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The Role of Attractive van der Waals Forces in the Catalysis of Michael Addition by a Phenyl Decorated Uranyl-Salophen Complex

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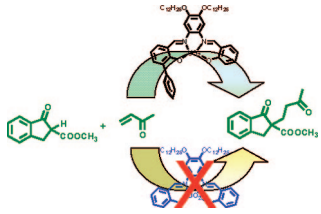

The Et_3N-assisted addition of β-ketoester **3** to MVK in chloroform is catalyzed with high turnover efficiency by the phenyl-substituted uranyl−salophen compound **2b** but not by the parent compound **1b**. A plausible mechanism is suggested, involving concomitant nucleophilic attack at the β-carbon and hydrogen bonding between the Et_3NH^+ countercation and the carbonyl oxygen of the *s-cis* conformation of the enone reactant. The role of the van der Waals interactions with the aromatic side arm of **2b** as a crucial driving force for catalysis is discussed.

A large number of uranium cation coordination complexes, particularly of the uranyl dication UO_2^{2+}, have appeared in the past decade.[1] Besides a general interest in the reactivity and coordination behavior of 5f-elements, motivations for such studies have been provided by the search for useful applications as molecular receptors in the area of supramolecular chemistry.

Our previous works in the field dealt with uranyl complexes of salicylaldehyde-derived $N_2O_2^{2-}$ ligands.[2] These complexes are generally found in a polygonal bipyramidal coordination, with the two oxygens of UO_2^{2+} in the apical positions.[3] After accommodation of the four donor groups of the $N_2O_2^{2-}$ ligand, a fifth site is still available in the equatorial plane for labile coordination to an additional ligand. Incorporation of uranyl−salen and −salophen units into more elaborate structures provided receptors for use in complexation of anions,[4] ion pairs,[5] and neutral molecules.[3a,6] The hard Lewis acid character of the uranyl center was further exploited in catalytic studies of reactions of carbonyl compounds.[7−9] The most carefully investigated reaction has been the conjugate addition of benzenethiol (T) to cyclic and acyclic enones (E), catalyzed with high turnover efficiency by a combination of tertiary amine (B) and uranyl−salophen catalyst (cat) in chloroform at room temperature.[8] The proposed mechanism (eq 1) is an extended complexation catalysis scheme, involving the reversible formation of a productive enone−catalyst complex (E•cat) and product inhibition caused by a product−catalyst complex (P•cat). The highest energy transition state has the composition of a quatermolecular complex arising from the addition of a base-activated thiol to the enone−catalyst complex, as schematically depicted in Figure 1. The parent catalyst **1a** binds to the enone substrates with low affinities, but complex stability is strongly enhanced by attractive van der Waals interactions of the bound substrates with the aromatic pendant in **2a**. For example, in chloroform at 25 °C, the complexation constant K_E (M^{-1}) of **1a** with 2-cyclopenten-1-one is 14, and that with

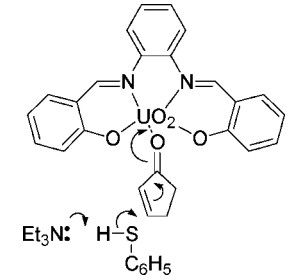

FIGURE 1. Schematic representation of the addition mechanism of benzenethiol to cyclopentenone catalyzed by uranyl−salophen complex **1a**.

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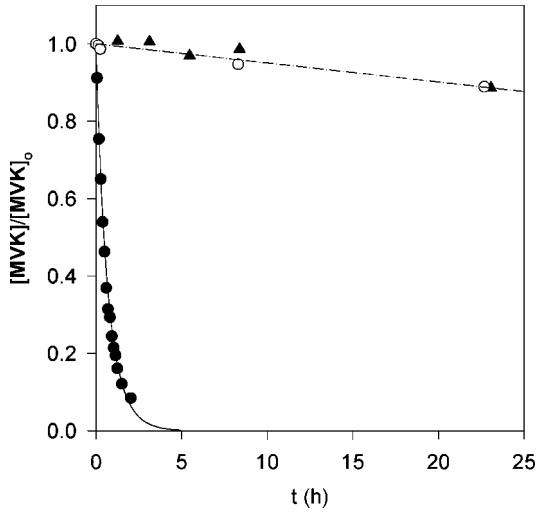


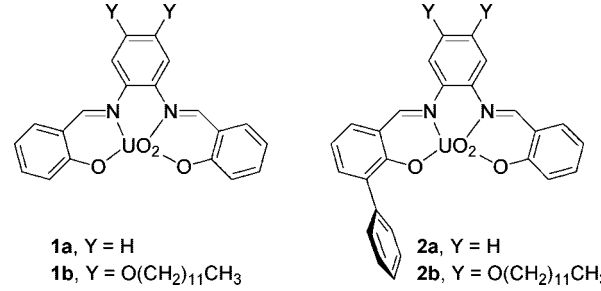
FIGURE 2. Time−concentration profiles for Michael addition of **3** to MVK in $CDCl_3$, at 25 °C. [MVK] = 0.10 M, [**3**] = 0.20 M, and [Et_3N] = 5.010^{-3} M. (●) [**2b**] = 2.010^{-3} M; (▲) [**1b**] = 2.010^{-3} M; (○) no metal catalyst. The points are experimental, and the curves are drawn for clarity purposes only.

2-cyclohexen-1-one is 7.6; the corresponding figures for **2a** are 870 and 320.[6b] In spite of the large differences in reactant state interactions, the two catalysts behave much in the same way in terms of k_{cat}/k_{uncat} values,[8d] showing that the additional binding energy rendered available by attractive interactions with the side arm of **2a** is realized equally well in the enone−catalyst complex and in the (transition state)−catalyst complex. Catalyst **2a** performs much more effectively than **1a** only under subsaturating conditions ($K_E \times [E] \ll 1$), where reactivity is determined by the $K_E \cdot k_{cat}$ product.[10]

$$E + cat \overset{K_E}{\rightleftharpoons} E \cdot cat \xrightarrow{k_{cat}[T][B]} P \cdot cat \underset{K_P}{\rightleftharpoons} P + cat \qquad (1)$$

To further explore the catalytic potential of uranyl−salophen compounds, it seemed worthwhile to extend our studies to the Michael addition, one of the oldest and most useful carbon−carbon bond forming reactions.[11] Complexes **1b** and **2b** were tested for catalytic activity in the model reaction of methyl 1-oxoindane-2-carboxylate (**3**) with methyl vinyl ketone (MVK) in chloroform solution (eq 2), on the basis of the working hypothesis that the catalytic mechanism outlined in Figure 1 would also operate for carbon nucleophiles. The dodecyloxy chains meet the demand for an increased solubility in chloroform, while exerting little or no effect on the Lewis acidity of the uranyl center, on account of the lack of through-resonance interactions between the alkoxy substituents and the imine nitrogens.[9]

Quite surprisingly, the reaction proved to be insensitive to the presence of complex **1b** but was catalyzed to a very remarkable extent by the phenyl derivative **2b**, as shown by typical time−concentration data from ^{1}H NMR analysis (Figure 2). In terms of initial rates, a quantity of **2b** as low as 0.02 molar equiv brings about a 330-fold rate enhancement, which is the highest enhancement recorded in reactions catalyzed by uranyl−salophen complexes. Similar results were obtained with methyl cyclopentan-1-one-2-carboxylate (see Supporting Information, Figure 1S), which was found to react with MVK an order of magnitude more slowly than **3** both in the absence and presence of catalyst **2b**. Thus, the aromatic ring in **3** increases the intrinsic reactivity of the Michael donor, presumably via an acidity enhancing effect, but hardly affects the extent of catalysis.



Much surprise was again caused by the finding that 2-cyclopenten-1-one and 2-cyclohexen-1-one react with **3** some 300 times more slowly than MVK,[12] whereas open chain and cyclic enones undergo thiol addition at very similar rates.[8c] It is very unlikely, therefore, that the Michael addition of eq 2 proceeds via the same mechanism as thiol addition, given that the two reactions respond in a markedly different way to structural variations in metal catalyst and substrate. As to the reaction in which the tertiary base is the sole catalyst, we suggest that the much higher reactivity of open chain enones is to be ascribed to activation of the enone carbonyl through hydrogen bonding[13] with the neighboring, anion-paired countercation, as shown in Figure 3. A necessary prerequisite for concomitant nucleophilic attack at the β-carbon and hydrogen bonding to the carbonyl oxygen is the *s-cis* conformation of the enone reactant, obviously available to MVK, but not to 2-cyclopenten-1-one. The lack of significant reactivity differences between open chain and cyclic enones in thiol addition would indicate that such a concerted mechanism is not feasible in this case, which is in accordance with the mechanistic picture previously proposed for that reaction.[8c]

Insight into the mechanism of the metal-catalyzed reaction was obtained from UV−vis and ^{1}H NMR spectroscopic observations. UV−vis titration experiments (typical titration plots are in Figures 1S and 2S in the Supporting Information) showed that not only MVK but also the β-ketoester reactant **3** and addition product **4** form complexes of definite stability with **2b** (Table 1). Thus in the time course of the reaction, both reactants and product compete for binding to catalyst **2b**.

Investigation by ^{1}H NMR spectroscopy revealed that the situation is made even more complex in the presence of Et_3N, on account of a strong influence of **2b** on the acidity of the

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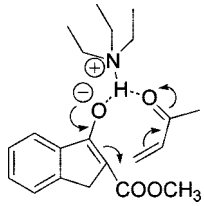

FIGURE 3. Proposed mechanism for the tertiary amine assisted addition of **3** to MVK.

TABLE 1. Association Constants for Complexes between Uranyl−Salophen Receptor 2b and Carbonyl Compounds MVK, 3, and 4 in $CHCl_3$ at 25.0 °C[a]

guest	K (M^{-1})[b]
MVK	84 ± 15
3	28 ± 3
4	49 ± 6

[a] Associations with the parent compound **1b** were in all cases negligibly low. [b] Errors are calculated as $\pm 2\sigma$ (95% confidence limit).

β-ketoester reactant **3** (see Supporting Information, Figures 4S and 5S). The concentration of deprotonated nucleophile is negligibly small in the absence of metal catalyst **2b** (eq 3, Nu-H = **3**) but becomes very significant in its presence (eq 4). Quantification of the acid−base equilibrium in eq 4 was prevented by the complexity of the ^{1}H NMR spectra of ternary mixtures, as well as by the erratic behavior displayed by their UV−vis spectra.[14] Whereas the reaction system does not appear to be amenable to quantitative kinetic analysis on account of the large number of simultaneous equilibria involved, the ^{1}H NMR suggests that the catalyst-bound enolate might be the actual reaction intermediate reacting with the unbound enone, as shown in eq 5. In other words, whereas in thiol addition the catalytic mechanism consists of activation of the enone reactant through complexation with the uranyl−salophen catalyst, in the present reaction the acidity enhancing effect arising from coordination to the metal center increases to a very large extent the enolate concentration and, consequently, the reaction rate. The intermediacy of metal-bound β-dicarbonyl enolates is well documented in transition-metal and lanthanide-catalyzed Michael additions.[15] A bimetallic mechanism involving delivery of a metal-bound nucleophile to a metal-activated electrophile is ruled out by the finding that initial rates of reaction of **3** with MVK display a first-order dependence on **2b** concentration (Figure 4). A bimetallic mechanism would require second-order dependence on catalyst concentration.[16] On the analogy with the concerted mechanism outlined in Figure 3, we speculate that activation of the Michael acceptor might arise from hydrogen bonding between the enone carbonyl and the Et_3NH^+ countercation, bound to the salophen framework by means of cation-π/CH-π interactions,[5e] as well as by means of cation−anion electrostatic attraction (Figure 5).

$$\text{Nu-H} + \text{Et}_3\text{N} \rightleftharpoons \text{Nu}^{\ominus}\cdots\text{H}^{\oplus}\text{NEt}_3 \quad (3)$$

$$\text{cat} + \text{Nu-H} \rightleftharpoons \text{cat-Nu-H} \underset{\text{Et}_3\text{N}}{\overset{\text{Et}_3\text{N}}{\rightleftharpoons}} \text{cat-}\overset{\ominus}{\text{Nu}}\cdots\overset{\oplus}{\text{H}}\text{NEt}_3 \quad (4)$$

$$\text{cat-}\overset{\ominus}{\text{Nu}}\cdots\overset{\oplus}{\text{H}}\text{NEt}_3 + \text{MVK} \longrightarrow \mathbf{4} + \text{cat} + \text{Et}_3\text{N} \quad (5)$$

A last comment is devoted to the comparison with the Diels−Alder addition of benzoquinone to 1,3-cyclohexadiene in chloroform solution that we recently reported[9] to be catalyzed with high turnover efficiency by the phenyl-substituted catalyst

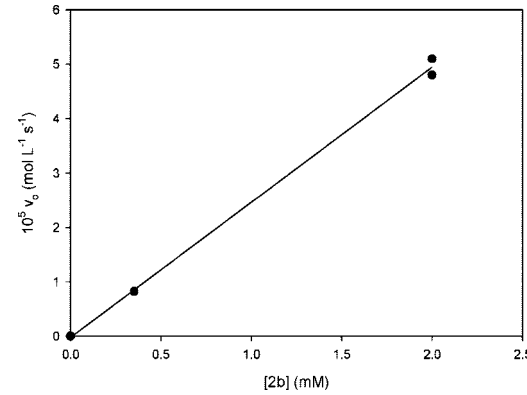

FIGURE 4. Plot of initial rates versus **2b** concentration in $CHCl_3$ at 25 °C. [MVK] = 0.10 M, [**3**] = 0.20 M, and [Et_3N] = 5.0×10^{-3} M in all runs.

2b, but not by the parent compound **1b**. Interestingly, catalyst **2b** showed no appreciable affinity toward reactants and product of the Diels−Alder reaction, at marked variance with the multiple equilibria involved in the catalyzed Michael addition. The two reactions proceed through very different mechanistic pathways—a multistep mechanism involving ionic intermediates in the Michael addition versus a concerted mechanism involving no intermediates in the Diels−Alder reaction—but share the propensity of electrophilic catalysis by metal ions.[15,17] The Lewis acid−base interaction between the uranyl center and substrate carbonyl is not sufficient *per se* for the catalysis to be effective but requires the concurrence of stabilizing van der Waals interactions with the aromatic side arm in both reactions.

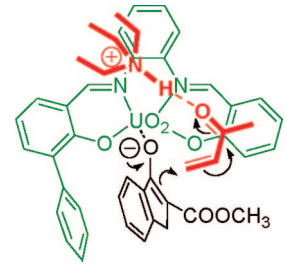

FIGURE 5. Schematic representation of the proposed mechanism for addition of **3** to MVK catalyzed by uranyl−salophen complex **2b**.

In conclusion, to the best of our knowledge, uranyl−salophen compound **2b** is the sole metal complex whose catalytic properties critically depend on the presence of an aromatic pendant proximal to the reaction zone. It is highly remarkable that the two reactions catalyzed by **2b**, namely, Michael addition and Diels−Alder reaction, belong to markedly different mechanistic types. The van der Waals interaction with the aromatic pendant is an effective force for catalysis in both reactions, thus providing examples of supramolecular catalysis with unique features.

Experimental Section

Materials. Methyl vinyl ketone was distilled over calcium hydride prior to use. 2-Cyclopenten-1-one and 2-cyclohexen-1-one

(14) Mixtures of **2b** and **3** showed stable and reproducible UV−vis spectra, but addition of Et_3N caused erratic and irreproducible spectral changes, suggesting the incursion of photoinduced side reactions.

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were used as received. Triethylamine was distilled over *p*-toluenesulfonyl chloride and then over sodium. Spectrophotometric grade chloroform and chloroform-d_1 were dried over 4 Å molecular sieves for at least 24 h prior to use. Compounds **1b** and **2b** were available from a previous work.[9] Methyl 1-oxoindane-2-carboxylate **3** was prepared according to a standard literature procedure[18] and showed spectral data consistent with those already reported.[19]

1-Oxo-2-(3-oxobutyl)indan-2-carboxylic acid methyl ester 4. Methyl vinyl ketone (140 μL, 1.63 mmol) was slowly added to a methanol solution (4 mL) of compound **3** (0.312 g, 1.64 mmol), quinuclidine (0.052 g, 0.47 mmol), and a catalytic amount of Li_2SO_4 at 0 °C. When the addition was complete, the reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for one night, after which time it was poured on 20 mL of water and extracted with 20 mL of diethyl ether. The organic phase was washed twice with 20 mL of 0.1 M HCl and with 20 mL of brine and dried over sodium sulfate. The title compound was obtained as a colorless oil in 94% yield after evaporation of the solvent and showed spectral data consistent with those reported in the literature.[20]

UV−Vis Titrations. Association constants were determined spectrophotometrically according to a previously described procedure.[6b]

^{1}H NMR 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 atmosphere. Calculated amounts of $CDCl_3$ solutions of triphenylmethane (internal standard) and of all of the reactants except the base were introduced into a NMR tube, and a spectrum (either at 200 or 300 MHz, T = 25.0 °C) was recorded at time zero. Then a known amount of base was added, and spectra were recorded at selected time intervals. The intensity of the vinyl resonances of MVK were compared with that of the signal of the internal standard. The disappearance of the enone reactant was accompanied by the equivalent formation of the arene product. No extra peaks due to reaction intermediates and/or side products were observed.

Acknowledgment. We acknowledge MUR, PRIN 2006, for financial support.

Supporting Information Available: Spectrophotometric titrations, ^{1}H NMR spectra of mixtures of **2b**, **3**, and Et_3N and of **3** and Et_3N in $CDCl_3$, plot of initial rates versus **2b** concentration, ^{1}H NMR spectrum of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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