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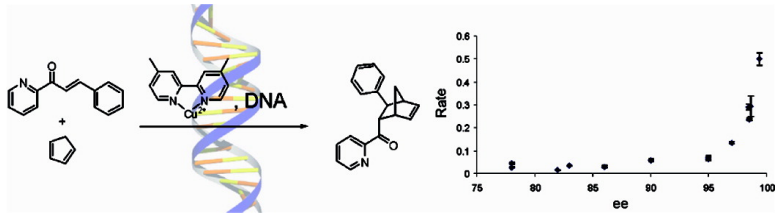

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DNA-Based Asymmetric Catalysis: Sequence-Dependent Rate Acceleration and Enantioselectivity

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Abstract: This study shows that the role of DNA in the DNA-based enantioselective Diels−Alder reaction of azachalcone with cyclopentadiene is not limited to that of a chiral scaffold. DNA in combination with the copper complex of 4,4′-dimethyl-2,2′-bipyridine (Cu−L1) gives rise to a rate acceleration of up to 2 orders of magnitude compared to Cu−L1 catalysis alone. Furthermore, both the enantioselectivity and the rate enhancement prove to be dependent on the DNA-sequence. These features are the main reasons for the efficient and enantioselective catalysis observed with salmon testes DNA/Cu−L1 in the Diels−Alder reaction. The fact that absolute levels of stereocontrol can be achieved with a simple and weak DNA-binding complex like Cu−L1 is a clear demonstration of the power of the supramolecular approach to hybrid catalysis.

Introduction

The concept of hybrid catalysis, in which catalytically active transition metal complexes are bound to biopolymer scaffolds, has proven to be remarkably versatile.[1] The chiral microenvironment that is created by binding of the transition metal cofactor to the biopolymer makes it possible to direct the catalyzed reaction toward one enantiomer of a chiral product, thus resulting in an enantiomeric excess. An attractive feature of the hybrid approach is that the biopolymer scaffold and the transition metal catalyst can be optimized independently by genetic, evolutionary, and synthetic methods.[2] Using proteins as the scaffold, a large variety of artificial metalloenzymes have been created. Enantioselective transformations that have been realized using this approach include hydrolyses,[3] hydrogenations,[4] transfer hydrogenations,[2a,5] allylic alkylations,[6] sulfoxidations,[7] epoxidations,[8] dihydroxylations,[9] Diels−Alder reactions,[10] and transaminations.[11] In many cases, the protein scaffold not only confers stereocontrol to the reaction, but also affects the reaction rate. Comparison of the available data shows that the kinetic effect can be either negative or positive; in some cases, the reaction is slower when the catalyst resides in the protein matrix,[10a,12] whereas in other cases, significant rate accelerations have been observed.[7b,c,13] Often this is even substrate-dependent,[12] consistent with the notion of an enzyme active site that prefers binding of some substrates over others or that is structurally compatible with certain activated complexes only.[14]

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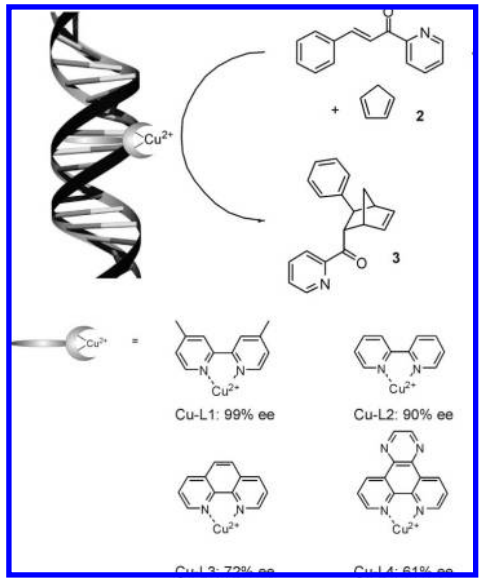
Scheme 1. Cu−L$(NO_3)_2$/DNA Catalyzed Diels−Alder Cycloaddition between **1** and **2**



Oligonucleotides have also been demonstrated to be versatile chiral scaffolds for enantioselective synthesis and catalysis.[15] Recently, we have introduced the concept of DNA-based asymmetric catalysis.[16] This involves the modular assembly of a DNA-based catalyst from natural duplex DNA, usually salmon testes DNA (st-DNA), and a copper complex of a nonchiral ligand that can bind to DNA. The first generation of copper complexes were based on ligands comprising a DNA-binding acridine moiety attached via a linker to a copper binding moiety. Using this design, enantioselectivities of up to 50% were obtained in the Diels−Alder reaction between azachalcone **1** and cyclopentadiene (**2**) in water (Scheme 1). The introduction of bipyridine-type ligands resulted in a dramatic increase in the enantioselectivity; up to 99% ee of the (+) enantiomer was obtained in the same reaction using the copper complex of 4,4′-dimethyl-2,2′-bipyridine (dm-bpy, L1).[17] The scope of this second generation of DNA-based catalysts has been extended beyond Diels−Alder reactions. Up to 99% ee was obtained in the DNA-based catalytic Michael addition reactions of malonates and nitromethane to α,β-unsaturated 2-acyl imidazoles and enantioselectivities up to 74% were reported for catalytic asymmetric fluorination reactions with the same catalytic system.[18,19] Both the Diels−Alder reaction and the Michael addition have been performed at synthetically relevant scales, and it was demonstrated that the catalyst solution can be recycled for subsequent transformations without a significant decrease of the yield or a loss of enantioselectivity.

In the course of our research, two observations suggested that DNA positively affects the rate of the Diels−Alder reaction of **1** with **2**. First, quenching of the reaction in the early stages, i.e., after a few hours, consistently showed a higher conversion of **1** when DNA was present. Second, the binding constants of the copper complexes Cu−L(1−3) to DNA are in the range of 10^3-10^4 M^{-1}. This means that under the reaction conditions, a significant fraction (≥5%) of the Cu^{2+} complex is not bound and, hence, catalyzes the reaction to produce the racemic products. Therefore, to achieve enantioselectivities up to 99%, the DNA-bound complex has to be a more efficient catalyst than the unbound complex.

Table 1. k_{app} of the Diels-Alder Reaction of **1** with **2** Catalyzed by Copper Complexes Cu−L(1−3) with and without st-DNA[a]

		k_{app} ($M^{-1}s^{-1}$)		
entry	complex	without st-DNA	with st-DNA[b]	rate acceleration ($k_{app,with\ DNA}/k_{app,w/o\ DNA}$)
1	Cu−L1	0.0069 ± 0.0003	0.40 ± 0.04	58
2	Cu−L2	0.0092 ± 0.0004	0.022 ± 0.001	2.4
3	Cu−L3	0.010 ± 0.001	0.023 ± 0.001	2.3
4	$Cu(NO_3)_2$	0.095 ± 0.006	0.040 ± 0.004	0.4

[a] [Cu−L] = 0.15 mM, 25.0 °C, MOPS buffer (20 mM, pH = 6.5), [**1**] = 6.0×10^{-3} mM, [**2**] = 0.5 − 2.0 mM. [b] Ratio of Cu−L to base pairs DNA 1:6.

The remarkable selectivities reached in this DNA-based asymmetric catalysis in water provided a strong incentive to focus our recent investigations on gaining a better understanding of the mechanistic aspects of the DNA-based catalytic asymmetric Diels−Alder reaction and, in particular, on the role that DNA plays in these reactions. The goal of this research was 2-fold: (1) to study the effect of DNA on the reaction rate, and (2) to determine the effect of the sequence of the DNA in which the copper complex resides. Herein, we will demonstrate that the presence of DNA results in a significant rate enhancement and that the DNA sequence has a significant effect on both the enantioselectivity and the reactivity, i.e., DNA sequences that induce the highest enantioselectivity also cause the largest rate enhancement.

Results and Discussion

Effect of st-DNA on the Reaction Rate. From the initial decrease in absorption of **1**, the apparent second-order rate constants (k_{app}) of the Diels−Alder reaction were determined. Comparison of the k_{app} values of the complexes based on L1−L3 in the absence of st-DNA revealed that all complexes react slower than free $Cu(NO_3)_2$ and that there are only minor differences between the different complexes (Table 1). In the presence of st-DNA, the reaction with $Cu(NO_3)_2$, which gives 10% ee of the (−) enantiomer,[16] is slower, whereas a modest 2-fold rate increase was observed for Cu−L2 and Cu−L3. Surprisingly, a much more pronounced effect was found in the case of Cu−L1, i.e., a 58-fold rate increase. The results show that the Cu−L1/DNA catalyst is also significantly faster than free $Cu(NO_3)_2$. Compared to L2, the only differences in the structure of ligand L1 are the 4- and 4′-methyl substituents. Yet, these methyl groups, which cannot interact with the substrates directly because they are remote from where the reaction occurs, appear to be a crucial factor in the design of the most active and enantioselective DNA-based catalyst.

The reaction catalyzed by Cu−L1/st-DNA was studied in more detail using the methods developed by Engberts et al.[20] Three parameters contribute to the overall rate of the reaction: the equilibrium constant (K_a) for the reversible binding of **1** to

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Scheme 2. Proposed Catalytic Cycle of the Cu^{2+} Catalyzed Diels-Alder Reaction of **1** with **2**[20]

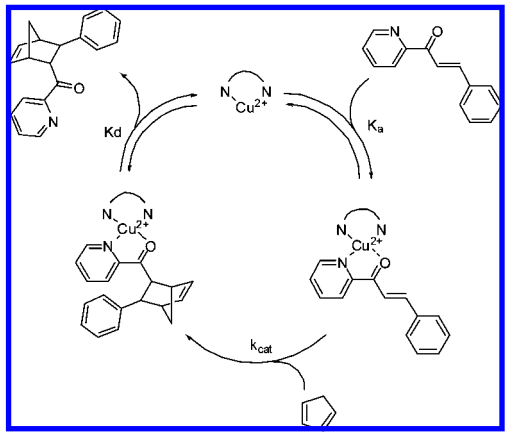
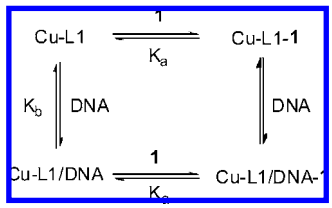


Table 2. Kinetic and Thermodynamic Parameters: K_a, k_{cat}, $k_{(-)}$, $k_{(+)}$, and the Isobaric Activation Parameters at 298 K[a,b]

	Cu−L1	Cu−L1/st-DNA[c]
K_a (M^{-1})	$(4.0 \pm 0.8) \times 10^2$	$(5.0 \pm 1.4) \times 10^2$
k_{cat} ($M^{-1}s^{-1}$)	$(4.5 \pm 1.2) \times 10^{-2}$	3.8 ± 0.8
$k_{(-)}$ ($M^{-1}s^{-1}$)	$(2.2 \pm 0.6) \times 10^{-2}$	$(5.8 \pm 1.2) \times 10^{-2}$
$k_{(+)}$ ($M^{-1}s^{-1}$)	$(2.2 \pm 0.6) \times 10^{-2}$	3.8 ± 0.8
$\Delta G^{\ddagger}$ (kcal/mol)	21 ± 1	18 ± 1
$\Delta H^{\ddagger}$ (kcal/mol)	10 ± 1	3.1 ± 0.5
$T\Delta S^{\ddagger}$ (kcal/mol)	-11 ± 1	-15 ± 1

[a] [Cu−L] = 0.10 − 0.25 mM, 25.0 °C, MOPS buffer (20 mM, pH = 6.5). [**1**] = 6.0×10^{-3} mM, [**2**] = 0.5 − 2.0 mM. [b] Conditions determination isobaric activation parameters; [Cu−L] = 0.1 mM, 25.0 °C, MOPS buffer (20 mM, pH = 6.5). [**1**] = 6.0×10^{-3} mM, [**2**] = 0.5 − 2.0 mM. See Supporting Information for the corresponding Eyring plots. [c] Fixed ratio of Cu-L1 to base pairs DNA 1:6.

Scheme 3. Possible Equilibria of **1** and Cu−L1 Involved in the Presence of DNA



the Cu^{2+} complex, the rate of the reaction of **2** with Cu^{2+}-bound **1** (k_{cat}), and the dissociation constant (K_d) for the release of **3** from the copper complex (Scheme 2). The kinetic studies were performed using a large excess of Cu−L1 with respect to **1**, which means that the K_d will not influence the overall rate (k_{app}). Consequently, a decrease in product inhibition can be excluded as a reason for the observed increase in k_{app} in the presence of st-DNA. The K_a was determined independently in titration experiments. From the K_a and the k_{app} values obtained at different concentrations of Cu−L1 the k_{cat} was determined (Table 2).[21] In principle, the determination of K_a in the presence of DNA is complicated by the fact that multiple binding equilibria are involved (Scheme 3); in addition to binding to Cu−L1/DNA, **1** can also bind to free Cu−L1, followed by binding of the resulting complex Cu−L1−**1** to DNA.

(21) Because **1** also has interactions with st-DNA, the absorption of **1** should also change upon addition of increasing amounts of st-DNA. The change in absorption of **1** was measured upon addition of st-DNA, and it was found that the difference is neglible with respect to the differences measured in the presence of a copper complex.

However, Scheme 3 can be simplified by the assumption that only the equilibrium of **1** binding to Cu−L1/DNA contributes significantly to the observed K_a. This is justified since it is easily rationalized that the concentration of Cu−L1−**1** is not significant at the concentrations employed. In view of the observed binding constants of Cu−L1 to DNA, it can be calculated that, at the concentrations employed, 95% of the copper complex is bound to st-DNA and only 5% of the Cu^{2+} is present as unbound Cu−L1 complex. The K_a of the binding of **1** to Cu−L1 in the absence of DNA is 4.0×10^2 M^{-1} (vide infra). In the presence of DNA, the concentration of unbound Cu−L1 is $\leq 1.3 \times 10^{-2}$ mM, making the amount of copper present in solution as Cu−L1−**1** insignificant.[22] Hence, it can be assumed that the experimentally determined K_a corresponds predominantly to the binding of **1** to Cu−L1/DNA.

From the data (Table 2) it is clear that the K_a does not change significantly due to the presence of st-DNA but that the k_{cat} is increased by 2 orders of magnitude. This means that the observed increase in reaction rate is not due to an increase of the affinity of **1** for the DNA-bound copper complex but rather that the Diels−Alder reaction is accelerated due to the presence of st-DNA. This result demonstrates that st-DNA provides not only a chiral microenvironment for the reaction, but also increases the reactivity in the Diels−Alder transformation using Cu−L1.

On the basis of the ee value obtained in the reaction at 25 °C, the k_{cat} was split into the rates leading to the minor (−), and major (+) enantiomers, i.e. $k_{(-)}$ and $k_{(+)}$, respectively.[23] It follows that the rate increase originates mainly from an increase of the rate leading to the major enantiomer and that the rate leading to the minor enantiomer did not change significantly in the presence of DNA.

The activation parameters were obtained from an Eyring plot of the apparent rate constant (k_{app}) measured at temperatures ranging from 288 to 308 K.[24,25] In the absence of DNA, the enthalpy and entropy of activation contribute equally to the Gibbs energy of activation (Table 2). The rate acceleration observed in the presence of st-DNA is the result of a decrease in the $\Delta H^{\ddagger}$, which is partially compensated by a negative effect on $\Delta S^{\ddagger}$. A similar pattern has been observed before in antibody catalyzed Diels−Alder reactions[26] and 1,3-dipolar cycloadditions.[27] In the case of the antibody catalyzed Diels−Alder reaction, transition-state stabilization due to chemical and shape complimentarity has been put forward as an explanation.[28] Even though the activation parameters for the DNA-based catalysis have been determined from a complex rate constant (k_{app}), which includes contributions from both k_{cat} and K_a, the unfavorable effect on the $\Delta S^{\ddagger}$ suggests that rate acceleration due to classical

(22) With the assumption that the binding of **1** to Cu-L1 outside the DNA is not influenced by the presence of DNA.
(23) See Supporting Information for the calculation of $k(-)$ and $k(+)$ from the ee and the k_{cat}.
(24) The binding affinity of Cu-L1 to DNA did not change significantly within this temperature window: K_b (288 K) = $(6.40 \pm 0.34) \times 10^3$ M^{-1}, K_b (308 K) = $(5.20 \pm 0.40) \times 10^3$ M^{-1}.
(25) This temperature window was selected because of experimental constraints. See also Supporting Information and Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241−4246.
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Table 3. Dependence of the ee on the DNA Sequence in the Case of Cu−L1

entry	oligonucleotide	T_m (ΔT_m with Cu-L1) (°C)	K_b[a] (DNA)/M^{-1}	ee (%)[b,c]	k_{app}[d] ($M^{-1}s^{-1}$)
1	no DNA			<5	$(5.05 \pm 0.07) \times 10^{-3}$
	double stranded DNA:				
2	st-DNA	63.0 (−0.5)	7.26×10^3	98.5 (+)	$(2.37 \pm 0.05) \times 10^{-1}$
3	poly d(AT):poly d(AT)		n.d.[e]	15 (−)[g]	
4	poly d(GC):poly d(GC)		n.d.[f]	78 (+)[h]	
5	$d(GCGCGCGC)_2$	38.0 (−1.0)	9.42×10^3	86 (+)	$(2.98 \pm 0.38) \times 10^{-2}$
6	$d(GCGCGCGCGCGC)_2$	45.5 (−6.0)	8.37×10^3	95 (+)	$(6.45 \pm 0.84) \times 10^{-2}$
7	$d(GACTGACTAGTCAGTC)_2$	33.0 (−2.0)	9.55×10^3	78 (+)	$(4.44 \pm 0.32) \times 10^{-2}$
8	$d(CAGTCAGTACTGACTG)_2$	32.5 (−0.5)	1.26×10^4	83 (+)	$(3.39 \pm 0.05) \times 10^{-2}$
9	$d(TCGCGATCGCGA)_2$	35.0 (−6.0)	1.17×10^4	78 (+)	$(2.67 \pm 0.11) \times 10^{-2}$
10	$d(TCGCGTACGCGA)_2$	34.0 (−5.5)	1.31×10^4	82 (+)	$(1.49 \pm 0.05) \times 10^{-2}$
11	$d(TCGGAATTCCGA)_2$	23.0 (−1.5)	1.33×10^4	90 (+)	$(5.75 \pm 0.52) \times 10^{-2}$
12	$d(TCGGTTAACCGA)_2$	22.0 (−2.5)	1.15×10^4	95 (+)	$(7.03 \pm 0.97) \times 10^{-2}$
13	$d(TCGGGATCCCGA)_2$	28.0 (−4.5)	1.35×10^4	98.4 (+)	$(2.92 \pm 0.13) \times 10^{-1}$
14	$d(TCGGGTACCCGA)_2$	27.0 (−4.5)	1.32×10^4	98.6 (+)	$(2.94 \pm 0.44) \times 10^{-1}$
15	$d(TCAGGGCCCTGA)_2$	30.0 (−5.0)	9.59×10^3	99.4 (+)	$(5.00 \pm 0.27) \times 10^{-1}$
16	$d(AGGGCCCT)_2$	28.0 (−4.0)	5.90×10^3	97 (+)	$(1.35 \pm 0.05) \times 10^{-1}$
	Single stranded DNA:				
17	dNTP			18 (+)	$(2.50 \pm 0.10) \times 10^{-3}$
18	d(GGG)			<5 (+)	
19	d(CCC)			<5 (+)	
20	d(TCAGGGCACT)			81 (+)	$(4.87 \pm 0.09) \times 10^{-3}$

[a] Determined at 18 °C, error <5% in all cases, [b] The 0.3 mM Cu-L1, 2 mM base pairs DNA, in MOPS buffer (20 mM, pH 6.5), at 5 °C. One mM **1**, and 8 mM **2**. The ee values are the average of two experiments, >80% conversion to **3** after 60 h unless noted otherwise, [c] Endo:exo >98:2. [d] Performed under standard kinetic conditions. [Cu−L1] = 0.10 mM, [**1**] = 6.0×10^{-3} mM, [**2**] = 1.5 mM, temperature 18.0 °C. All measurements were performed 3×. [e] Not determined because a new complex was formed according to UV−vis spectroscopy. [f] Not determined because an irregular change in absorption was observed upon titration of oligomer. [g] Conversion 7%. [h] Conversion 15%.

hydrophobic interactions is unlikely.[29] The observed pattern has been noted for nonclassical hydrophobic interactions,[30] which could imply that favorable arene−arene interactions of the activated complex with the nucleobases play a role.

Effect of DNA Sequeence. Salmon testes DNA is a polymer of high molecular weight and, for the purpose of this study, its sequence can be considered to be random. Loadings of up to 1 complex per 6 base pairs have been used in the catalytic experiments, which means that the DNA-based catalyst is in fact a heterogeneous mixture of Cu−L1 complexes that are all residing in a different chiral microenvironment. The effect of the structure of this microenvironment on the activity and selectivity of the catalyst was investigated by using synthetic oligonucleotides of defined sequences. A set of self-complimentary oligonucleotides was selected that covered a large range of sequences; 16-mers $d(GACTGACTAGTCAGTC)_2$ and $d(CAGTCAGTACTGACTG)_2$, alternating dGC sequences of different length, and poly d(AT):poly d(AT). Furthermore, variations of the sequence $d(TCGGGATCCCGA)_2$ were tested by systematic variation of the central AT base pairs and the size of the G-tract. The latter sequence has been the subject of an NMR study by Collins et al.,[31] and it was observed that small cationic metal complexes bind either to the G-trimer or to the central AT base pairs.

The melting temperatures of the corresponding duplexes were in the range of 22 to 35 °C (Table 3). In the presence of Cu−L1 the melting temperatures decreased slightly, indicating that the duplexes are destabilized by binding of Cu−L1. Molecules that bind DNA strongly via an intercalative binding mode often increase the melting temperature.[32] Indeed, this was observed for Cu−L4,[33] which has been established to bind via intercalation.[34] This suggests that intercalation may not be the dominant binding mode for Cu−L1. From the data, it can be concluded that all the employed oligonucleotides exist as duplexes at the temperatures of the physical measurements as well as the catalysis, i.e., 18 °C and 5 °C, respectively.

The binding affinities of Cu−L1 to the different DNA's (K_b), with the exception of poly d(AT):poly d(AT) and poly d(GC):poly d(GC) (vide infra), were similar to those obtained for st-DNA. The measured K_b's were all in the same range, i.e., 10^3-10^4 M^{-1} and no apparent sequence-selectivity was found. Hence, the presence of more or less unbound complex can be excluded as the origin for the observed differences in enantioselectivity.

Significant enantioselectivities were obtained with all synthetic duplexes that were tested in the Cu−L1 catalyzed Diels−Alder reaction (Table 3). However, the enantioselectivity and the absolute configuration of the Diels−Alder product proved to be highly dependent on the sequence. Poly d(GC):poly d(GC) gave rise to a decreased ee, compared to st-DNA, whereas poly d(AT):poly d(AT) resulted in a low ee of the (−) enantiomer of the product (entries 3 and 4). Furthermore, in both cases, low conversions were obtained, which could be due to a decreased binding affinity of the complexes to the DNA,[35]

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(33) See Supporting Information for the catalysis experiments and binding affinities of Cu-L2 and Cu-L4 with synthetic oligomers.
(34) Navarro, M.; Cisneros-Fajardo, E. J.; Sierralta, A.; Fernández-Mestre, M.; Silva, P.; Arrieche, D.; Marchán., E. *J. Biol. Inorg. Chem.* **2003**, *8*, 401–408.
(35) It was not possible to determine the K_b of the binding of Cu-L1 to poly d(GC):poly d(GC) due to the small bathochromic shift in the absorption of the complex induced by poly d(GC):poly d(GC).

or complexation of the base pairs to the copper.[36] Full conversion and good ee's were obtained with shorter alternating GC sequences, although the ee was lower with the shorter sequence (entries 5 and 6).

The sequences d(GACTGACTAGTCAGTC)$_2$ and d(CAGTCAGTACTGACTG)$_2$ gave rise to enantioselectivities around 80% (entries 7 and 8). With the first generation of catalysts, which contain the acridine-based ligands, enantioselectivities comparable to those achieved with salmon testes were obtained with d(GACTGACTAGTCAGTC)$_2$.[16] These observations underline that the first and second generation of catalysts have different requirements regarding the DNA structure. The other sequences containing an alternating pyrimidine-purine motif, i.e., d(TCGCGATCGCGA)$_2$ and d(TCGCGTACGCGA)$_2$, also gave enantioselectivities around 80% (entries 9 and 10). The presence of two consecutive G's resulted in an increase of the ee to 90−95% (entries 11 and 12). Extension of this G-tract to three G's led to enantioselectivities comparable to those obtained with salmon testes DNA (entries 13 and 14). Finally, removal of the central AT base pairs led to an improvement of the ee to >99% (entry 15). Hence, it can be concluded that the presence of G-tracts is important to achieve the highest enantioselectivities. When the length of the oligonucleotide was reduced from a dodecamer to an octamer, the ee dropped slightly to 97% (entry 16).

The apparent rate constants (k_{app}) were determined for all oligonucleotide/Cu−L1 combinations (Table 3) at a concentration of 0.10 mM Cu−L1. Compared to Cu−L1 alone, i.e., in the absence of DNA, >10-fold increases in k_{app} were found for all the oligonucleotides. The highest reaction rate was observed with d(TCAGGGCCCTGA)$_2$; a 100-fold increase compared to Cu−L1 without DNA (entry 1), and a 2-fold increase compared to st-DNA. In addition, this oligonucleotide also provided the highest enantioselectivity, i.e., an enantiomeric excess of 99.4%, which is also higher than what was obtained with st-DNA. Further analysis of the data revealed the existence of a relationship between the enantioselectivity and the k_{app} of the Diels−Alder reaction (Figure 1A). The double stranded oligonucleotide/Cu−L1 combinations showing the highest enantioselectivity invariably also gave rise to the largest rate accelerations.

A linear correlation was found between the log k_{app} and the difference in $\Delta G^{\ddagger}$ toward each of the two enantiomers (Figure 1B). The results with st-DNA also fit this trend. Clearly, the microenvironment in which Cu−L1 resides influences the reaction since it affects both the rate and the enantioselectivity.

Single-Stranded DNA. From these results, it is not obvious that the DNA duplex structure is required to achieve rate enhancement and enantioselectivity. Therefore, a small series of DNA sequences not capable of forming duplex DNA were examined (Table 3). The use of single nucleotides, i.e., a mixture of dNTP's, resulted in an ee of 18% (entry 17). However, the reaction rate proved to be lower than Cu-L1 in the absence of DNA. Most likely the nucleobase competes with the azachalcone for binding to Cu^{2+}. Single stranded G and C-tracts resulted only in trace amount of racemic product (entries 18 and 19).

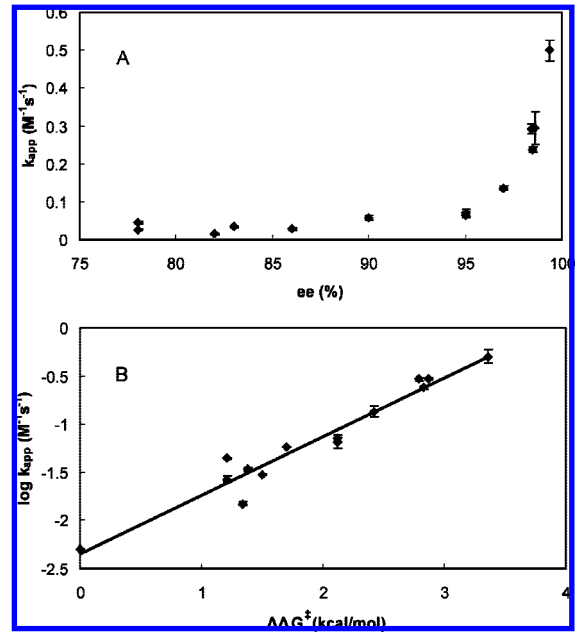

Figure 1. (A) Relationship between the k_{app} and the ee obtained with different double stranded oligonucleotides and st-DNA. (B) Relationship between log k_{app} and the $\Delta\Delta G^{\ddagger}$.[37]

Interestingly, with a longer, non- self-complementary DNA sequence an ee of 81% was obtained (entry 20). Apparently, single stranded DNA can also provide a chiral microenvironment for the catalyzed reaction. However, no rate enhancement was found, suggesting that the duplex DNA structure is required to achieve both high reactivity and enantioselectivity. Indeed, these single-stranded DNA sequences and single nucleotides do not fit the correlation observed with duplex DNA.

CD Spectroscopy. Since the results above clearly indicate that the microenvironment provided by the DNA is an important factor in the catalysis, we decided to further investigate the structure of the DNA sequences using CD spectroscopy. The spectra of four representative oligonucleotides and st-DNA are shown in Figure 2.[38]

The characteristic CD spectrum of B-DNA was obtained for oligomers that do not contain the G-triplet, i.e., iii−v.[39] A distinctly different CD spectrum was observed for sequences containing the G triplets. Compared to the typical B-DNA spectrum, the major absorptions are blue-shifted (a positive band around 265 nm, a negative band around 237 nm, and a crossover around 248 nm). This blue shift is not observed in the UV−vis spectra. The binding of Cu−L1 to the DNA causes the appearance of an additional feature at 300−320 nm, which can be attributed to the induced CD of the copper complex.[17b,40]

A CD and FTIR study of the structural effect of the presence of G-tracts in similar sequences has been reported.[41] Furthermore, the crystal structure of d(CATGGGCCCATG)$_2$, which contains the same central six basepair G-tract as the best oligonucleotide for the catalytic reaction, is available.[42] From these studies, it was concluded that the corresponding duplexes

(36) The addition of poly d(AT):poly d(AT to a solution of Cu-L1 gave rise to a new band in the UV-vis spectrum at 275 nm, and the disappearence of the bands at 300 and 307 nm of the complex, suggesting that a different complex was formed.
(37) Calculated using $\Delta\Delta G^{\ddagger} = -RT\ln(er)$, in which er is the enantiomeric ratio.
(38) See Supporting Information for a complete overview.
(39) Johnson, W. C.; In *Circular Dichroism: Principles and Applications*; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; 2nd edition.
(40) See Supporting Information
(41) Lindqvist, M.; Gräslund, A. *J. Mol. Biol.* **2001**, *314*, 423–432.
(42) Ng, H. -L.; Kopka, M. L.; Dickerson, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2035–2039.

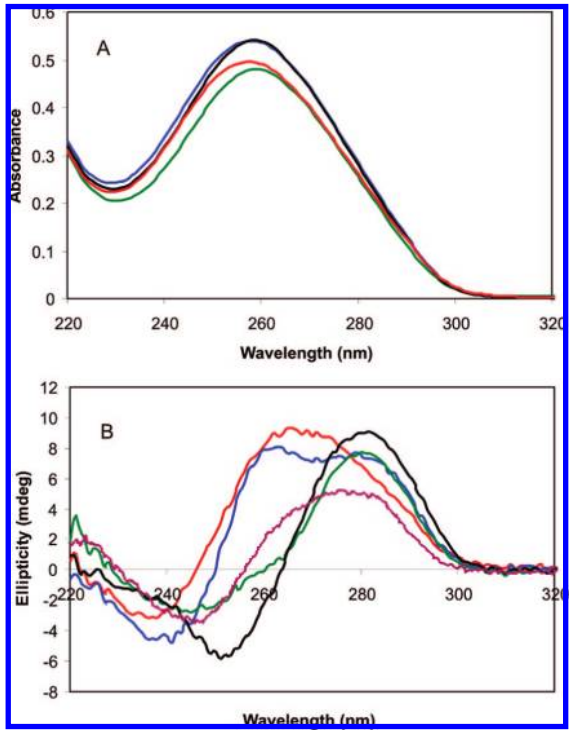

Figure 2. (A) UV-vis and (B) CD spectra of (i) d(TCAGGGCCCTGA)$_2$ (red); (ii) d(TCGGGATCCCGA)$_2$ (blue); (iii) d(TCGGAATTCCGA)$_2$ (green); (iv) d(TCGCGATCGCGA)$_2$ (black); and (v) st-DNA (purple) in MOPS buffer (20 mM, pH = 6.5), at 18.0 °C.

of these sequences are still B-type DNA, but with a distortion toward A-DNA. The main structural characteristics identified were a wider minor groove due to a lack of a propeller twist, the absence of a roll, and an 1.5 Å slide of the nucleobases. As a result, the structure of the microenvironment provided by the DNA might be better suited to achieve high enantioselectivity and rate accelerations. However, these results do not rule out alternative explanations. For example, since G-trimers have the highest electronegative potential,[43] it might also be that electrostatic interactions direct the copper complexes to the middle of the duplex, thereby reducing the chance that a complex is bound at the terminus, where the effect of the chiral environment of the DNA may be less pronounced.

Salmon Testes DNA/Cu−L1 as a Highly Active Enantioselective Catalyst. The main findings presented in this paper are (a) DNA-bound Cu−L1 accelerates the reaction by up to 2 orders of magnitude compared to unbound ("free") Cu−L1; (b) the enantioselectivity of the Diels−Alder reaction is strongly dependent on the DNA sequences in which Cu−L1 resides; and (c) the DNA sequences that lead to the highest enantioselectivities also give rise to the highest rate enhancement.

The combined results explain why st-DNA/Cu−L1 is such an efficient and enantioselective catalyst for the Diels−Alder reaction, even though Cu−L1 has only moderate binding affinity for DNA and the DNA-based catalysts are a heterogeneous mixture of Cu−L1 complexes that are all in a different microenvironment. The activity of unbound Cu−L1 is negligible compared to that of DNA-bound Cu−L1 since *DNA accelerates the reactions and the correlation between reaction rate and DNA sequence indicates that of all the different catalytic sites present at the DNA after copper complex binding, those that lead to the highest ee's dominate the reaction due to their propensity to enhance the reactivity most.* This means that the ee induced by st-DNA is not the average of equally contributing sequences, but is the weighted average.

At present, the origin of the rate enhancement observed for st-DNA/Cu−L1 as a catalyst is not well understood. On the basis of the results, several possible explanations can be put forward; (i) The concentration of **2** could be higher in the groove, resulting in an increased rate, analogous to micellar catalysis.[44] However, this is unlikely to be the main reason, since the observed rate enhancement is only 2−3 fold when the similar catalysts Cu−L2 and Cu−L3 are used. (ii) It is also not likely that the lower pH of the DNA groove[45] compared to the bulk medium is responsible for the rate enhancement, because the reaction rate in the absence of DNA is comparable at pH 5.5 and 6.5.[46] (iii) Another possibility is that the DNA increases the activity of the copper complex by interactions of the DNA with the copper complex or a change in coordination geometry, possibly resulting in a change in the Lewis acidity. We did not, however, observe an increase in K_a, which would be expected with a stronger Lewis acid, unless this effect is counteracted by steric effects resulting from the close proximity of the active complex to the DNA. (iv) A DNA−Cu complex, e.g. without ligand, can be excluded as major contributor since st-DNA/Cu^{2+} gives rise to the opposite enantiomer and deceleration of the reaction. (v) Secondary interactions of the DNA with **2** could help to further activate the dienophile. However, also in this case a change in K_a would be likely.

It is not unlikely that several of the factors above contribute at least partly to the observed effect of DNA on the reaction. However, on the basis of the evidence presented here, we propose that the main explanation for the observed rate enhancement and enantioselectivity of Cu−L1/DNA is that the DNA provides a favorable microenvironment for the catalyzed Diels−Alder reaction, which stabilizes the activated complex, resulting in both rate acceleration and enantioselectivity. This could be the result of chemical or shape complementarity of the DNA groove to the activated complex, analogous to what has been proposed in the case of catalytic antibodies. Support for this hypothesis is found in the observed effect on the activation parameters, i.e., that the rate acceleration is enthalpic in origin. Furthermore, the rate enhancement is mainly caused by an increase in $k_{(+)}$, while $k_{(-)}$ does not change significantly. This suggests that the transition state leading to the (+) enantiomer is stabilized more and, hence, the catalytic pocket is structurally better compatible with this transition state. Finally, the large effect of the DNA sequence and, hence, DNA structure also suggests the importance of the structure of the microenvironment provided by DNA, consistent with the notion of shape or chemical complementarity to the activated complex. One could argue that contradicting this hypothesis is the observation that higher conversions have also been observed in the Michael addition[18] and the fluorination reaction[19] catalyzed by Cu−L1/st-DNA compared to free Cu−L1 or

(43) Pullman, A.; Pullman, B. *Q. Rev. Biophys.* **1981**, *14*, 289–380.
(44) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517–9525.
(45) Lamm, G.; Pack, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9033–9036.
(46) The k_{app} at pH 5.5 was $(9.6 \pm 0.1) \times 10^{-3}$ M^{-1}, while the k_{app} at pH 6.5 was $(9.7 \pm 0.2) \times 10^{-3}$ M^{-1}, with [Cu-L1] = 0.2 mM, 25.0 °C.

other Cu^{2+} complexes with DNA, since these reactions involve structurally different transition states. However, in the absence of kinetic data, it is at present not possible to determine whether the rate enhancement observed in these reactions has a similar origin as the Cu−L1/st-DNA catalyzed Diels−Alder reaction presented here.

The interactions between the active complex and DNA is currently the subject of detailed spectroscopic and structural studies.

Materials and Methods

General Remarks. Salmon testes DNA and dNTP were obtained from Sigma, pAT and pGC were obtained from GE Healthcare. Cyclopentadiene (**2**) was freshly prepared from its dimer prior to use. Azachalcone (**1**), Cu(4,4′-dmbpy)$(NO_3)_2$ (Cu−L1), Cu(bpy)$(NO_3)_2$ (Cu−L2), Cu(phen)$(NO_3)_2$ (Cu−L3), and Cu(dpq)$(NO_3)_2$ (Cu−L4) were prepared following published procedures.[17b] To ensure that the oligonucleotides are duplexes, all physical measurements were performed at 18 °C. Salmon testes DNA was dialyzed extensively against MOPS buffer (20 mM, pH 6.5) prior to use.

Physical Methods, General Remarks. Circular Dichroism spectra were measured on a JASCO J-715 spectropolarimeter, with a temperature control attachment. The UV−vis spectra were measured on a JASCO V-560 or a JASCO V-570 with a temperature control attachment. The ee's were determined by HPLC analyses performed on a Shimadzu 10AD-VP system equipped with a Diacel chiralcel OD-H column, heptane/*i*PrOH 98:2, 0.5 mL/min. The activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$,[47] and the binding constants K_b[17a] have been determined using methodology described previously.

Dissolution of Synthetic Oligonucleotides. The synthetic oligonucleotides were obtained from BioTez. The lyophilized powder was dissolved in buffer (20 mM MOPS, pH 6.5). The solution was heated to 94 °C and slowly cooled to 5 °C, and left for 2 h at 5 °C prior to usage. The concentration was determined by UV−vis spectroscopy at 18 °C.

Determination of k_{app}. The procedures to determine k_{app}, K_a, and k_{cat} were adapted from Engberts et al.[20] A 2.0-μL portion of a fresh solution of azachalcone (1.0 mg/mL in CH_3CN) was added to the appropriate catalyst in buffer (20 mM MOPS, pH 6.5) in a quartz cuvette. After the absorption stabilized, 1−10 μL of a freshly prepared cyclopentadiene solution in CH_3CN was added, resulting in a final concentration of 0.5−2.0 mM. The cuvette was closed immediately and sealed tightly to prevent evaporation of cyclopentadiene. The reaction was monitored at 326 nm, at the appropriate temperature, on a JASCO V-560 or a JASCO V-570 spectrophotometer. The decrease in absorption of **1** was followed for the first 15% of the reaction, and the following expression was used to calculate k_{app}:

$$k_{app} = \frac{dA_1}{dt} \cdot \frac{1}{d \cdot (\varepsilon_1 - \varepsilon_3) \cdot [\mathbf{1}]_0 \cdot [\mathbf{2}]_0}$$

in which ϵ_1 and ϵ_3 are the extinction coefficients of **1** and **3**, respectively, and d is the path length of the cuvette. The observed rate constants were determined at different concentrations of **2**, after which the k_{app} was extracted from the slope of the resulting plot. Thus, reactions other than the reaction of **1** with **2** were excluded. In the case of the synthetic oligonucleotides, the absorption of **1** without **2** proved to be sufficiently stable, and the k_{app} was therefore determined from three independent measurements with the same concentration of **2**.

(47) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books; Sausolito, CA, 2006.

Determination of K_a and k_{cat}. The equilibrium constant K_a was determined by measuring the extinction coefficient of the partially complexed azachalcone as a function of the concentration of copper complex. The temperature was stabilized at 25.0 °C. The following equation was then applied:

$$\frac{[Cu^{2+}]}{\epsilon_1 - \epsilon_{obs}} = \frac{1}{(\epsilon_1 - \epsilon_{complex}) \cdot K_a} + \frac{[Cu^{2+}]}{\epsilon_1 - \epsilon_{complex}}$$

The concentration of copper complex was varied between 0.1−0.6 mM in the absence of DNA, and 0.1−0.3 mM of copper complex in the presence of DNA. In all of the measurements the ratio of copper complex to base pairs DNA was kept at 1:6. Because of the low concentration of copper complex, the constant was determined from three independent measurements. The concentration of azachalcone was 6.0×10^{-3} mM.

The k_{cat} was determined by applying the following equation, which was obtained from Engberts et al.[48]

$$k_{app} = \frac{k_0 \cdot [\mathbf{1}]_f}{[\mathbf{1}]_t} + \frac{K_a \cdot [Cu^{2+}]_f}{K_a \cdot [Cu^{2+}]_f + 1} \cdot k_{cat}$$

Herein, $[\mathbf{1}]_f$ is the concentration of unbound **1**, $[\mathbf{1}]_t$ is the total amount of **1**, and k_0 is the second-order rate constant for the uncatalyzed reaction. The concentration of unbound **1** can be determined from the measured K_a. The k_{app} was determined as a function of the concentration of copper complex $[Cu^{2+}]_f$, which was varied between 0.10 and 0.25 mM while maintaining a constant Cu^{2+} complex to DNA ratio, since this ratio was observed to have an effect on the k_{app}.[49] This concentration range was selected due to solubility problems and increased viscosities of the solutions at higher DNA concentrations. Moreover, this concentration range corresponds to the concentration of copper complex applied in the preparative experiments. The k_{cat} was determined from the slope of a plot of the k_{app} versus $K_a \cdot [Cu^{2+}]_f/K_a \cdot [Cu^{2+}]_f + 1$.

Melting Temperatures. The melting temperatures of the synthetic oligonucleotides were measured using a Jena Specord 250 spectrophotometer with a temperature control attachment. The absorbance was measured at 260 nm for solutions of 2×10^{-4} M [DNA] in buffer (20 mM MOPS, pH 6.5). The final concentration of Cu−L1 was 7×10^{-5} M. The absorption was monitored over a temperature range of 5 to 90 °C, with 0.5 °C incremental steps in temperature. The melting temperatures were determined from three independent measurements and proved to be reproducible within 1 °C.

Reactions in the Presence of Synthetic Oligonucleotides. Into a 2 mL Eppendorf container was loaded 400 μL of oligomer solution in buffer (20 mM MOPS, pH 6.5), copper complex in 200 μL of buffer, and 6 μL of a solution of azachalcone (0.5 mg/mL) at 5 °C. To this solution was added 0.8 μL of freshly distilled cyclopentadiene via a microsyringe. The reaction was mixed by continuous inversion for 3 days at 5 °C. After extraction with Et_2O, drying with Na_2SO_4, and concentration under reduced pressure, the reaction products were analyzed by HPLC.

Conclusions

In the present work, we show that the role of DNA in the DNA-based enantioselective Diels−Alder reaction of **1** with **2** is not limited to that of a chiral scaffold. DNA in combination with Cu−L1 gives rise to a rate acceleration of up to 2 orders of magnitude compared to Cu−L1 alone. Furthermore, both the enantioselectivity and the rate enhancement proved to be dependent on the DNA-sequence.

(48) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798–6806.

(49) See Supporting Information for the plot of the DNA/Cu-L1 ratio vs. the k_{app}.

These features are the main reasons for the efficient and enantioselective catalysis observed with salmon testes DNA/Cu−L1 in the Diels−Alder reaction. The fact that this can be achieved with a simple and weak DNA-binding complex like Cu−L1 is a clear demonstration of the power of the supramolecular approach to hybrid catalysis.

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Supporting Information Available: A plot of the k_{app} versus the ratio DNA concentration: Cu−L1, Eyring plots, calculation of $k_{(-)}$ and $k_{(+)}$, CD, and UV−vis spectra of the oligonucleotides in the presence and absence of Cu−L1, and catalysis data of Cu−L2 and Cu−L4 in the presence of different oligonucleotides. This material is available free of charge via the Internet at http://pubs.acs.org.

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