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# The Synthesis of a New Type of Anthracene DNA Intercalator

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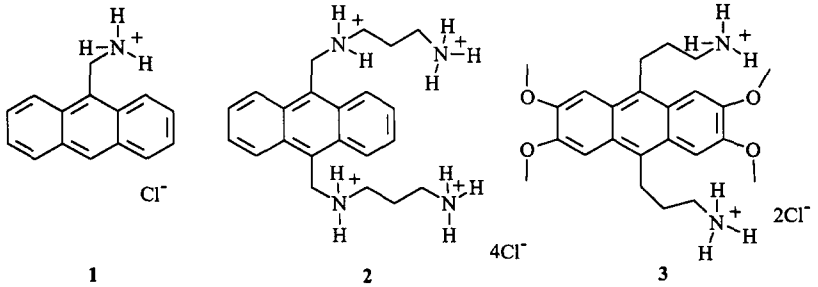
***Abstract:***. A new type of DNA intercalator based on anthracene **3** was synthesized. Preliminary binding studies show high affinity of this probe to CT-DNA. Higher binding constant of this compound ($4.0 \times 10^4$ $M^{-1}$) as compared with that known for 9-aminomethylanthracene, is caused presumably by enhanced electrostatic interaction. © 1998 Elsevier Science Ltd. All rights reserved.

During our studies towards synthesis of a new type of DNA intercalating agent we turned our attention on anthracene derivatives.[1] It has been pointed out that anthracene-shape compounds intercalate without supporting positive charges with $\Delta G_I$= 26-27 kJ/mol.[2] When supporting aminoalkyl substituents are present this intercalation is enhanced by 5 kJ increment for each ion pairing. Indeed, 9-aminomethylanthracene (**1**) binds to natural and synthetic DNA with high affinity.[3] Increased electrostatic interaction due to four positive $N^+$ groups present in compound **2** (prepared by Czarnik and Van Aman) enhanced its intercalation to DNA.[4]

Since we were interested in a simple model for DNA ligand interaction studies, we turned our attention to compound **1,** which was difficult to be synthesized using the known methods.[3,5]




**1** **2** **3**

Chart 1

The synthesis of 9-aminomethylanthracene (**1**) was performed using our own concept.[6] Unfortunately, compound **1** decomposes slowly in solution what reduces its potential application. Therefore we synthesised another type of compound of structure **3** possessing two amino groups and four methoxy groups. We turned our attention on reaction of aldehydes with veratrol catalyzed by sulfuric acid.[7] After many trials we found that direct acid promoted condensation of veratrol with 4-aminobutyraldehyd-diethyl acetal led to formation of aminoanthracene **3** in 55% yield.[8] For DNA binding studies hydrochloride of compound **3** was obtained.

Binding studies of **3** to DNA were performed using absorption and fluorescence spectroscopy. In the presence of increasing amount of CT DNA a strong decrease in the peak intensities (hypochromicity) was observed together with broadening and red shift in UV spectra. [1]

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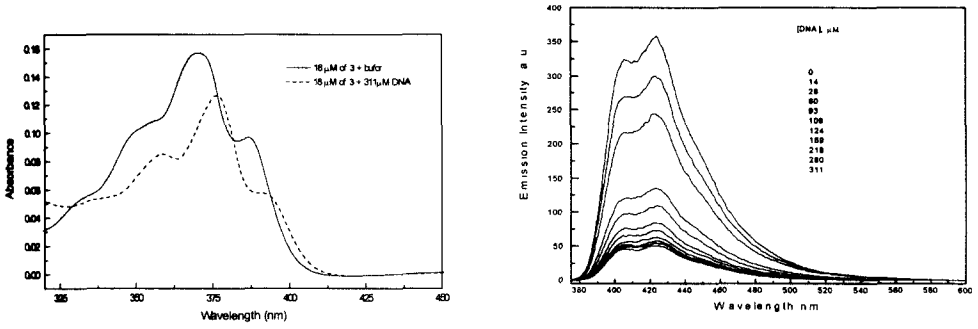


Figure 1. The changes in UV (left, dotted line) and fluorescence spectra of compound **3** (85 mmol $dm^{-3}$) upon addition of CT DNA ( in 50 mM NaCl water solution, at pH = 7.0).

Fluorescence studies proved that upon addition of CT DNA to the solution of **3** quenching of fluorescence by DNA bases was observed. Analysis of the fluorescence data according to Stern-Volmer equation[3] allowed us to calculate the binding constant of 4.0 x $10^4$ $M^{-1}$, which is higher than the value obtained for probe **1**[3] (1.0 x $10^4$ $M^{-1}$). Better binding of our probe to CT-DNA is probably enhanced by the electrostatic interactions due to the presence of the second amino group.[2]

Functionalization of compound **3** and detailed studies of ligand-DNA interaction are in progress in our laboratories.

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6. Commercially available 9-anthraldehyde was reduced by sodium borohydride to the corresponding alcohol in 88% yield. This compound reacted with $PBr_3$ to afford 9-bromomethylanthracene in 77% yield. Halogen substitution proceeds smoothly in DMSO containing $NaN_3$, at 50°C in 90% yield. Reduction was performed in THF solution at temperature below 30°C using $LiALH_4$. Treatment of free amine in toluene with gaseous HCl precipitated pure hydrochloride **1**.
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8. To the intensively stirred, cooled to 5°C solution of sulfuric acid (10 ml, 84%), a mixture of 4-aminobutyraldehyd-diethyl acetal (10 mmol) and veratrol (3 mmol) was added slowly, keeping temperature of the reaction mixture below 10°C. The reaction mixture was stirred at this temperature for 1 h. Then water (20 ml) was added followed by ammonium hydroxide to reach pH 11. Crude amine was extracted with chloroform, and purified by recrystallization from toluene. Hydrochloride **3** was precipitated from the chloroform solution after treatment of the amine with gaseous HCl. Overall yield 55%. $^1$H NMR (DMSO-$d_6$) δ 1.99 (4H, br s, -$CH_2CH_2N$), 3.10 (4H, t, J = 6.8 Hz, -$CH_2CH_2N$), 3.46-3.58 (4H, m, Ar$CH_2$-), 4.02 (18H, br s, -$OCH_3$ + $NH_3$), 7.41 (4H, s, Ar**H**); $^{13}$C NMR ($CDCl_3$) δ 25.3, 28.2, 56.1, 96.0, 102.9, 125.5, 128.4, 149.6. Anal. Calcd. for $C_{24}H_{34}O_4Cl_2$+$H_2O$ 57.26; H, 7.21; N, 5.56. Found: C, 57.02; H 7.50; N, 5.34.