Supramolecular Catalysis of 1,4-Thiol Addition by Salophen−Uranyl Complexes

Valeria van Axel Castelli, Antonella Dalla Cort, and Luigi Mandolini*,‡

Dipartimento di Chimica and Centro CNR Meccanismi di Reazione Università La Sapienza Box 34, Roma 62, 00185 Roma, Italy

David N. Reinhoudt*,§

Department of Supramolecular Chemistry and Technology MESA Research Institute University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

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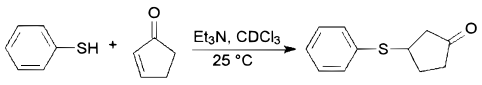
An exciting challenge of supramolecular chemistry is the construction of abiotic catalysts of reasonably low molecular weight that share with the natural enzymes a number of fundamental features related to efficient catalysis.[1] Enzyme properties such as preferential stabilization of the transition state over reactant state (large rate enhancements), selective binding and recognition of the substrate over reaction product (low product inhibition), and high turnover values (low catalyst-to-substrate ratios) are worth mimicking in synthetic catalytic systems. Although some beautiful enzyme models have been developed,[2] systems that mimic all of the above characteristics are rare.[3]

We report here that the robust complexes **1** and **2**[4] are effective catalysts of 1,4-thiol addition with high turnover efficiency and low product inhibition. The model reaction of thiophenol with 2-cyclopenten-1-one in the presence of Et_3N in chloroform (eq 1) was chosen for our studies. Despite the importance of the



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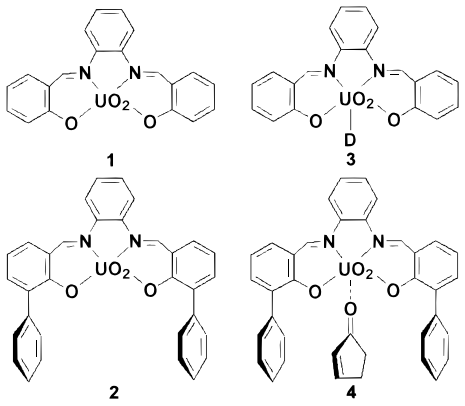
Michael-type addition of thiols both in biochemical processes[5] and in synthesis,[6] to the best of our knowledge this is the first quantitative study of metal-ion catalysis of this class of reactions.[7] Our catalyst design was based on the well-known property of salophen−uranyl complexes[8] to bind donor groups (D), such as anions[9] and polar neutral molecules,[10] in an equatorial coordination site (**3**) as well as on our recent finding[11] that a neighboring uranyl

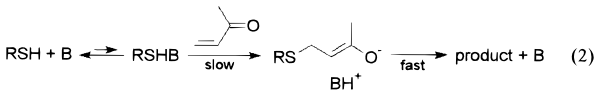


center provides an ester carbonyl with Lewis acid activation toward nucleophilic addition.

The binding properties of **1** and **2** have been assessed by a UV−vis titration technique.[11] From the results listed in Table 1 the following conclusions can be drawn: (i) because of the strong conjugation of the double bond with the carbonyl group, the α,β-unsaturated ketone is a stronger Lewis base than the saturated ketones, (ii) interaction of the ketone guests with the aromatic cleft walls reinforces the binding, and (iii) the weaker binding of 3-(phenylthio)cyclopentanone to **2** compared to cyclopentanone points to an adverse influence of the bulky 3-phenylthio substituent. The picture that emerges is clearly one in which the ketone guests are coordinated to the metal center and, in the case of **2**, are situated between the cleft walls as shown in **4**. This picture is further confirmed by IR and ^{1}H NMR data (see footnote b to Table 1) and is in agreement with previous findings.[4]

The catalytic activities of **1** and **2** are illustrated by the time−concentration profiles shown in Figure 1.[12] Ten turnovers are seen in these experiments, in which the catalyst amount was 10 mol %. In other experiments[13] a quantity as low as 1 mol % of catalyst was enough for the catalyzed reaction to occur significantly faster than the reference reaction.

The accepted mechanism[14] of the tertiary base (B)-catalyzed thiol addition to electron-poor olefins in apolar aprotic solvents involves the rate-limiting addition of the thiolate portion of a 1:1 complex of thiol and base, followed by fast proton transfer (eq 2). Since there is insignificant formation of the thiol−base



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adduct,[14] the mechanism of eq 2 leads to a simple third-order

‡ Fax: 39 (06) 490−421. E-mail: lmandolini@axrma.uniroma1.it.

§ Fax: Int. code + (53)4894645. E-mail: d.n.reinhoudt@ct.utwente.nl.

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Table 1. Equilibrium Constants K (M^{-1})[a] for 1:1 Association between Ketones and Salophen-Uranyl Complexes **1** and **2** in Chloroform at 25.0 °C

	1	**2**
2-cyclopenten-1-one	14 ± 2	460 ± 20[b]
3-(phenylthio)cyclopentanone	<2	68 ± 12
cyclopentanone	<2	136 ± 18

[a] Data from UV−vis titration of 0.1 mM metal complexes with ketones. [b] Upon addition of **2** to a $CHCl_3$ solution of 2-cyclopenten-1-one (IR = 1708 cm^{-1}, C=O) a new band appears at 1657 cm^{-1}, whose intensity increases upon increasing **2**. ^1H NMR (300 MHz) titration of 1 mM 2-cyclopenten-1-one with **2** in $CDCl_3$ at 25 °C showed upfield shifts of the methylene H(5) protons that were consistent with fast 1:1 complexation, $K = 520 \pm 80$ M^{-1}, $\Delta\delta_\infty = -0.38$ ppm. Analogous behavior was exhibited by the methylene H(4) protons ($\Delta\delta_\infty = -0.30$) and the H(2) vinylic proton ($\Delta\delta_\infty = -0.17$).

Table 2. Addition of Thiophenol (0.050 M) to 2-cyclopenten-1-one (0.010 M) in the Presence of Et_3N (1.00 mM) in $CDCl_3$ at 25.0 °C.[a] Catalytic Parameters

catalyst[b]	k_{cat} ($s^{-1}\,M^{-2}$)	k_{cat}/k_o	$k_{cat}K_E$ ($s^{-1}\,M^{-3}$)	$K_{T\neq}$[c] (M^{-1})	tf[d] (s^{-1})
1	14.3×10^2	9.5×10^2	2.0×10^4	1.3×10^4	1.43
2	6.3×10^2	4.2×10^2	2.9×10^5	1.9×10^5	0.63

[a] $k_o = 1.51$ s^{-1} M^{-2}. [b] The catalyst concentration is 1.00 mM. [c] Calculated as $(k_{cat}/k_o)K_E$. [d] Turnover frequency at 1 M thiophenol and 1 mM Et_3N.

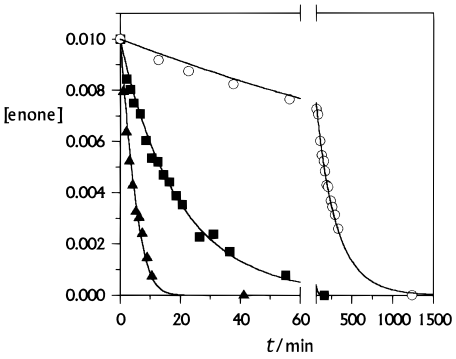

Figure 1. Time−concentration profiles for reaction 1. Reaction conditions are defined in Table 2. (○) Et_3N alone ($t_{1/2}$ 162 min); (■) Et_3N + **1** ($t_{1/2}$ 13.4 min); (▲) Et_3N + **2** ($t_{1/2}$ 3.8 min). The points are experimental, and the curves are calculated from the second-order rate equation for reactions carried out with Et_3N alone and from eq 6 when in the presence of metal catalyst.

equation (eq 3), in which E denotes the enone substrate and T

$$v = k_o[B][E][T] \tag{3}$$

the thiol. The reaction was actually reported to obey third-order kinetics,[14] first-order in each of the reactants and in the base. Consistent with the above findings, the reference reaction was found to display a clean second-order time dependence (Figure 1). The pseudo-second-order rate constant was translated into the third-order rate constant $k_o = 1.51$ s^{-1} M^{-2}. Not surprisingly, the second-order rate equation gave a very poor fit to data points for the metal-catalyzed reactions, for which we propose a mechanism (eq 4) involving rate-limiting thiol addition on an enone−catalyst

$$E + cat \overset{K_E}{\rightleftharpoons} E{\cdot}cat \xrightarrow{k_{cat}[T][B]} P{\cdot}cat \overset{K_P}{\rightleftharpoons} P + cat \tag{4}$$

complex (E·cat) and inhibition due to formation of a product−catalyst complex (P·cat). Equation 4 translates into the rate expression of eq 5,

$$v = \frac{k_{cat}K_E[B][T][E][cat]_{tot}}{1 + K_E[E] + K_P[P]} \tag{5}$$

from which eq 6 is obtained by integration. Since K_E and K_P are

$$\left(K_E - \frac{1 + [T]_oK_P}{[T]_o - [E]_o}\right)\ln\frac{[T]_o}{[T]_t} + \left(\frac{1 + [E]_oK_P}{[T]_o - [E]_o}\right)\ln\frac{[E]_o}{[E]_t} = k_{cat}K_E[B][cat]_{tot}t \tag{6}$$

independently known (Table 1), eq 6 contains k_{cat} as the only unknown quantity. Numerical values of k_{cat} were obtained from the least-squares slopes of plots of the left side of eq 6 against time. The close adherence of data points to the calculated profiles (Figure 1) indicates the validity of the proposed mechanism.

The kinetic parameters for the metal-catalyzed reactions are collected in Table 2. The k_{cat}/k_o values show that the complexes with **1** and **2** are 950 and 420 times more reactive, respectively, than the uncomplexed 2-cyclopenten-1-one. It seems likely that this difference is due to the same factor that makes 3-(phenylthio)-cyclopentanone a weaker ligand of **2** than cyclopentanone. Whereas k_{cat} is higher for **1** than for **2**, the reverse order is found in the $k_{cat}K_E$ product. This finding has important consequences on the relative efficiency of the two catalysts. Under subsaturating conditions ($K_E[E] \ll 1$) the catalytic process is governed by $k_{cat}K_E$ and **2** is more efficient than **1**. But under conditions approaching saturation ($K_E[E] \gg 1$) the catalytic process is governed by k_{cat} and the reactivity order is **1** > **2**. Indeed we found that experiments run at higher concentration showed the expected inversion of catalytic efficiency.[13]

The quantity $K_{T\neq}$, operationally defined as $(k_{cat}/k_o)K_E$, has the meaning of the binding constant of the catalyst to the transition state.[15] The calculated values in Table 2, compared with the corresponding values in Table 1, show to what an extent the transition state, on account of its enolate character, binds to the catalysts more tightly than both the reactant and product. The last column in Table 2 shows that in a minute each catalyst molecule delivers several tens of activated enone molecules to the tiny amount of thiol−base complex formed at 1 M thiol and 1 mM base.

In conclusion, our catalysts mimic the behavior of a metalloenzyme, in that they bind 2-cyclopenten-1-one and promote reaction of the bound substrate. Release of the addition product, followed by preferential binding to another enone molecule, ensures the onset of a catalytic cycle with high turnover efficiency. The salophen−uranyl unit will prove useful in the design and construction of more elaborate metallocatalysts with ligase activity. Most promising in this perspective is metallocleft **2**, for which an interesting property such as shape selectivity is easily foreseen.

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(12) The kinetics were monitored by ^1H NMR spectroscopy. The decrease as a function of time of the intensity of the signal of the α-vinylic proton of the enone at δ 6.2 was accompanied by an increase in intensity of the signal of the H(3) proton of 3-(phenylthio)cyclopentanone at δ 3.9. No extra peaks due to side products were observed.

(13) Kinetic experiments run at the following initial concentrations $[E]_o = 0.1$ M, $[T]_o = 0.2$ M, [B] = 1 mM, [cat] = 1 mM, showed a half-life of 6.6 min for **1** and 10.4 min for **2**. The half-life for the reference reaction was 38 min. The enone concentration at which the two catalysts show the same efficiency in terms of initial rate is calculated from eq 5 to be 0.042 M.

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