashion.[30] An investigation of the kinetics shows that the highest-energy transition state is a complex of thiol, enone, and base in a 1:1:1 ratio, but it does not allow us to locate its position along the reaction coordinate with any precision.

The Metal-Catalysed Reaction

In the presence of catalytic amounts of metal catalysts **1** and **2**, the reaction of benzenethiol and 2-cyclopenten-1-one is accelerated significantly and no longer exhibits a simple second-order time dependence.[22] This is because the metal catalysts **1** and **2** bind rapidly and reversibly to the enone reactant − and in the case of catalyst **2**, also to the addition product − to give adducts of 1:1 stoichiometries. UV/Vis, ^{1}H NMR, and FT-IR spectroscopic measurements have provided unequivocal evidence for their existence, as well as structural information and an assessment of the relevant binding constants.[22−24,31]

In these complexes, the carbonyl oxygen atom occupies the fifth equatorial site of the uranyl ion, where a Lewis acid−base interaction is established. In chloroform at 25 °C uranyl−salophen complex **1** binds weakly to 2-cyclopenten-1-one ($K = 14 \pm 1$ M^{-1}) and even more weakly with 3-(phenylthio)cyclopentanone ($K < 5$ M^{-1}), in which absence of the conjugated olefinic unit causes a reduction in Lewis basicity.[31] Much stronger associations are seen with metallocleft **2** [$K = 460 \pm 40$ M^{-1} with 2-cyclopenten-1-one; $K = 68 \pm 6$ M^{-1} with 3-(phenylthio)cyclopentanone], wherein attractive van der Waals interactions are established between the guests and the cleft's walls.[31] The greater affinity that the metal catalysts have toward the enone reactant over the ketone product has an important influence on the efficiency of catalysis because it reduces the adverse effects of product inhibition.

The enone−catalyst complex plays a key role in the catalytic process, because coordination of the carbonyl oxygen atom to the uranyl ion activates the enone toward nucleophilic attack at the β-carbon atom. Thus, the proposed mechanism [Equation (5)] involves reaction of a base-activated thiol with an enone−catalyst complex (E·cat), accompanied by inhibition due to the formation of a product−catalyst complex (P·cat). Application of the equilibrium parameters for the formation of the enone−catalyst and product−catalyst complexes leads to Equation (6), which holds whenever [E·cat] << [E]. Analytical integration of Equation (6) has been reported previously.[22] When, as was often the case in the present work, the rate of the background reaction is significant compared with that of the metal-catalysed reaction, it is more appropriate to use a general expression [Equation (7)] in which the overall rate is given by the sum of background and metal-catalysed reactions. Analytical integration of Equation (7) is more difficult, but still achievable by standard integration methods. The form that the integrated equation takes depends on whether the reactant concentrations are equal or not. Equation (8), in which the quantities a and b are defined in Equations (9) and (10), respectively, holds when initial concentrations of enone and thiol are equal.

$$\mathrm{E + cat} \underset{}{\overset{K_E}{\rightleftharpoons}} \mathrm{E \cdot cat} \xrightarrow{k_{cat}\,[T][B]} \mathrm{P \cdot cat} \underset{K_P}{\rightleftharpoons} \mathrm{P + cat} \tag{5}$$

$$v_{cat} = \frac{k_{cat} K_E [E][T][B][cat]_{tot}}{1 + K_E [E] + K_P [P]} \tag{6}$$

$$v_{tot} = k_o [E][T][B] + \frac{k_{cat} K_E [E][T][B][cat]_{tot}}{1 + K_E [E] + K_P [P]} \tag{7}$$

$$-\frac{1}{a^2}\left[([E]-[E]_o)\left(\frac{a(1+K_P[E]_o)}{[E][E]_o} + b(1+K_P[E]_o)\right) + \left(a(K_E - K_P) - b(1+K_P[E]_o)\right) \ln\frac{[E]\,(a+b[E]_o)}{[E]_o(a+b[E])}\right] = t \tag{8}$$

$$a = k_{cat} K_E [B][cat]_{tot} + k_o [B](1 + K_P [E]_o) \tag{9}$$

$$b = k_o (K_E - K_P)[B] \tag{10}$$

For the case of unequal reactant concentrations, the integrated equation takes the form of Equation (11),[23] in which m and n are defined in Equations (12) and (13), respectively.

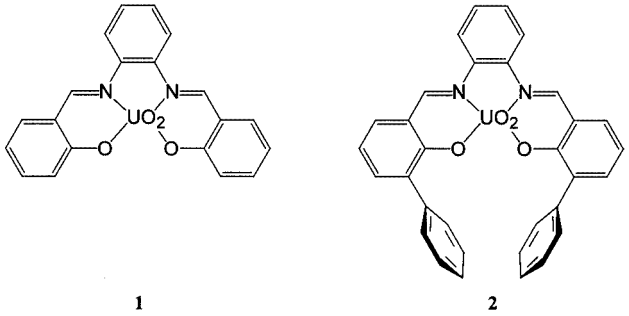
$$\frac{1+K_P[E]_o}{m([T]_o-[E]_o)} \ln\frac{[E]_o}{[E]} + \left(\frac{K_E - K_P}{m-n} - \frac{1+K_P[E]_o}{(m-n)([T]_o-[E]_o)}\right) \ln\frac{[T]_o}{[T]} + \frac{(K_E - K_P)\,k_{cat} K_E [B][cat]_{tot}}{m(m-n)} \ln\left(1 - \frac{(K_E - K_P)\,k_o ([E]_o - [E])}{k_o + k_{cat} K_E [cat]_{tot} + k_o K_E [E]_o}\right) = t \tag{11}$$

$$m = k_o [B](1 + K_P [E]_o) + k_{cat} K_E [B][cat]_{tot} \tag{12}$$

$$n = k_o [B]([T]_o - [E]_o)(K_P - K_E) \tag{13}$$

Since the values of k_o, K_E, and K_P are known from independent measurements, and since the composition of the mixture as a function of time is known from ^{1}H NMR spectroscopic analyses, both Equations (8) and (11) contain k_{cat} as the only unknown quantity. For each catalysed reaction, a value of k_{cat} was selected in such a way that plots of the left-hand sides of Equations (8) and (11) against time ap-

pear as straight lines with unit slopes and zero intercepts. A typical plot is shown in Figure 1.



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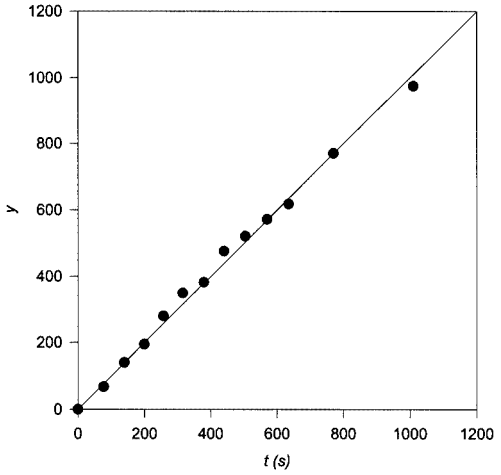


Figure 1. Plot of the left side of Equation (8) against time for the addition of benzenethiol to 2-cyclopenten-1-one catalysed by quinuclidine and **1**, with k_{cat} = 7100 $M^{-2}s^{-1}$; the straight line has a slope of 1 and an intercept of 0

Table 2. Kinetic data for the addition of benzenethiol (T) to 2-cyclopenten-1-one (E) in the presence of Et_3N (B) and metallocatalyst **1** in chloroform at 25.0 °C

Entry[a]	T [M]	E [M]	B [mM]	**1** [mM]	k_{cat} [$M^{-2}s^{-1}$]
1	0.050	0.010	1.00	1.00	1380
2	0.102	0.026	2.15	0.98	1360
3	0.100	0.048	2.12	0.93	1440
4	0.097	0.097	2.06	0.90	1550
5	0.100	0.100	2.15	0.26	1450
6	0.100	0.100	2.15	0.38	1580
7	0.100	0.100	2.15	0.77	1460
8	0.100	0.100	2.15	0.98	1450
9	0.100	0.100	2.15	1.52	1520
10	0.100	0.100	2.15	2.18	1550
11	0.200	0.100	1.00	1.00	1380
12	0.092	0.183	1.94	0.85	1610
13	0.098	0.374	2.16	0.99	1500
					mean 1480 ± 80

[a] Entries 4–10 refer to kinetic runs in which thiol addition is only 96 ± 1% complete. Since the extent of the reverse reaction is negligibly small up to 60% conversion, for these experiments time/concentration data only in the range of 0–60% conversion were used in the least-squares fitting to Equation (8). For all other experiments, in which thiol addition is virtually complete, Equation (11) was used.

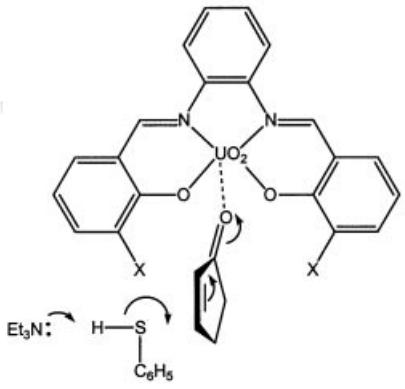
Table 3. Kinetic data for the addition of benzenethiol (T) to 2-cyclopenten-1-one (E) in the presence of Et_3N (B) and metallocatalyst **2** in chloroform at 25.0 °C

Entry	T [M]	E [M]	B [mM]	**2** [mM]	k_{cat} [$M^{-2}s^{-1}$]
1	0.029	0.010	0.38	0.52	639
2	0.029	0.010	0.38	1.03	664
3	0.029	0.010	1.06	1.03	622
4	0.050	0.010	1.00	1.00	623
5	0.101	0.029	2.14	1.08	591
6	0.062	0.030	0.38	1.03	602
7	0.062	0.030	0.38	1.03	592
					mean 620 ± 27

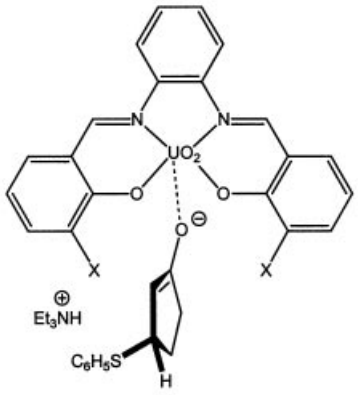
The results collected in Tables 2 and 3 show that the values of k_{cat} are virtually independent of variations in concentrations of reactants and catalysts over sizeable ranges. Furthermore, in all cases time/concentration profiles are reproduced to a very good precision by Equations (8) and (11) with the introduction of the optimised values of k_{cat}. These findings show clearly that the rate Equation (6) describes adequately the uranyl–salophen-catalysed addition of thiols to 2-cyclopenten-1-one. Consistently, the reaction mechanism is depicted reasonably as a quatermolecular process, in which a 1:1 adduct of uranyl–salophen catalyst and enone reacts with a weak 1:1 complex of thiol and base (**6**).

The kinetics of the reaction reveal the composition of the rate-limiting transition state as a quaternary complex of the two reactants and two catalysts, but again we cannot ascertain whether it is the formation or disruption of a uranyl–salophen-complexed enolate intermediate **7** that is rate-limiting. Given that interaction with the uranyl ion should stabilise the enolate intermediate strongly, the possibility that proton transfer from the ammonium counterion is rate-limiting is definitely more likely in the presence of the metal catalysts than in their absence.

Comparison of rate data collected in Table 4 shows that thiol addition to the complex formed between 2-cyclopenten-1-one and **1** is almost 900 times faster than addition to the uncomplexed substrate, and some 2.4 times faster than addition to the corresponding complex with **2**. It is understandable that **1** is more effective as a catalyst than is **2** under saturating conditions (i.e., when the reactivity is determined by k_{cat}) because of the moderately adverse steric clash of the enone with the cleft walls of **2**. On the other hand, under subsaturating conditions, i.e., when the reactivity is governed by the product of k_{cat} and K_E (see footnotes [a] in Table 4, **2** turns out to be more effective than **1** as a catalyst by one order of magnitude, which indicates that the additional binding energy rendered available by the interaction between the guest substrate and the cleft's walls is largely translated into catalysis.



6, X = H, C_6H_5



7, X = H, C_6H_5

Table 4. Kinetic data for the addition of benzenethiol to 2-cyclopenten-1-one and ethyl vinyl ketone in the presence of Et_3N (B) and in the absence and presence of metallocatalysts **1** and **2** in chloroform at 25.0 °C [the various quantities are defined in Equations (2) and (5); rate constants k_o and k_{cat} have units of $M^{-2}\ s^{-1}$; equilibrium constants K_E and K_P have units of M^{-1}]

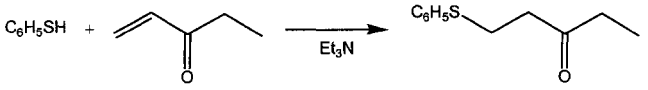
			1			**2**	
	k_o	k_{cat}	$k_{cat}K_E$	k_{cat}/k_o	k_{cat}	$k_{cat}K_E$	k_{cat}/k_o
2-Cyclopenten-1-one[a]	1.64	1480	$2.1\ 10^4$	900	620	$2.8\ 10^5$	380
Ethyl vinyl ketone[b]	5.45		$5.5\ 10^4$		1760	$2.8\ 10^5$	320

[a] With **1**: $K_E = 14 \pm 2$, $K_P < 2$; with **2**: $K_E = 460 \pm 40$, $K_P = 68 \pm 12$. Rate constants are taken from Tables 1–3. [b] With **1**: K_E and K_P too low to measure (i.e., < 2); with **2**: $K_E = 163 \pm 15$, $K_P = 62 \pm 6$. Estimated uncertainties in k_o and k_{cat} are in the order of ± 5–10%.

Open-Chain versus Cyclic Enones

Given that all of the available kinetic studies of conjugate additions of thiols have employed cyclic substrates,[22–27] we were interested in obtaining some quantitative information on the behaviour of open-chain enones for comparison with their cyclic counterparts.

We found that benzenethiol adds smoothly and quantitatively to ethyl vinyl ketone in chloroform at 25 °C in the presence of catalytic amounts of triethylamine to give 1-(phenylthio)-3-pentanone [Equation (14)] as the sole product detectable by ^1H NMR spectroscopy.[32]



(14)

The rate of addition was enhanced significantly by the presence of catalytic amounts of uranyl–salophen complexes **1** and **2**. In both the absence and presence of metal catalysts, we analysed the kinetics as described above for the reactions of 2-cyclopenten-1-one. The only significant difference observed was that, unlike 2-cyclopenten-1-one, ethyl vinyl ketone does not form a significantly stable complex with **1**, and neither does its addition product. The kinetics of thiol addition to ethyl vinyl ketone in the presence of **1** were analysed by means of Equation (15), which is the simple form to which the general Equation (6) reduces whenever the quantities of both K_E[E] and K_P[P] are much smaller than 1. The fourth-order rate expression of Equation (15) implies a simple second-order time dependence, first-order in both enone and thiol, which was strictly obeyed by time/concentration data.

$$\text{rate} = k_{cat}K_E[E][T][B][cat]_{tot} \quad (15)$$

The results of the kinetic experiments are summarised in Table 4. 2-Cyclopenten-1-one is geometrically constrained in the *s-trans* conformation, whereas ethyl vinyl ketone is conformationally disordered, yet the background reactivity of the latter is higher than that of the former, which is consistent with the known adverse effect on the rate of alkyl substitution at the β-carbon atom.[24]

The two substrates respond to the presence of metal catalysts much in the same way, in terms of values of both $k_{cat}K_E$ – available for both metal catalysts – and k_{cat}/k_o available only for catalyst **2**. We conclude, therefore, that there seem to be no major differences of a mechanistic nature for conjugate thiol addition that are attributable to the cyclic or acyclic nature of the enone reactant.

Effect of Base Structure

Given that electrostatic interactions are highly dependent on the distance between oppositely charged ions, it seemed likely that the stability of the presumably tight enolate–trialkylammonium ion-pair intermediate(s) depicted in Equation (4) would be influenced by the relative positions of the two partners. Consequently, changes in the steric bulk of the base catalyst are expected to affect the rate of thiol addition. To test this idea, complete sets of rate constants, both in the absence and presence of metal cata-

Table 5. Kinetic data for the addition of benzenethiol to 2-cyclopenten-1-one in chloroform at 25.0 °C assisted by tertiary amines in the absence and presence of metallocatalysts **1** and **2** [rate constants k_o and k_{cat} are defined in Equations (2) and (5) and have units of M^{-2} s^{-1}; estimated uncertainties are in the order of ± 5−10%]

			1		**2**	
	pK_a [a]	k_o	k_{cat}	k_{cat}/k_o	k_{cat}	k_{cat}/k_o
Ethyldimethylamine[b]	10.16	0.42	460	1100	240	570
Triethylamine[c]	10.75	1.64	1400	850	620	380
Hünig's base	11.44	1.18	570	480	27	23
Quinuclidine[d]	10.95	11.4	7300	640	5700	500

[a] In water at 25.0 °C. Data for ethyldimethylamine, triethylamine, and quinuclidine taken from: *IUPAC Dissociation Constant of Organic Bases in Aqueous Solution*, Butterworths, London, **1965**. The value of pK_a of Hünig's base is taken from: T. Fujii, H. Nishida, Y. Abiru, M. Yamamoto, M. Kise, *Chem. Pharm. Bull.* **1995**, *43*, 1872−1877. Values of pK_a in polar aprotic solvents reported in footnotes [b−d] taken from: K. Izutsu, *IUPAC Acid−Base Dissociation Constants in Dipolar Aprotic Solvents*, Blackwell Scientific Publications, Oxford, **1990**. [b] pK_a = 17.77 ± 0.10 in nitromethane. [c] pK_a = 18.35 ± 0.10 in nitromethane; pK_a = 18.53 in acetonitrile; pK_a = 9.0 ± 0.2 in dimethyl sulfoxide. [d] pK_a = 19.51 ± 0.11 in acetonitrile; pK_a = 9.8 in dimethyl sulfoxide.

lysts **1** and **2**, were obtained using ethyldimethylamine, ethyldiisopropylamine (Hünig's base), and quinuclidine as base catalysts. The results are collected in Table 5; the corresponding data for the triethylamine-catalysed reactions from Tables 1−3 are also reported for comparison.

The background reaction appears to be quite sensitive to the nature of the tertiary amine base, as shown by values of k_o spanning over a wide range. In the presence of quinuclidine, the most effective base catalyst in the series, k_o is 27 times larger than the value observed in the presence of ethyldimethylamine. Ethyldimethylamine, triethylamine, and Hünig's base form a homologous series of dialkyl(ethyl-)amines in which each member differs from the previous one by the presence of two additional methylene groups. In this series the catalytic efficiency decreases in the order triethylamine > Hünig's base > ethyldimethylamine, a series that hardly can be rationalised on the basis of steric effects alone, and suggests that base strength may also play a role. It is unfortunate that no information is available on the base strength of these amines in chloroform, an apolar aprotic solvent in which structure effects on basicity do not necessarily parallel those in water, for which a complete set of values of pK_a is available (Table 5). A comparison of base strengths of ethyldimethylamine and triethylamine shows that the latter is 3.9 times more basic in water, and 3.8 times in the aprotic solvent nitromethane (see footnotes [b] and [c] in Table 5). These values are virtually identical to the ratio of 3.9 found between the values of k_o measured for the conjugate additions in the presence of the two bases. Assuming that the relative basicities in water and nitromethane are a good measure of relative basicity in chloroform, we reach the conclusions that (i) the higher catalytic efficiency of triethylamine compared to ethyldimethylamine is due solely to a difference in base strength, with a negligible influence of steric effects, and (ii) proton transfer to the nitrogen atom in the transition state is essentially complete.[33]

The situation is different for Hünig's base, for which no value of pK_a in solvents other that water is available. The lack of a link between base strength − the highest in this study − and catalytic efficiency suggests an adverse influence of the large steric hindrance of the bulky Hünig's base.

Quinuclidine is slightly more basic than triethylamine in water, but the difference in the values of pK_a of the two bases is 1.0 in acetonitrile and 0.8 in dimethyl sulfoxide (see footnotes [c] and [d] in Table 5). Thus, if the relative base strength of quinuclidine and triethylamine in chloroform is well modelled by the values in water, the higher catalytic efficiency of quinuclidine, where the substituents on the nitrogen atom are held back, argues in favour of low steric interference with the enolate partner. If, however, the relative basicity in chloroform bears a closer resemblance to the situations observed in the aprotic solvents acetonitrile and dimethyl sulfoxide, then the difference in catalytic efficiency of the two bases is accounted for entirely on the basis of the difference in base strength, with little or no influence in steric effects. In the absence of additional information, it is difficult to make a definite choice for either of these interpretations, but the latter appears to be more likely in view of the closer similarity of chloroform to aprotic solvents than to water.

In the presence of metallocatalyst **1**, the values of k_{cat} roughly parallel the corresponding values of k_o and, consequently, the k_{cat}/k_o ratios are affected only to a moderate extent by the nature of the base catalyst. This finding suggests that in the transition state for the reaction catalysed by **1** there is essentially a full hydrogen−nitrogen bond, and indicates that both metal-catalysed and background reactions are sensitive to the steric bulk of the base in a similar way; this conclusion is not really surprising in view of the open structure of catalyst **1**. More surprising is the finding that the reactions of ethyldimethylamine, triethylamine, and quinuclidine, in the presence of metallocleft **2**, exhibit values of k_{cat}/k_o that are very similar to each other, and only slightly lower than in the presence of catalyst **1**, in spite of the fact that in the former cases the reaction takes place within narrow clefts. Only with the relatively bulky Hünig's base is there a marked reactivity drop (by 20fold) observed on going from catalyst **1** to catalyst **2**, which clearly is due to a steric effect.

We conclude, therefore, that the relative catalytic efficiency of ethyldimethylamine, triethylamine, and quinuclidine, is determined essentially by differences in base strength, both in the background and metal-catalysed reactions, with little or no influence of the steric bulk of the base. The operation of an adverse steric influence on catalytic efficiency is apparent only in the Hünig's base mediated reactions. This adverse influence is particularly severe when the bulkiest base in the series is combined with the sterically demanding metallocleft **2**.

Experimental Section

Instruments and Methods: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with either a Bruker AC 200 or a Bruker AC 300 spectrometer. UV/Vis spectra were recorded in $CHCl_3$ with a Perkin−Elmer Lambda 18 spectrophotometer. Non-linear least-squares calculations were carried out using the programme SigmaPlot for Windows, 8.0 (Jandel Scientific).

Materials: Benzenethiol (Fluka) was distilled under reduced pressure prior to use. Triethylamine (Aldrich), ethyldimethylamine (Aldrich) and ethyldiisopropylamine (Aldrich) were distilled from *p*-toluenesulfonyl chloride and then from sodium. Ethyl vinyl ketone was distilled under reduced pressure from calcium hydride. Spectrophotometric grade chloroform (Aldrich) and [D_1]chloroform were dried with 4-Å molecular sieves for at least 24 h prior to use. 2-Cyclopenten-1-one (Aldrich) was used as received. 1-(Phenylthio)-3-pentanone was prepared according to a standard literature procedure[34] and showed spectroscopic data consistent with the expected structure. Salophen−uranyl complexes **1** and **2** were available from previous studies.[22,23]

Equilibrium Measurements: Association constants between 1-(phenylthio)-3-pentanone and uranyl−salophen complexes were determined spectrophotometrically as described previously.[22,23]

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[28] In a number of kinetic runs (not reported in Table 1) carried out at benzenethiol concentrations on the order of 0.5 M, the third-order specific rates turned out to be higher by some 15−20% than those measured at lower concentrations. This finding might indicate the existence of a modest second-order contribution in benzenethiol, or might well be ascribed to non-ideal behaviour in the relatively concentrated benzenethiol solutions.
[29] To the best of our knowledge, the only available evidence for the existence of a thiolate−ammonium ion-pair was obtained in CHF_2Cl at 123 K (see: G. S. Denisov, N. S. Golnber, *J. Mol. Struct.* **1981**, *75*, 311−326). Under the given conditions the ion pair is in equilibrium with the hydrogen-bonded adduct.
[30] In line with the definition of conjugate additions as 1,4-additions (see: T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, **1987**, p. 662) the possibility of proton transfer from the ammonium ion to the enolate oxygen atom to give the enol form of **5** should also be considered. ^1H NMR spectroscopic data suggest that this thermodynamically unstable enol does not accumulate in the reaction medium, which implies that any enol possibly formed must revert rapidly to the parent enolate, thus providing a possible reaction path for the *endo*/*exo* interconversion [Equation (4)]. Values of equilibrium constant in the range of $10^{-7.2}$−$10^{-7.9}$ have been reported for the keto/enol equilibrium involving cyclopentanone; see: J. Toullec, "Keto-Enol Equilibrium Constants" in *The Chemistry of Enols* (Ed.: Z. Rappoport), Wiley, New York, **1990**, p. 321.
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[32] Analogous results were observed with methyl vinyl ketone, which gave the addition product 4-(phenylthio)-2-butanone in virtually quantitative yield at a comparable rate. In the presence of the uranyl−salophen catalyst, however, the kinetics showed considerable scatter that was reduced, but not eliminated, when methyl vinyl ketone was freshly purified by distillation from calcium hydride in vacuo. Better reproducibility of results occurred also when ethyl vinyl ketone was distilled.
[33] This conclusion is consistent with the observation of an adverse kinetic isotope effect reported in ref.[25] for the triethylamine-catalysed addition of butanethiol to maleic anhydride in toluene. An inverse kinetic isotopic effect presumably is due to the fact that the frequency (3100−3200 cm^{-1}) of an N−H stretching mode in a protonated tertiary amine that is not involved in hydrogen bonding is higher than the typical stretching frequency (2550−2600 cm^{-1}) of the S−H unit (see: R. H. Nuttal, D. W. A. Sharp, T. C. Waddington, *J. Chem. Soc.* **1960**, 4965).
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