Asymmetric Catalysis

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DNA-Accelerated Catalysis of Carbene-Transfer Reactions by a DNA/Cationic Iron Porphyrin Hybrid

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Dedicated to Professor Ben L. Feringa on the occasion of his 65th birthday

Abstract: *A novel DNA-based hybrid catalyst comprised of salmon testes DNA and an iron(III) complex of a cationic meso-tetrakis(N-alkylpyridyl)porphyrin was developed. When the N-methyl substituents were placed at the ortho position with respect to the porphyrin ring, high reactivity in catalytic carbene-transfer reactions was observed under mild conditions, as demonstrated in the catalytic enantioselective cyclopropanation of styrene derivatives with ethyl diazoacetate (EDA) as the carbene precursor. A remarkable feature of this catalytic system is the large DNA-induced rate acceleration observed in this reaction and the related dimerization of EDA. It is proposed that high effective molarity of all components of the reaction in or near the DNA is one of the key contributors to this unique reactivity. This study demonstrates that the concept of DNA-based asymmetric catalysis can be expanded into the realm of organometallic chemistry.*

Inspired by enzymes, second-coordination-sphere interactions are increasingly being recognized as key elements for the design of highly active and selective catalysts.[1] The concept of DNA-based catalysis, in which a transition-metal complex is embedded in a DNA scaffold that provides the chiral second coordination sphere, is a powerful illustration of this principle.[2] DNA-based catalysis has been applied successfully in a variety of copper(II)-catalyzed (that is, Lewis acid catalyzed) reactions with high catalytic activity and enantioselectivity.[3] However, expansion of the reaction scope beyond Lewis acid catalysis has so far proven to be challenging. Jäschke and co-workers reported a catalytic allylic amination with a DNA-based catalyst comprising a covalently attached iridium complex.[4] Although catalysis was demonstrated, the enantioselectivity of the reaction was low. Recently, enantioselective sulfoxidation with a DNA G-quadruplex based copper catalyst was described.[5] Previously, we reported the first example of a DNA-based copper-catalyzed intramolecular cyclopropanation reaction.[6] Although this transformation demonstrated the feasibility of DNA-based organometallic catalysis, it also illustrated the challenges that are involved, since the reactions required strictly anaerobic conditions, the yields of products were low, and the substrate scope was limited. We now introduce a novel DNA/cationic-iron-porphyrin-based hybrid catalyst that enables highly DNA accelerated catalysis of carbene-transfer reactions, such as enantioselective cyclopropanation, under mild conditions and an ambient atmosphere.

[Fe(TPP)Cl] (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine) and related iron porphyrins have been employed successfully in carbene-transfer reactions, even in aqueous media.[7] Elegant recent studies with engineered P450[8] or myoglobin artificial metalloenzymes[9] and in combination with living cells[10] have demonstrated that these reactions are biocompatible: excellent catalysis of carbene-transfer reactions, such as enantioselective cyclopropanation, has been reported, albeit mostly under strictly anaerobic conditions.

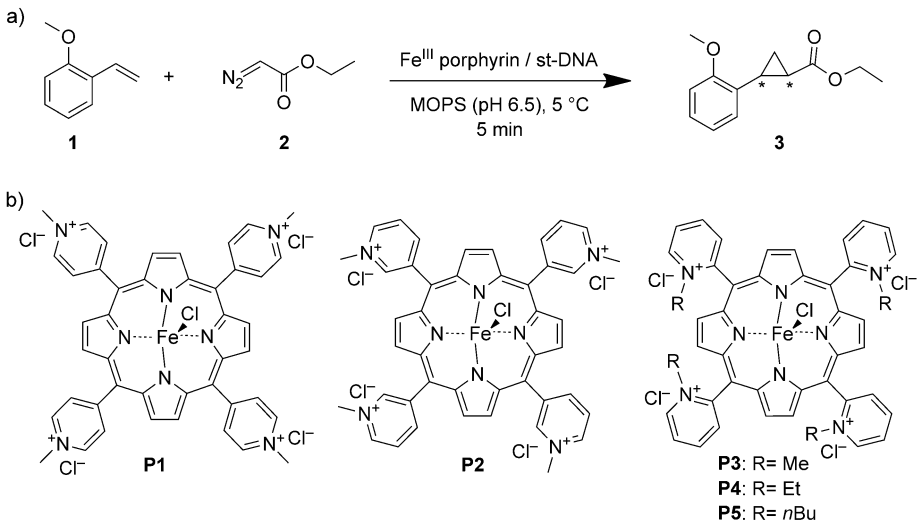
For this study, a variety of iron(III) complexes of cationic porhyrins, that is, *meso*-tetrakis(*N*-alkylpyridyl)porphyrins differing in the position of the *N*-alkyl substituent and the length of the alkyl chain, were selected as catalysts (Scheme 1 b). This class of iron(III) porphyrins has been studied extensively, for example, as mimics of the enzyme Superoxide dismutase.[11] They are known DNA binders, and it has been reported that their interaction with DNA, as well as their physical properties, are very much dependent on the position of the *N*-alkyl moiety and the length of the alkyl chain.[11,12]

The cyclopropanation of *o*-methoxystyrene (**1**) with ethyl-diazoacetate (EDA, **2**) as the carbene precursor was selected as the benchmark reaction (Scheme 1 a). The DNA-based catalyst was self-assembled by combining the iron(III) porphyrin (75 μM, 1.5 mol%) with salmon testes DNA (st-DNA, 6 mM in base pairs) in 20 mM 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer at pH 6.5, which was found to be the optimal pH value with regard to both activity and selectivity (see Table S1 in the Supporting Information). The *ortho*-substituted porphyrins **P3**–**P5**[11] were used as mixtures of atropoisomers.

The catalytic reactions were performed at 5 °C under an ambient atmosphere with a 10-fold excess of **2**, and the reaction mixture was mixed by continuous inversion. First, the three isomeric iron porphyrins **P1**–**P3** with *N*-methyl groups were evaluated as catalysts. In the absence of DNA, the reaction was sluggish and resulted in low yields of the cyclopropanation product **3** (Table 1, entries 1, 3 and 5), even after prolonged reaction times. In the presence of st-DNA

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Scheme 1. a) Enantioselective cyclopropanation reaction catalyzed by a DNA-based iron porphyrin. b) Iron(III) complexes of *meso*-tetrakis(*N*-alkylpyridyl)porphyrins used in this study.

Table 1: Enantioselective cyclopropanation of **1** with EDA under the catalysis of iron porphyrins in the presence and absence of st-DNA.[a]

Entry	Porphyrin	st-DNA [mM]	Yield [%][b]	TTN[c]	*ee* [%][b]
1	**P1**	–	≤3	–	–
2	**P1**	6	≤3	–	–
3	**P2**	–	≤3	–	–
4	**P2**	6	≤3	–	–
5	**P3**	–	≤3	–	–
6	**P3**	6	14±2	9	42
7[d]	**P3**	6	16±4	22	40
8[e]	**P3**	–	≤3	–	–
9	**P3**	3	22±1	14	33
10	**P3**	1.5	25±0	17	24
11	**P4**	–	33±3	22	–
12	**P4**	6	15±0.5	10	23
13	**P5**	–	26±0	17	–
14	**P5**	6	11±1	7	5

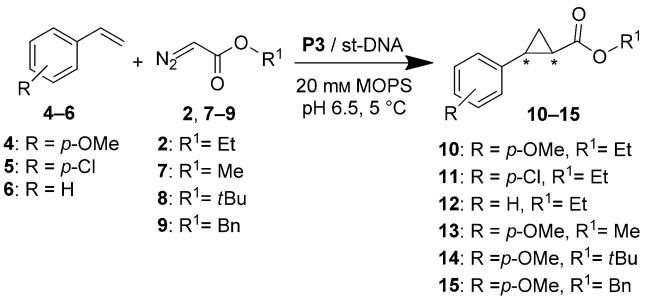
[a] The experiments were carried out with **1** (5 mM), **2** (50 mM), st-DNA (6 mM in base pairs), and the Fe^{III} porphyrin (75 μM) in 20 mM MOPS buffer (pH 6.5) containing acetonitrile (3% v/v) for 5 min at 5 °C, unless otherwise specified. Yields and *ee* values are based on the areas of HPLC and GC peaks as compared to those of 2-methyl anisole as an internal standard. All data were averaged over two or more experiments. Errors reported are standard deviations. [b] The yield and *ee* value (reproducibility: ±3% *ee*) of the *trans* isomer are given. The diastereomeric ratio of the product ranged from 88:12 to 95:5. [c] TTN = total turnover number. [d] Metalloporphyrin concentration: 37.5 μM. [e] Metalloporphyrin concentration: 7 μM.

(6 mM in base pairs), low activity was again observed in the case of the *para* and *meta* isomers **P1** and **P2** (Table 1, entries 2 and 4). Surprisingly, with the *ortho* isomer **P3**, immediate and vigorous evolution of N_2 was observed, which ceased after approximately 5 min. It was found that at this time all EDA had been consumed. The *trans* isomer of the cyclopropanation product **3** (*trans*/*cis* ≥ 12:1)[13] was obtained in 14% yield, which amounts to 9 turnovers of the Fe catalyst, with a promising *ee* value of 42% (Table 1, entry 6). A large fraction of the EDA was converted into side products, the most important detectable side product being diethyl maleate, which results from the dimerization of EDA.

Interestingly, the Fe porphyrins **P4** and **P5**, which contain an *N*-ethyl and an *N*-butyl moiety, respectively, showed high activity, even in the absence of DNA (Table 1, entries 11–14). With these porphyrins, the yield of **3** was found to be lower in the presence of DNA, whereas the *ee* value of the product **3** was lower than that observed with the corresponding *N*-methyl derivative **P3**. Since the highest enantioselectivity was observed with **P3**, in combination with the intriguing acceleration effect of DNA on the catalysis, we decided to focus our further studies on this complex.

We varied the concentration of **P3** with the concentration of st-DNA fixed at 6 mM in base pairs. When the concentration of the metalloporphyrin was halved, the total number of turnovers increased, whereas the enantioselectivity remained the same (Table 1, entry 7). Therefore, 37.5 μM was used as the optimal concentration for our catalysis. Since a solution of DNA with a concentration of 6 mM in base pairs is very viscous, the DNA concentration was also varied. Lowering of the concentration of st-DNA at a fixed concentration of porphyrin resulted in an increase in yield, which is tentatively ascribed to increased diffusion of the substrates owing to the lower viscosity of the solution. This increase in yield was accompanied, however, by a decrease in enantioselectivity (Table 1, entries 9 and 10).

The scope of the reaction with respect to the styrene substrate was investigated by using *p*-methoxystyrene (**4**), *p*-chlorostyrene (**5**), and styrene (**6**) in the reaction with **2** as the diazo compound (Scheme 2, Table 2). In all cases, a significant amount of the cyclopropanation product was only obtained in the presence of DNA (entries 1–6). The trend observed is consistent with an electrophilic carbene as the active species, that is, styrenes **1** and **4** containing electron-donating groups were converted into the corresponding cyclopropanation



Scheme 2. Investigation of the scope of the enantioselective cyclopropanation under DNA-based iron porphyrin catalysis. Bn = benzyl.

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Table 2: Investigation of the scope of st-DNA/**P3**-catalyzed enantioselective cyclopropanation reactions with **2**.[a]

Entry	Styrene	Product	DNA [mM]	Yield [%][b]	TTN	*ee* [%][b]
1	**4**	**10**	–	3 ± 3	4	–
2	**4**	**10**	6	32 ± 6	43	50
3	**5**	**11**	–	≤ 3	–	–
4	**5**	**11**	6	4 ± 1	5	41
5	**6**	**12**	–	≤ 3	–	–
6	**6**	**12**	6	12	16	53

[a] The experiments were carried out with the styrene substrate (5 mM), **2** (50 mM), st-DNA (6 mM in base pairs), and **P3** (37.5 μM) in 20 mM MOPS buffer (pH 6.5) containing acetonitrile (3% v/v) for 5 min at 5 °C. Yields and *ee* values were determined by HPLC and GC with 2-methyl anisole as an internal standard. All data were averaged over two or more experiments. Errors reported are standard deviations. [b] The yield and *ee* value (reproducibility: ±3% *ee*) of the *trans* isomer are given.

products (**3** and **10**) in higher yield than those substrates containing electron-withdrawing groups. The somewhat lower activity towards **1** (Table 1, entry 7) as compared to **4** (Table 2, entry 2) is attributed to steric hindrance by the *ortho* methoxy group. The *ee* values observed ranged from 40% *ee* in the case of **1** (Table 1, entry 7) to 53% *ee* in the case of styrene (Table 2, entry 6).

The scope of the reaction with respect to the diazo compound was investigated in the reaction of **4** with alkyl diazoacetates **2**, **7**, **8**, and **9** (Scheme 2). It was found that bulkier groups R^1 resulted in lower or even no yield of the cyclopropanation product (see Table S2). Conversely, with methyl diazoacetate, the corresponding product was obtained in 44% yield (TTN: 59) with 50% *ee* (see Table S2). Notably, in this case activity was observed in the absence of DNA (TTN: 31; see Table S2), albeit significantly lower than in the presence of DNA.

The observed DNA acceleration of catalysis was further studied by determining the kinetics of the reaction of **4** with EDA in presence and absence of DNA. However, the analysis is complicated by the fact that the cyclopropane is not the only product formed in the reaction: a significant amount of side products was formed. The most important detectable side product was diethyl maleate, resulting from the reaction of the carbene with another molecule of **2**.[14] Therefore, the formation of diethyl maleate over time was monitored by GC both in the presence and absence of st-DNA and/or **4** (see Figure S1 in the Supporting Information). After a reaction time of 5 min, diethyl maleate was obtained in approximately 30% yield (TTN: ca. 200) in the presence of st-DNA versus 1% yield in the absence of st-DNA. In the absence of **4**, the same trend was observed, but the yields were slightly lower.

The formation of N_2 was measured during 5 min by using a gas burette (see Figure S2). For experimental reasons, it was necessary to switch from continuous inversion to orbital mixing, which is a less efficient method of mixing and, as a consequence, gave rise to a decrease in the yield of **10**. However, the trends in reactivity in the presence and absence of DNA and the enantioselectivity remained the same (see Table S3).[15] In the absence of DNA, hardly any evolution of N_2 was observed (Figure 1). In contrast, in the presence of st-DNA, after a short lag phase, a significant amount of released N_2 (3.9 mL) was measured. The lag phase is tentatively ascribed to slow release of N_2 from the solution owing to its viscosity.

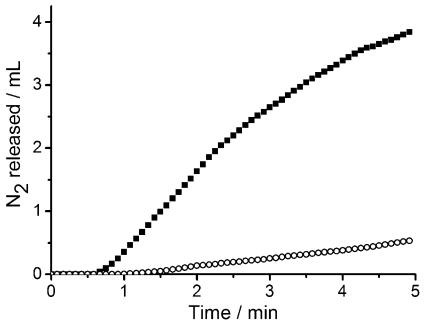


Figure 1. Evolution of N_2 over time in the **P3**-catalyzed decomposition of EDA in the presence (solid squares) and absence (open circles) of st-DNA.

Arguably one of the intriguing aspects of this reaction is the observed DNA-induced rate acceleration in catalysis by **P3**. At present it is difficult to quantify the effect of DNA on the reaction rate owing to the presence of several competing side reactions that are each affected differently by the presence of DNA. However, on the basis of the data presented above, the acceleration by DNA can be estimated to be at least between one and two orders of magnitude. Although it is not possible at present to explain this phenomenon in full molecular detail, a few important observations can be made:

1) The reaction does take place in or close to the DNA, as is evidenced by the enantioselectivity observed in the formation of the cyclopropanation product.

2) It is unlikely DNA accelerates the catalysis by providing an activating axial ligand to the iron ion, as has been observed for P450-catalyzed cyclopropanation reactions[8b] and in the [Fe^{III}(TPP)Cl]-catalyzed dimerization of **2**, in which case a significantly increased reaction rate was observed in the presence of pyridine.[16] If anything, the presence of the *ortho N*-methyl groups is known to reduce the interaction of metalloporphyrins with DNA owing to steric hindrance.[11b,17] Moreover, in control experiments in the absence of st-DNA, but in the presence of a mixture of the four DNA nucleobases (adenine, thymine, guanine, and cytosine), benzyl amine and pyridine in all cases showed no release of N_2, and the results of the catalysis were comparable to those observed in absence of st-DNA.

3) The DNA acceleration effect was observed in the case of the *ortho*-substituted *N*-methylpyridinium porphyrin **P3**, but not with *meta* and *para* isomers **P1** and **P2**, which gave rise to sluggish reactions both in the presence and absence of DNA. This result suggests that the different DNA-binding mode of the iron porphyrins is important in catalysis.[12] **P3** predominantly interacts with DNA through groove binding in AT-rich regions.[12b] Groove binding of the catalyst would make the catalytic site readily accessible for substrates, since it is more at the periphery of the DNA structure.

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4) Conversely, iron porphyrin derivatives with larger alkyl substituents at the pyridyl nitrogen atom, such as **P4** and **P5**, already promote very fast reactions in the absence of DNA, thus suggesting that a more hydrophobic environment around the metal site is beneficial for catalysis.

On the basis of these combined observations, we propose that the binding of **P3** to DNA gives rise to the formation of hydrophobic pockets along the DNA in which the reaction partners, that is, the EDA and the styrene derivative, are concentrated. The resulting high effective molarity of all reaction components then is a key contributor to the observed rate acceleration of catalysis. This hypothesis is in agreement with the micellar rate enhancement observed in iron-metalloporphyrin-catalyzed cyclopropanation[10,17] and mechanistically similar epoxidation reactions.[18] Also, the significant rate acceleration observed in cyclopropation reactions catalyzed by artificial metalloenzymes that present a large hydrophobic cavity[8,9,19] and cobalt porphyrins encapsulated in hydrophobic metallocages supports this hypothesis.[20] Finally, effective molarity has been proposed to be important in DNA-accelerated Lewis acid catalyzed reactions as well,[21] thus suggesting that this feature is a general hallmark of the concept of DNA-based catalysis.

In conclusion, we have described the use of a novel DNA/cationic iron porphyrin hybrid catalyst for carbene-transfer reactions in water under mild conditions and an ambient atmosphere. This system was applied to the catalytic enantioselective cyclopropanation of styrene derivatives, and the corresponding cyclopropanation products were obtained with promising *ee* values. However, arguably the most intriguing observation in this study is the large DNA-induced rate acceleration in the case of **P3**. It is proposed that high effective molarity of the reaction partners in hydrophobic pockets provided by the DNA/**P3** hybrid as a result of the unique DNA-binding mode of **P3** is a key contributor to the observed rate acceleration. The results presented herein convincingly demonstrate that the concept of DNA-based asymmetric catalysis can be expanded beyond Lewis acid catalyzed reactions. In view of the broad catalytic scope of metalloporphyrins, it is envisioned that the novel design presented herein is general and will allow further expansion of the concept of DNA-based catalysis into the realm of organometallic chemistry.

Experimental Section

Representative procedure: Salmon testes DNA (6.0 mg mL^{-1}; 9.0 mM in base pairs) was dissolved in a 20 mM solution of MOPS buffer (pH 6.5) 2 days before use. The following final concentrations were used in catalysis: 5 mM of the substrate 4-methoxystyrene (**4**), 50 mM of ethyl diazoacetate (**2**), 37.5 μM of the iron porphyrin, and 6 mM of DNA (in base pairs). A 1.125 mM solution of the iron porphyrin (250 μL) was added to MOPS buffer (pH 6.5, 2.0 mL) in a 15 mL Greiner tube. Then, 5 mL of the st-DNA solution was added, and the mixture was mixed by continuous inversion at 5 °C. After incubation for 30 min, 50 μL of a 750 mM solution of 4-methoxystyrene (**4**) in acetonitrile and 200 μL of a 1.875 M solution of ethyl diazoacetate (**2**) in acetonitrile were added to start the catalytic reaction. After 5 min, the product was extracted with diethyl ether (3 × 5 mL). The organic layer was washed with brine (1 × 5 mL). After drying (Na_2SO_4) and evaporation of the solvent, the crude product was analyzed by HPLC and GC with 2-methylanisole as an internal standard.

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