Exclusive transition state stabilization in the supramolecular catalysis of Diels–Alder reaction by a uranyl salophen complex†

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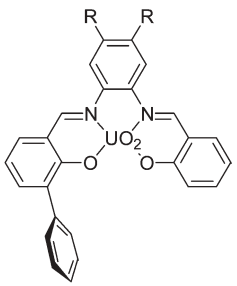
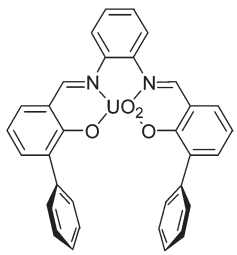
Whereas the parent uranyl salophen is catalytically inactive, its phenyl derivative effectively catalyses with turnover the reaction of benzoquinone with 1,3-cyclohexadiene, while showing no appreciable affinity towards reactants and product.

Disclosing the mechanism of enzyme catalysis has revealed that enzymes form complexes of definite stability with their substrates, and that the catalytic event takes place in the confines of the enzyme–substrate complex. It is no wonder, therefore, that since Cramer's very early investigations of the enzyme-like catalytic properties of cyclodextrins in the fifties,[1] research into supramolecular catalysis has been either explicitly or implicitly dominated by the notion that strong binding between catalyst (host) and substrate (guest) is a prerequisite for efficient catalysis. Indeed, the very existence of saturation kinetics resulting from noncovalent binding of substrate to catalyst is generally viewed as a convincing mimicry of the Michaelis–Menten kinetics typical of enzyme catalysis. Yet, a straightforward application of transition state theory has made it clear that catalysis is the result of a differential binding of the catalyst to the transition state and the reactant(s).[2] As pointed out by Schowen in a lucid analysis of catalytic power and transition state stabilization, the binding of the transition state produces catalysis, whereas inhibition arises from the binding of other species (reactants and products).[3] In a sense, therefore, an ideal catalyst is one in which a high affinity for the transition state is accompanied by a negligible affinity for the reactant(s) and product(s). It should be admitted that catalysts displaying such a behavior are rare even in nature. Here we report that the metal catalyst **1b** behaves in such an ideal way, in that it binds strongly to the transition state of a Diels–Alder reaction and negligibly so to reactants and product.

In previous works[4] we used uranyl–salophen complex **2** as a metallocleft receptor to achieve catalysis with a high turnover efficiency in the 1,4-thiol addition to enones. For example, benzenethiol reacts with complex **2** with 2-cyclopenten-1-one 420 times more rapidly than with uncomplexed 2-cyclopenten-1-one. The driving force for complexation results from a combination of a Lewis acid–base interaction of the carbonyl oxygen with the uranyl centre in its equatorial plane, and stabilizing van der Waals interactions with the cleft walls, as indicated by the data in Table 1.



1a R = H
1b R = $OC_{12}H_{25}$



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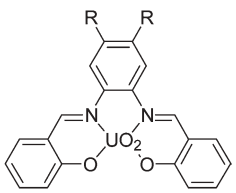

3a R = H
3b R = $OC_{12}H_{25}$

To further explore the catalytic potential of uranyl–salophen compounds, we turned our attention to Diels–Alder additions of enone dienophiles, in view of their synthetic value and well known sensitivity to Lewis acid catalysis.[5] However, it was felt that the enone dienophile, when buried into the cleft of **2**, would hardly be accessible to an external diene. Therefore, we resorted to compound **1b** where the long alkyl chains meet the demand for an increased solubility compared with that of **1a**. The Lewis acidity of the uranyl group is little affected by the alkoxy substituents, as shown by the fact that 2-cyclopenten-1-one binds to **1a** and **1b** with comparable affinities (see footnote *a* to Table 1). This is consistent with the lack of through-resonance interactions between the alkoxy substituents and the imine nitrogens. The choice of the "half-cleft" compound **1b** was based on the finding that **1a** binds to ketones with affinities comparable to those of **2** (Table 1).[6] The underlying idea was that substrate binding would be favored by

Table 1 Binding constants (K/M^{-1}) of complexes of ketones with uranyl–salophen compounds in chloroform at 25 °C (from ref. 6)

Ketone	**3a**	**2**	**1a**
cyclopentanone	<3	140	260
2-cyclopenten-1-one	14	460	870[a]

[a] The equilibrium constant for binding of 2-cyclopenten-1-one to **1b** under the same conditions is 820 ± 60 M^{-1} (this work).

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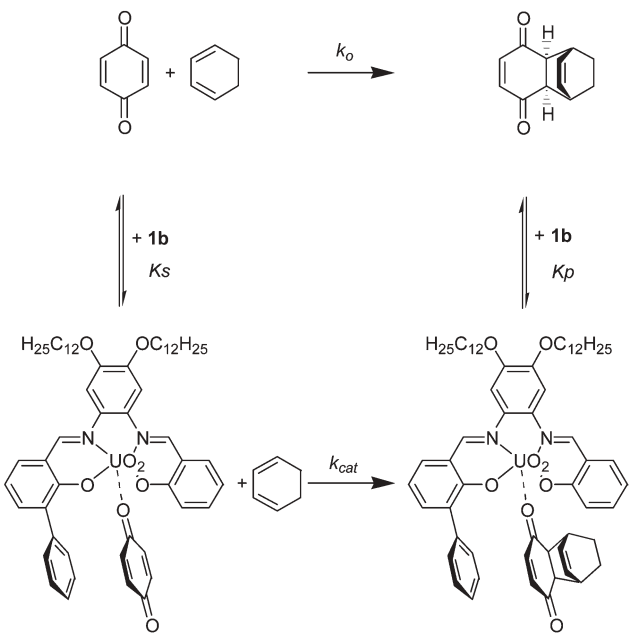
† Electronic supplementary information (ESI) available: synthesis of compounds **1b** and **3b** and calculated geometry of the transition state of the uncatalysed Diels–Alder reaction. See http://dx.doi.org/10.1039/b504713g

interaction of the phenyl substituent in **1b** with one face of the complexed enone, whereas the other face would be available for reaction with the diene. This is illustrated in Scheme 1 for the reaction of benzoquinone with 1,3-cyclohexadiene, which affords the *endo* adduct as the sole detectable product in quantitative yield.[7] This reaction was chosen as the test reaction because its rate could be conveniently monitored at room temperature by ^{1}H NMR spectroscopy.

The results were disappointing at first, as no evidence was found by ^{1}H NMR and UV-vis spectroscopy for the expected complexation of the quinone reactant and reaction product with the sidearmed compound **1b**, as well as with the parent compound **3b**. Yet, the rate of addition of the quinone to the diene was significantly enhanced by the presence of **1b**, whereas **3b** had a negligible influence (Fig. 1). Time–concentration data recorded in the presence of catalyst **1b**, like in its absence, showed in all cases a close adherence to the standard second-order rate equation, with second-order rate constants k_{obs} independent of a four-fold variation in initial quinone concentration (Table 2, entries 1–3 and 5–7). Thus, the kinetics are consistent with a lack of significant association of the catalyst with the reactant enone and the addition product, as well as with the diene. The linearity of the plot of k_{obs} against catalyst concentration (Fig. 2) shows that the catalyzed reaction is an overall third-order process, first-order in each reactant and catalyst. This is in accordance with eqn. (1), which is easily derived from Scheme 1 and applies whenever the fraction of catalyst sequestered by any of the components of the reaction mixture is negligibly small. The numerical value of the third-order rate coefficient $k_{cat}K_S$ is equal to the slope of the straight line in Fig. 2, but the individual factors remain unknown. Thus, eqn. (1) is of limited utility in a discussion of the catalytic mechanism. According to the transition state theory,[2] the quantity $K_T^{\ddagger}$ defined by eqn. (2) has the meaning of the equilibrium constants for the complexation of the catalyst-free transition state $T^{\ddagger}$ to one



Scheme 1 Diels–Alder addition of benzoquinone to 1,3-cyclohexadiene. Complexation catalysis involving noncovalent binding of benzoquinone to catalyst **1b**.

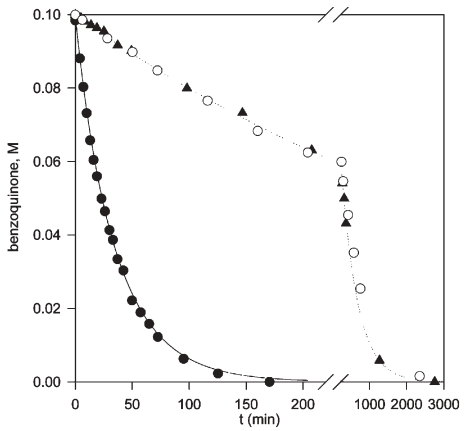


Fig. 1 Diels–Alder addition of benzoquinone to 1,3-cyclohexadiene in $CDCl_3$ at 25 °C. The dienophile is 0.1 M and the diene is 0.7 M. Time–concentration profiles correspond to the entries given in Table 1: ○ uncatalysed reaction, entry 2; ▲ in the presence of **3b**, entry 4; ● in the presence of **1b**, entry 6. The points are experimental and the curves are plots of the second-order rate equation.

Table 2 Kinetic data for the Diels–Alder addition of benzoquinone to 1,3-cyclohexadiene in $CDCl_3$ at 25 °C[a,b]

Entry	Quinone/M	Catalyst/mM	$10^5\ k_{obs}/M^{-1}\ s^{-1}$
1	0.074	none	5.4 ± 0.2
2	0.100		5.0 ± 0.3
3[c]	0.331		5.22 ± 0.04
4	0.100	**3b**, 18.9	5.5 ± 0.1
5	0.051	**1b**, 19.4	71 ± 1
6	0.098	19.1	72 ± 2
7	0.200	19.4	71 ± 1
8	0.099	9.2	37 ± 1
9	0.098	5.6	25.4 ± 0.4

[a] Based on ^{1}H NMR spectra of the reaction mixture, unless otherwise stated. The disappearance of the dienophile at δ = 6.78 ppm and the appearance of the adduct at δ = 6.64 ppm were monitored at selected time intervals. [b] In all experiments the initial concentration of 1,3-cyclohexadiene was in the range 0.68–0.90 M. Experimental errors were calculated as $\pm 2\sigma$. [c] From UV-vis measurements at λ = 347 nm. Erratic results were obtained in the presence of uranyl–salophen compounds, possibly due to photoinduced reactions.

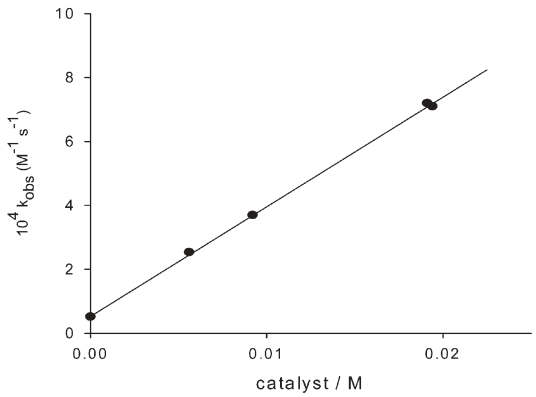


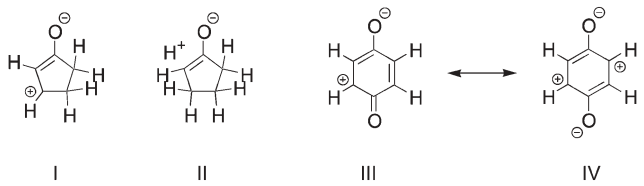
Fig. 2 Plot of k_{obs} *versus* concentration of catalyst **1b** (data from Table 1). The slope of the straight line is 3.43×10^{-2} and the intercept is 5.2×10^{-5}.

containing one molecule of catalyst, $T^{\ddagger}$·cat. From the ratio of the slope to the intercept of the straight line in Fig. 2 one obtains $K_T^{\ddagger} = 660\ M^{-1}$, which is a measure of the affinity of catalyst **1b** towards the transition state. In terms of eqn. (2), understanding why **1b** catalyses the reaction of benzoquinone with 1,3-cyclohexadiene, whereas **3b** does not, largely resolves itself into questions of why the transition state forms a complex of significant stability with **1b**, but not with **3b**, and why neither **3b** nor **1b** bind to the benzoquinone reactant to an appreciable extent.

$$k_{obs} = k_o + k_{cat}K_S[cat] \quad (1)$$

$$K_T^{\ddagger} = K_S(k_{cat}/k_o) \quad (2)$$

An important factor at play is the Lewis basicity of the carbonyl oxygen. The finding that 2-cyclopenten-1-one binds more strongly than cyclopentanone to the parent uranyl–salophen compound **3a** (Table 1), in which no sidearm is present, argues in favor of the stronger Lewis basicity of the former. This indicates that conjugation with the double bond in 2-cyclopenten-1-one, structure I, is more important than hyperconjugation in cyclopentanone, structure II.[8] If we now consider the canonical structures that can be drawn for benzoquinone, we see that III is strongly destabilized by the presence of a positive charge adjacent to an electron-withdrawing carbonyl, whereas IV is antiaromatic. Thus, qualitative valence-bond theory suggests a very low basicity of the carbonyl oxygens of benzoquinone. In fact, the basicity is so low that, unlike cyclopentanone, no significant complexation is observed even in the presence of a potential stabilizing interaction with the sidearm in **1b**. On the other hand the sidearm is essential for the catalysis, since no catalysis is seen with **3b**. ESP charges calculated on the B3LYP/6-31G* optimized geometry indicate that in the transition state the benzoquinone moiety gains a negative charge of about 0.22 au, a major share of which is taken by the carbonyl groups. This rules out the possibility that the aromatic sidearm is involved in dynamic binding, *i.e.*, in a stabilizing interaction that is stronger at the transition state level.[9] Such an interaction should either decrease during the activation process or remain constant at best. We conclude therefore that the only possible source of dynamic binding is the interaction of the uranyl centre with one of the benzoquinone oxygens, whose Lewis basicity increases during the activation process as a result of the transfer of negative charge from the diene. This interaction, however, is not sufficient *per se* to impart appreciable stability to the transition state complex for which the concurrence of the passive binding[9] provided by the aromatic sidearm is necessary. Thus, compound **1b** behaves as a supramolecular Lewis acid catalyst, in that weak interactions with the sidearm are utilized in the catalysis.



In conclusion, neither the reactant(s) nor the addition product are good models for the transition state of the Diels–Alder reaction at hand, as long as interactions with catalyst **1b** are concerned. This is clearly at variance with Diels–Alder catalysis by antibodies[10] in which shape complementarity instead of electronic complementarity is exploited for eliciting effective catalysis. When combined with our recent discovery of inherently chiral uranyl–salophen complexes,[11] the results of the present work offer the prospect of exploiting such complexes as catalysts of enantioselective Diels–Alder reactions of prochiral enones.

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