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Short Communication

1,4-Michael additions of cyclic-β-ketoesters catalyzed by DNA in aqueous media

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ABSTRACT

In this work, we describe the 1,4-Michael addition of the 1,3-dicarbonyl compounds to activated ethylenes under st-DNA catalysis in water. The reaction of the β-ketoester **4** with nitroolefins and conjugated carbonyls proceeds quite well, whereas other less activated ethylenes exhibit low or null reactivity. The catalyst can be recovered and reused for several catalytic cycles without significantly diminishing its efficiency. These reactions are similarly catalyzed by GMP, methyl-adenine and ethyl guanine, which suggests that the catalytic activity of st-DNA could be associated to the basic nature of their nucleotides' integrants.

1. Introduction

The development of sustainable chemical processes is one of the most important features in modern chemistry. It has become a worldwide key research area to provide solutions to important societal demands by optimizing the use of natural resources and minimizing waste and environmental impact. Thus, European society has recently realized the importance of implementing sustainable chemistry in our industry by creating the European Technology Platform (ETP) for Sustainable Chemistry (http://www.suschem.org/). Among the relevant methods toward achieving this goal, catalysis represents a key and central approach. Both *Organocatalysis* [1] and *Metal Catalysis* [2] have emerged as solutions for the problems originated in this context. Despite the enormous advances made toward both types of catalysis, there is still a search for more efficient and general catalysts or methods, and challenges remain from economic and ecological points of view. The use of new ligands in metal-catalysis and also new organocatalysts requires the design and synthesis of complicated structures with a large sequence of steps, especially for carrying out the asymmetric version of the chosen reaction [3].

Nature, our bioinspiration, controls chemical reactivity with different approaches, mainly by the use of enzymes which are able to select between hundreds of reactants in solution at very low concentrations. Biopolymers such as DNA are potentially interesting as catalysts as far as it could ideally coordinate two reagents (A and B) through different non-covalent interactions producing their approach and making easier their reaction. The resulting product would be released from the DNA, which could be incorporated again into the catalytic cycle (Fig. 1). The low price of DNA (compared with that of the most widely used ligands for metal catalysis or organocatalysts), its multiple binding sites (allowing the reaction to proceed with low catalyst loadings), and its compatibility with the use of inexpensive "green" solvents such as water [4] (which in its turn allows reusing it after recovering them from the aqueous solution) are three features conferring it an additional interest in catalysis.

Despite this potential interest, only two papers [5,6] have been reported that concern the use of the DNA as the only catalyst. Both of them describe 1,2-additions to carbonyl groups and evolve with scarce stereochemical control [7]. Thus, it would be highly desirable to explore the DNA catalytic ability in other reactions. In this sense, we fixed our attention in the behavior of double bonds bearing EWG and in this paper we describe the 1,4-addition of β-ketoesters to different Michael acceptors catalyzed by st-DNA [8].

2. Experimental

2.1. Material and methods

All reagents and chemicals were purchased from commercial sources (Sigma-Aldrich, U.S.A.) and used without further purifications. Solvents were purified by standard procedures [9]. NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode.

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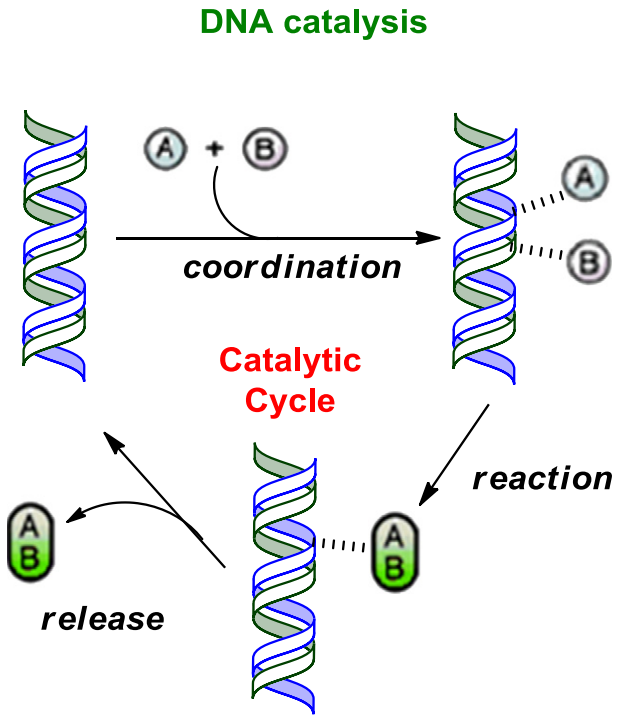


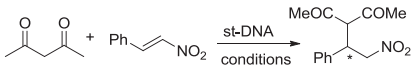
Fig. 1. Proposed catalytic cycle to be developed in this work.

2.2. General procedure for the synthesis of compound **3** (Table 1)

2.2.1. 3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (**3**)

To a solution of st-DNA (5.0 mL of a 2.0 mg mL^{-1} solution of st-DNA dissolved in 20 mM MOPS buffer, pH 6.5, and prepared 24 h in advance) were added 5.0 mmol of pentane-2,4-dione (**1**) and 0.5 mmol of nitroalkene **2a**. The reaction was allowed to continue for the indicated time in Table 1 at rt and mixing continuously by a stirring shaker. The product was isolated by extraction with CH_2Cl_2 (2 × 5.0 mL). After drying (Na_2SO_4) and removal of the solvent, the crude product was analyzed by ^1H NMR spectroscopy and was purified by flash chromatography (Hexanes/AcOEt: 2/1) as a yellow oil (yield = 45%). The product matched with the previous spectroscopic data described in the literature [10]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 3H), 7.21–7.12 (m, 2H), 4.64–4.57 (m, 2H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.23–4.15 (m, 1H), 2.24 (s, 3H), 1.89 (s, 3H).

Table 1
Michael addition of **1** to nitroalkene **2a** catalyzed by st-DNA[a].



1 2a 3

Entry	Buffer	Time (days)	Note	Conversion(%)
1	–	1	–	25
2	CHES(5 mL)	1	–	22
3	MES (5 mL)	1	–	27
4	MOPS (5 mL)	1	–	35
5	MOPS (5 mL)	7	–	75
6	MOPS(2.5 mL)	3	10 mol% TBAI	70
7	–	3	10 mg of st-DNA in 0.5 mL CH_2Cl_2	7

[a] All the reactions were carried out with 0.5 mmol of **2a**, 5.0 mmol of **1** and st-DNA (2.0 mg mL^{-1}).

2.3. General procedure for the synthesis of compound **6** (Table 2)

To a solution of st-DNA (2.5 mL of a 2.0 mg mL^{-1} solution of st-DNA dissolved in 20 mM MOPS buffer, pH 6.5, and prepared 24 h in advance) were added 0.1 mmol of β-ketoesther **4** and 1.0 mmol of the corresponding electrophile **2**. The reaction was allowed to continue for the indicated time in Table 2 at rt, while mixing continuously by a stirring shaker. The product was isolated by extraction with CH_2Cl_2 (2 × 5.0 mL). After drying (Na_2SO_4) and removal of the solvent, the crude product was analyzed by ^1H NMR spectroscopy and was purified by flash chromatography.

2.3.1. Methyl 2-(2-nitro-1-phenylethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**6a**)

The product was directly obtained following the standard procedure as colorless oil (87% yield) after flash chromatography (2:1, Hexanes: AcOEt) as mixture of diastereoisomers (50:50). The product matched with the previous spectroscopic data described in the literature [11]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.52–7.44 (m, 4H), 7.39–7.30 (m, 10H), 5.56 (dd, *J* = 13.6, 3.7 Hz, 1H), 5.32 (dd, *J* = 13.4, 10.9 Hz, 2H), 5.19 (dd, *J* = 13.4, 3.6 Hz, 1H), 4.61 (dd, *J* = 11.0, 3.6 Hz, 1 H), 4.34 (dd, *J* = 10.8, 3.7 Hz, 1 H), 3.87 (s, 3H), 3.82 (s, 3H), 3.77 (d, *J* = 17.7, 1H), 3.64 (d, *J* = 17.7 Hz, 1H), 3.34 (d, *J* = 17.7 Hz, 1H), 3.29 (d, *J* = 17.7 Hz, 1H).

2.3.2. Methyl 1-oxo-2-(3-oxobutyl)-2,3-dihydro-1H-indene-2-carboxylate (**6b**)

The product was directly obtained following the standard procedure as colorless oil (75% yield) after flash chromatography (3:1, Hexanes: AcOEt). The product matched with the previous spectroscopic data described in the literature [12]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 6.0 Hz, 1H), 7.63 (t, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.41 (t, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 3.66 (d, *J* = 17.4 Hz, 1H), 3.03 (d, *J* = 17.4 Hz, 1H), 2.62–2.36 (m, 2H), 2.20–2.12 (m, 2H), 2.06 (s, 3H).

2.3.3. Methyl 1-oxo-2-(3-oxopropyl)-2,3-dihydro-1H-indene-2-carboxylate (**6c**)

The product was directly obtained following the standard procedure as colorless oil (82% yield) after flash chromatography (3:1, Hexanes: AcOEt). The product matched with the previous spectroscopic data described in the literature [13]. ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 3.69 (d, *J* = 15.9 Hz, 1H), 3.67 (s, 3H), 3.04 (d, *J* = 17.3 Hz, 1H), 2.70–2.47 (m, 2H), 2.40–2.20 (m, 2H).

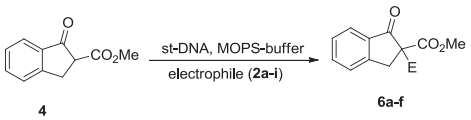
2.3.4. Methyl 1-oxo-2-(4-oxobutan-2-yl)-2,3-dihydro-1H-indene-2-carboxylate (**6d**)

The product was directly obtained following the standard procedure as colorless oil as a mixture of diastereoisomers (56% yield) after flash chromatography (2:1, Hexanes:AcOEt). The product matched with the previous spectroscopic data described in the literature [14]. ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 9.67 (s, 1H), 7.78–7.74 (m, 2H), 7.66–7.61 (m, 2H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 3.72 (s, 3H), 3.68 (s,3H), 3.80–3.63 (m, 2H), 3.34–3.26 (m, 2H), 3.09 (d, *J* = 17.0 Hz, 1H), 3.06 (d, *J* = 17.7 Hz, 1H), 2.67 (d, *J* = 16.2 Hz, 1H), 2.35–2.13 (m, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

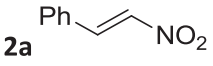
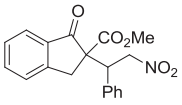
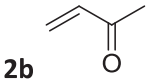
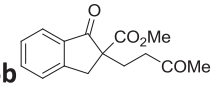
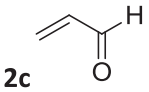
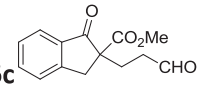
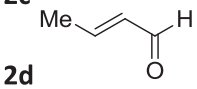
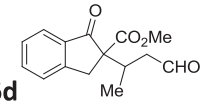
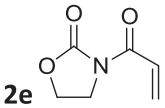
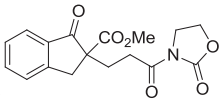
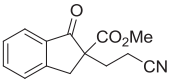
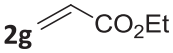
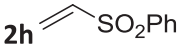
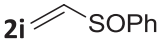
2.3.5. Ethyl 1-oxo-2-(3-oxo-3-(2-oxooxazolidin-3-yl)propyl)-2,3-dihydro-1H-indene-2-carboxylate (**6e**)

The product was directly obtained following the standard procedure as yellow oil (42% yield) after flash chromatography (3:1, Hexanes: AcOEt). The product matched with the previous spectroscopic data described in the literature [15]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.40

Table 2
Reaction of the β-ketoesther **4** to different electrophiles **5**[a].



4 6a-f

Entry	Electrophile	Product	Conversion (%)	Time (h)	Yield (%)
1	 **2a**	 **6a**	>99	24	87[b]
2	 **2b**	 **6b**	>99	24	75
3	 **2c**	 **6c**	>99	24	82
4	 **2d**	 **6d**	80	168	56[b]
5	 **2e**	 **6e**	50	72	42
6	 **2f**	 **6f**	23	168	7
7	 **2g**	–	–	168	Nr
8	 **2h**	–	–	168	Nr
9	 **2i**	–	–	168	Nr

[a] All the reactions were carried out with 1 mmol of the electrophile, 0.1 mmol of the nucleophile **4**, and 2.5 mL of MOPS buffer with 2.0 mg mL^{-1} of st-DNA.
[b] In this case a mixture of diastereoisomers 50:50 was obtained.

(d, J = 7.4 Hz, 1H), 4.39 (t, J = 8.0 Hz, 2H), 4.02–3.96 (m, 2H), 3.72 (d, J = 18.7 Hz, 1H), 3.69 (s, 3H), 3.16 (d, J = 17.4 Hz, 1H), 3.15–30.5 (m, 1H), 2.97–2.87 (m, 1H), 2.56–2.46 (m, 1H), 2.23–2.15 (m, 1H).

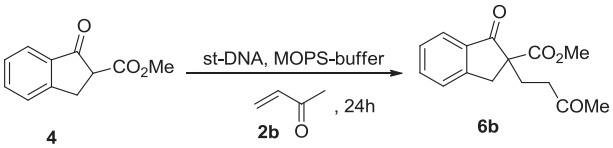
*2.3.6. Methyl 2-(2-cyanoethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**6f**)*

The product was directly obtained following the standard procedure as colorless oil (7% yield) after flash chromatography (3:1, Hexanes: AcOEt). The product matched with the previous spectroscopic data described in the literature [16]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 3.77 (d, J = 17.0 Hz, 1H), 3.70 (s, 3H), 3.16 (d, J = 17.4 Hz, 1H), 2.64–2.55 (m, 2H), 2.44–2.22 (m, 2H).

3. Results and discussion

We first studied the reaction of 1,3-dicarbonyl compounds with nitroalkenes. This reaction has been described with good results under thiourea [17] and squaramide [18] bifunctional catalysis (5–20 mol% catalytic loading) in toluene or CH_2Cl_2 and in some cases with lower catalytic loading (up to 0.1 mol%) [19]. The reaction of **1** with **2a** did not work in the absence of DNA, but in its presence the Michael product **3** was obtained in a moderated conversion after 24 h (entry 1, Table 1). The use of basic or acidic buffers (MES and CHES) did not improve the previous results (entries 2, and 3, Table 1), which were slightly better with a neutral buffer (MOPS, entry 4). An increase in the reaction time to 7 days was beneficial for the reaction, and we found a much better conversion (entry 5). This result clearly indicates that st-DNA is the real catalyst of this reaction. In order to increase the conversion, we found that the addition of a phase transfer catalyst (PTC), increasing in this manner the contact of the two phase (organic-reagent and aqueous), led a conversion of 70% (entry 6). Since other authors have studied the solubility of DNA in organic solvents [20], we also tried the reaction of DNA in CH_2Cl_2. However, we observed a very low solubility of the st-DNA and a quite poor conversion in the reaction (entry 7). Unfortunately, in all these reactions we only obtained racemic compounds (*ee* ranges between 1 and 4%), indicating that the aqueous media would be interrupting the plausible chiral pocket for the stereoselective processes or would be an inefficiency of DNA to induce asymmetry. After these initial results, we decided to study other Michael-type additions (Table 2) in order to increase the scope and also to find new results

Table 3
Several catalytic cycles by using st-DNA in the Michael addition[a].

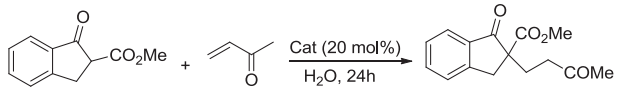


4 2b 6b

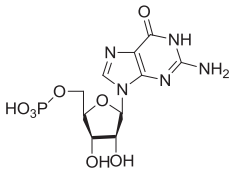
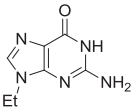
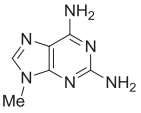
Entry	Catalytic cycle	Conversion (%)	Yield (%)
1	1	>99	86
2	2	>99	93
3	3	>99	80
4	4	>99	78
5	5	>99	70

[a] All the reactions were carried out with 1 mmol of the electrophile **2b**, 0.1 mmol of the nucleophile **4**, and 2.5 mL of MOPS buffer with 2.0 mg mL^{-1} of st-DNA.

Table 4
Reaction carried out with GMP, ethylguanine and methyladenine[a].



4 2b 6b

Entry	Catalyst (10 mol%)	Time (h)	Conversion (%)	Yield (%)
1	 GMP	24	>99	92
2	 Ethyl-guanine	24	>99	94
3	 Methyl-adenine	24	>99	68

[a] All the reactions were carried out with 0.5 mmol of the vinyl methyl ketone **2b**, 0.05 mmol of **4**, and 1.25 mL of MOPS buffer with 20 mol% of the catalyst.

that could give more information about the catalytic activity of the st-DNA as a catalyst.

Due to the low reactivity of the 1,3-dicarbonyl compound **1**, we studied the addition of the more reactive β-cyclic ketoesther **4** to different Michael acceptors **2** (Table 2) [21]. Full conversion was observed after 24 h in the reaction with the nitroalkene **2a**, affording **6a** in 87% isolated yield as a 1:1 mixture of diastereoisomers (entry 1). Similar results were obtained with ketone **2b** and aldehyde **2c**, which were completely transformed into **6b** (75% yield) and **6c** (82% yield) after 24 h (entries 2 and 3, Table 2). The β-substituted aldehyde **2d** required longer reaction times (7 days, entry 4) to afford **6d** (56% yield) as 1:1 mixture of diastereoisomers and the Evans' oxazolidinone derivative **2e** gave **6e** in 42% yield after 72 h (50% conversion, entry 5). Reactivity of acrylonitrile (**2f**) was lower (23% conversion after 7 days), affording **6f** in a poor yield (7%, entry 6), and other ethylene derivatives bearing EWG like esther, sulfoxide or sulfone, did not react, even increasing the time reaction to one week (entries 7, 8 and 9).

Then, we focused our attention in recycling the st-DNA (Table 3). With this aim, we carried out the reaction of β-ketoester **4** and vinyl methyl ketone **2b**. The reaction proceeds quite well after five catalytic cycles. In all of them we observed full conversion after 24 h and excellent yields.

After this initial studies about the 1,4-Michael addition, we studied which is the plausible cause of the catalytic activity of the st-DNA. Therefore, we carried out the reaction with a more basic unit of the DNA (GMP) in MOPS buffer and the same reaction conditions used for st-DNA. To our surprise, the reaction gave the final product **6b** with 20 mol% of the catalyst in 24 h (entry 1, Table 4). Thus, we decided to eliminate the sugar from GMP, and therefore we carried out the reaction with methyl-adenine and ethyl-guanine, in both cases with a 20 mol% (entries 2 and 3). We found exactly the same results, obtaining the product **6b** with excellent yields in 24 h. These results suggest that the more basic nitrogen (N-7) is acting as a base and the high polarity of these molecules allows them to perform the reaction in water. Besides our initial objective was the use of DNA as a catalyst for asymmetric reactions (instead of complex chiral catalysts), we have found that only racemic products were obtained and we have demonstrated that the catalytic activity was due to the basic nature of the DNA (similar to the result obtained from Et_3N [22]).

In conclusion, we have found that the 1,4-Michael addition of 1,3-dicarbonyl compounds can be carried out with st-DNA as catalyst. The reaction proceeds quite well for high activated double bonds and can be carried out in water. The st-DNA can be recovered and reused for further catalytic cycles without diminishing its activity. Finally, the similar or even larger efficiency of some nucleotides or nucleosides as catalysts of these reactions suggests that the basic nitrogen of the st-DNA could be responsible of the catalytic activity. Further research is needed in order to carry out the asymmetric version of this reaction and also mechanistic studies are in progress and will be reported at a later date.

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