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Pyrrole macrocyclization promoted by the cooperative effects of DNA–Lewis acid: synthesis of calix[5]pyrroles

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ABSTRACT

The condensation of a pyrrole and acetone or cyclohexanone that gives the corresponding tetrameric calix[4]pyrrole, catalyzed by $HAuCl_4$ or $Bi(NO_3)_3$, was tuned to yield the pentameric macrocycle calix[5]pyrrole as the major product in the presence of the biomolecule DNA obtained from salmon sperm in the reaction mixture. The DNA affected the ratio of the tetrameric to the pentameric macrocycle when present in adequate amounts in the reaction medium.

KEYWORDS: DNA, cooperative effect, gold, bismuth, calixpyrrole

1. INTRODUCTION

Macrocycles are commonly defined as molecules containing at least one large ring composed of a certain number of atoms, usually 9 or more. These are very important in areas such as medicinal and supramolecular chemistry. In medicinal chemistry, compounds such as vancomycin, erythromycin, rapamycin, and their derivatives are relevant in the treatment of infectious diseases. Supramolecular chemistry molecules, such as cyclodextrins, calixarenes, and calixpyrroles, which are specific anions, cations, or ion pair-recognizing molecules, are relevant to sensor applications and other technologies. In general, the capacity of the host to recognize an anion lies in the host's ability to coordinate with the anion via Lewis acid, electrostatic, or hydrogen bonding interactions.

Macrocyclization reactions are generally challenging, provide low synthetic yields, and usually require high dilutions to avoid intermolecular reactions or entropy-driven limitations on the reaction [1]. In biological systems, macrocyclization is controlled by modulating the effective molarity of highly dilute reactants through macromolecule-templated synthesis reactions [2]. A very interesting tool, DNA-templated synthesis, was recently described as applicable in the synthesis of macrocycles [2, 3]. This technique can be applied in both aqueous and organic solvents [4]. Although DNA-templated synthesis tends to produce a very complex product mixture, simple strategies using DNA as a catalyst have been recently developed for use in a variety of catalytic enantioselective reactions [5] under typical flask laboratory conditions. Readily available salmon sperm DNA has been used in these reactions. DNA intercalators [6] are typically used to induce asymmetric reactions [7].

Some of the most elusive supramolecularly relevant macrocycles are the calix[5]pyrroles (Figure 1). Since the discovery that calixpyrroles recognize anions, significant efforts have been made towards obtaining the pentameric macrocycles. Only a few successful cases have been reported, which include the use of electron withdrawing groups on the pyrrole [8], $Bi(NO_3)_3$ salts [9, 10, 11], or the use

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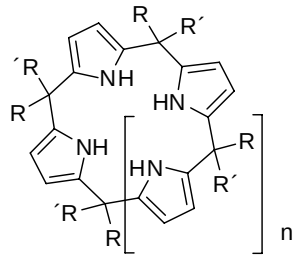


Figure 1. Structure of calix[n]pyrrole.

of highly diluted solutions of pyrrole [12]. An isotopic labeling experiment using acetone-d_6 was used to elucidate the mechanism underlying the formation of calix[5]pyrroles relative to calix[4]pyrroles. The study concluded that thermodynamic reaction control leads to the calix[4]pyrrole whereas kinetic reaction control leads to the formation of the expanded calix[5]pyrrole [13].

Here we describe the macrocyclization of pyrrole to give calix[5]pyrrole **1** (R, R´= CH_3 or $–(CH_2)_5$-) and calix[4]pyrrole **2** (R, R´= CH_3 or $–(CH_2)_5$-) in the presence of a catalyst comprising of HAuCl4, $Bi(NO_3)_3$, and DNA.

Hydrogen tetrachloroaurate (III) hydrate ($HAuCl_4$) has not been widely explored in organic synthesis. It is an interesting homogeneous catalyst in that it differs from other gold salts. Unlike other gold catalysts, $HAuCl_4$ is soluble in both water and organic solvents, and it is stable in solution. As such, this catalytic system is relatively environment friendly [14].

In view of the previous methods in which DNA was used as a catalyst in reactions involving carbonyls [15] or as a template for the synthesis of certain macrocycles [3], we decided to examine the condensation of pyrrole and ketones (propanone and cyclohexanone) in the presence of DNA and $HAuCl_4$ in water to explore the cooperative effects between DNA and the catalyst. Macrocyclization reaction conditions were used here. To our knowledge, these conditions have not yet been studied. With the aim of comparing the results of these conditions with other Lewis acid-catalyzed reactions, the reaction was also carried out in the presence of $Bi(NO_3)_3$. $Bi(NO_3)_3$ has been demonstrated to interact with calf thymus DNA and has been widely used as a catalyst in a variety of organic reactions [16], yielding substantially good results in the synthesis of calixpyrroles [9, 10, 17].

2. MATERIALS AND METHODS

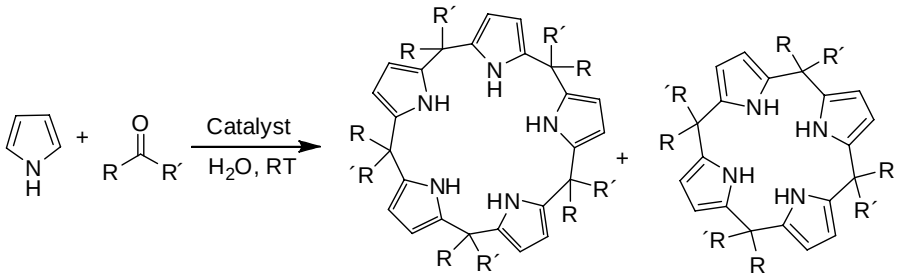
Nuclear magnetic resonance spectra were recorded on a Varian Gemini 200 and Mercury 400. ^{1}H NMR spectra were recorded at 200 and 400 MHz and are reported as follows: chemical shift in ppm relative to TMS as an internal standard (for spectra obtained in $CDCl_3$), signal multiplicity is given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances. In a typical reaction, catalyst and the corresponding ketone and 0.1 mL of distilled pyrrole were mixed by stirring at room temperature. The reaction mixture was filtered and the solvent was evaporated by using nitrogen. Heat was avoided throughout the process. Compounds **1** and **2** were characterized according to the spectroscopic information described in previous reports [9, 10].

3. RESULTS AND DISCUSSION

In the first stage, the reaction was tested using different concentrations of the Lewis acid in the absence of DNA to determine the best conditions for exploring the effects of the DNA. Unlike in other calix[5]pyrroles syntheses, the reaction described here was conducted in water to provide environment-friendly reaction conditions. The results are listed in Table 1. It can be seen that total pyrrole conversion was obtained in the presence of acetone to yield **1** and **2** in a ratio of 2:1, in the presence of 5 mg $Bi(NO_3)_3$ and 3.3:1 in the presence of 15 mg $HAuCl_4$. The use of less molar equivalents of the acid resulted in an incomplete reaction. The presence of $Bi(NO_3)_3$ yielded **1** and **2** in a ratio of 2:1, which was similar to the optimal ratio reported under organic solvent conditions; however, the use of $HAuCl_4$ with limited amount of acetone, that is two molar equivalents, yielded **1** and **2** in a ratio 50% higher than that obtained using $Bi(NO_3)_3$ alone [9].

The effect of the ketone as a solvent was apparent in the reaction conducted with cyclohexanone. The use of $Bi(NO_3)_3$ (100 mg) with an excess of cyclohexanone (2 mL) yielded only **2**, but both **1** and **2** in a ratio of 5.3:1 were obtained upon the addition of 0.4 mL ketone. The ratio of **1** and **2** was found to vary with the concentration of $Bi(NO_3)_3$.

Table 1. Ratios between **1** and **2**, determined from the NMR spectra of the crude reaction product obtained under different reaction conditions and catalyzed by $Bi(NO_3)_3$ and $HAuCl_4$.



1 **2**

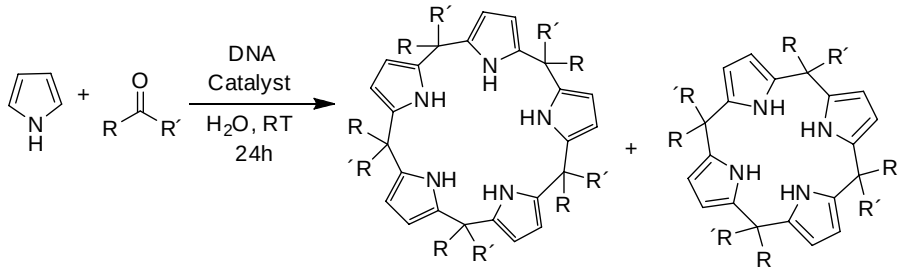
Entry[a]	Reaction Time (h)	R, R	RCOR´ (mL)	Catalyst	Catalyst (mg)	Rate **1/2**
1	24	CH_3	2	$Bi(NO_3)_3$	1	[b]
2	24	CH_3	2	$Bi(NO_3)_3$	3	1.3[b]
3	24	CH_3	2	$Bi(NO_3)_3$	5	2
4	24	CH_3	2	$Bi(NO_3)_3$	40	1.6
5	24	CH_3	2	$Bi(NO_3)_3$	80	0.2
6	24	$-(CH_2)_5-$	2	$Bi(NO_3)_3$	100	< 0.1
7	24	$-(CH_2)_5-$	0.4	$Bi(NO_3)_3$	100	5.3
10	24	CH_3	2	$Bi(NO_3)_3$	100	0.2
11	24	CH_3	0.4	$HAuCl_4$	5	[b]
12	48	CH_3	0.4	$HAuCl_4$	5	[b]
13	24	CH_3	0.4	$HAuCl_4$	15	3.3
14	96	$-(CH_2)_5-$	0.4	$HAuCl_4$	3	6.7
15	24	$-(CH_2)_5-$	0.4	$HAuCl_4$	3	6.7
16	24	$-(CH_2)_5-$	0.4	$HAuCl_4$	7	7.6
17	24	$-(CH_2)_5-$	0.4	$HAuCl_4$	14	5.3
18	24	$-(CH_2)_5-$	0.4	$HAuCl_4$	25	3
19	24	$-(CH_2)_5-$	0.4	$HAuCl_4$	40	0.8
20	24	$-(CH_2)_5-$	0.4	$HAuCl_4$	60	[c]
21	24	$-(CH_2)_5-$	2	$HAuCl_4$	50	<< 0.1

[a]Conditions: 0.1 mL pyrrole, 1 mL water, at room temperature. [b]the reaction did not reach completion under these conditions. [c]the reaction was not quantitative, and other products were observed.

The ratio of **1** to **2** increased significantly, from the reported value of 2.3 [10] to 6 in the presence of $Bi(NO_3)_3$, and 7.6 in the presence of $HAuCl_4$. An excess of **2** could be obtained by adding an excess of the catalyst [17], indicating that the solvent itself played a crucial role in favoring the formation of **1** in water. The addition of 60 mg HAuCl4 resulted in the precipitation of polymeric products, and the calixpyrrole yield decreased. The NMR spectrum of the crude reaction product indicated the presence of additional products that probably resulted from a side reaction that yielded gold nanoparticles, as reported previously under similar conditions [18].

Once the conditions where standardized, we proceeded to study the role of DNA in the reaction. The results of the studied reactions are summarized in Table 2. The reaction in the presence of DNA and

Table 2. Ratios between **1** and **2**, determined from the NMR spectra of the crude reaction product obtained under different reaction conditions and catalyzed by $Bi(NO_3)_3$ and $HAuCl_4$ in the presence of DNA.



Entry[a]	R, R	RCOR´ (mL)	Catalyst	Catalyst (mg)	DNA[b] (mg)	Rate **1/2**
1	CH_3	2	-	-	80	[c]
2	$-(CH_2)_5-$	2	-	-	80	[c]
3	CH_3	2	$Bi(NO_3)_3$	100	-	0.2
4	CH_3	2	$Bi(NO_3)_3$	100	10	0.6
5	CH_3	2	$Bi(NO_3)_3$	100	80	1.2
6	CH_3	2	$Bi(NO_3)_3$	100	160	1.2
7	$-(CH_2)_5-$	2	$Bi(NO_3)_3$	100	-	< 0.1
10	$-(CH_2)_5-$	0.4	$Bi(NO_3)_3$	100	-	5.3
11	CH_3	2	$HAuCl_4$	5	40	[d]
12	CH_3	2	$HAuCl_4$	50	40	< 0.1
13	CH_3	0.4	$HAuCl_4$	15	-	3
14	CH_3	0.4	$HAuCl_4$	25	5	3
15	$-(CH_2)_5-$	2	$HAuCl_4$	50	-	< 0.05
16	$-(CH_2)_5-$	2	$HAuCl_4$	50	40	1.2
17	$-(CH_2)_5-$	2	$HAuCl_4$	15	40	[d]
18	$-(CH_2)_5-$	0.4	$HAuCl_4$	7	-	7.6
19	$-(CH_2)_5-$	0.4	$HAuCl_4$	7	10	7.6
20	$-(CH_2)_5-$	0.4	$HAuCl_4$	7	20	8.3
21	$-(CH_2)_5-$	0.4	$HAuCl_4$	14	10	4.27
22	$-(CH_2)_5-$	0.4	$HAuCl_4$	14	20	7.8
23	$-(CH_2)_5-$	0.4	$HAuCl_4$	14	80	8.5
24	$-(CH_2)_5-$	0.4	$HAuCl_4$	30	7	1
25	$-(CH_2)_5-$	0.4	$HAuCl_4$	30	50	2.75
26	$-(CH_2)_5-$	0.4	$HAuCl_4$	60	-	[e]
27	$-(CH_2)_5-$	0.4	$HAuCl_4$	60	40	[e]
28	$-(CH_2)_5-$	0.4	$HAuCl_4$	60	80	[e]
29	$-(CH_2)_5-$	0.4	$HAuCl_4$	60	160	[e]

[a]Conditions: 0.1 mL pyrrole, 1 mL water, stirring 24 h, room temperature. [b]Commercial salmon sperm DNA was used without purification. [c]0% pyrrole conversion. [d]The reaction did not reach completion under these conditions. [e]The reaction was not quantitative, and other products were observed.

in the absence of catalyst was not productive. Even after several days of reaction time, only pyrrole was recovered. Also, an excess of acetone in the presence of DNA did not improve the proportion of **1** relative to the reaction yield obtained in the presence of acetone and the absence of DNA; however, the proportion of **1** clearly increased as the amount of DNA in the reaction medium was increased.

The use of an excess of cyclohexanone altered the ratio of **1** to **2**, and this change was considerably more significant in the presence of large amounts of DNA, and 50 mg of HAuCl4 (entries 15–16, Table 2). Under these conditions, the ratio of **1** and **2** increased from < 0.1 to 1.2 upon the addition of DNA (40 mg).

A higher ratio of **1** was obtained in the presence of smaller quantities of cyclohexanone (0.4 mL). The use of 14 mg $HAuCl_4$ increased **1** by a factor of two as the quantity of DNA was increased from 10 to 20 mg. Interestingly, the same effect was not observed in the presence of small (7 mg) or large (60 mg) quantities of the catalyst.

4. CONCLUSION

In summary, we studied a new environment-friendly method for synthesizing calixpyrroles under mild reaction conditions using $HAuCl_4$ or $Bi(NO_3)_3$ as the catalyst and water as the reaction medium. The reaction was conducted at room temperature. DNA was found to alter the ratio of **1** and **2** macrocycles. The mechanism underlying the interactions of DNA with the supramolecular assembly could not be elucidated [19]. It is possible that the DNA interacted with a reactive intermediate, [11], acted as a buffer to provide kinetically favorable conditions [13], or some other mechanism not yet considered may have been operational. The DNA certainly affected the ratio of the tetrameric to the pentameric macrocycle when present in adequate amounts in the reaction medium. This observation could be helpful for the synthesis of other macrocycles that are more difficult to obtain. To our knowledge, the use of DNA for this purpose has not been reported previously.

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CONFLICT OF INTEREST STATEMENT

The authors confirm that this article content has no conflict of interest.

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