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Original scientific paper

Electrochemical and UV-visible spectroscopic investigation of anthranilic acid interaction with DNA

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Abstract

The interaction between anthranilic acid (Aa) and DNA was studied by cyclic voltammetry and UV-visible spectroscopy. Cisplatin (Cis), a drug that is known to interact with DNA, was used as a reference. The electrochemical response showed that the anodic peak potential of Aa shifted downward by 35.1 mV (from 934.4 to 899.3 mV) in the presence of DNA (18 µM). The shift suggests the occurrence of electrostatic interactions between Aa and the DNA backbone. Binding constant (7.08×10^4 M^{-1}) and free energy (-26.85 kJ mol^{-1}) for Aa-DNA were derived from suppressed anodic peak current density, while Cis was found to have stronger binding (19.49×10^4 M^{-1}) under identical conditions. UV-visible spectroscopy confirmed hypochromicity at 324 nm for Aa, which is consistent with groove binding, while the distinct mechanism of Cis most likely involves covalent cross-linking. Larger binding site size of Aa (5.76 base pairs) and decreased diffusion coefficients compared with Cis smaller footprint (0.56 base pairs), pointed to differences in mechanisms. These results highlight anthranilic acid as a promising DNA-targeting agent with potential applications in antimicrobial and anticancer drug development, providing a comparative context with the well-established pharmacology of cisplatin.

Keywords

DNA binding; binding energy; bioactive compound; hydrogen-bonded network; cyclic voltammetry

Introduction

Anthranilic acid (2-aminobenzoic acid, Aa) is an aromatic natural compound, especially in the family of aromatics. A common structural motif in some bioactive compounds, Aa and its related derivatives have become increasingly relevant in drug development as therapeutic agents [1-6]. The bioactivity and potential biological activities of Aa, and more particularly its derivatives, have generated a great deal of interest in the study of the molecular mechanisms of interaction with DNA,

one of the most fundamental targets of therapeutic agents. The lack of understanding of how Aa interacts with DNA contrasts strongly with that of several well-characterized DNA-binding drugs, including cisplatin, one of the most widely used chemotherapeutic agents. Cisplatin binds to DNA through covalent cross-linkages. This interaction initiates replication inhibition and leads to apoptosis in cells. Its mechanism of action is well known, but many small molecules are capable of binding to DNA in non-covalent and possibly nonspecific ways [7-11]. These interactions, such as intercalation or groove binding, can influence the stability and function of DNA and its replication products in a very specific manner.

To understand the mechanism of DNA and Aa binding, we use cyclic voltammetry and UV-visible spectroscopy to study the binding affinity of Aa-DNA, using the analogous binding concentration of cisplatin. CV gives quantitative information about the Aa redox behaviour, binding kinetics, and thermodynamics, as well as the binding affinity and mode of interaction between Aa and Cis [12-17].

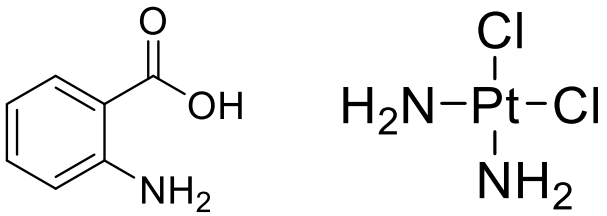
This study is an important step towards an in-depth biophysical understanding of the interactions of the ligand Aa with the DNA molecule and contributes to the further advancement of novel DNA-targeted therapeutics. By consolidating the electrochemical and spectral data, we offer a new approach for rational drug design, which represents an excellent basis for the development of alternative DNA-binding agents with unique mechanistic properties. Moreover, the non-covalent interactions of Aa with DNA provide new directions for antimicrobial and anticancer drug research in cases where less aggressive DNA modification might have therapeutic implications. The work contributes to establishing Aa as a novel therapeutic target that potentially offers advantages in various fields of molecular biophysics and pharmaceutical development.

Experimental

Chemicals and reagents

All chemicals used in this experiment were analytical grade and manufactured at various commercial suppliers to the laboratory and directly used without further purification. Tetrabutyl-ammonium tetrafluoroborate (Bu_4NBF_4, electrochemical grade, 99 % purity) was purchased from Fluka (Switzerland) and further purified by recrystallization in methanol before use.

Anthranilic acid (Aa) was obtained from Sigma-Aldrich. Its stock solution was prepared in 10 % aqueous ethanol. The system was buffered at pH 7.2 by phosphate buffer (0.1 M KH_2PO_4 + + 0.1 M NaOH). Cisplatin (Cis) was supplied by a local healthcare institution in El Oued region (Algeria). Its stock solution was prepared following the same procedure described for anthranilic acid. Molecular structures of Aa and Cis are presented in Figure 1.



anthranilic acid ***cisplatin***

Figure 1. *Molecular structure of the investigated compounds*

DNA extraction

DNA was isolated as described in our previous work [18,19], and its purity was measured by the absorbance ratio at 260 nm (A260) and 280 nm (A280). The ratio A_{260}/A_{280} = 1.98, which clearly

indicates a high degree of DNA purity [20] and DNA concentration was measured by the absorbance of UV light at 260 nm using a molar extinction coefficient of 6600 M^{-1} cm^{-1}[21].

Apparatus and procedures

Cyclic voltammetry (CV) experiments were conducted using a PGZ301 potentiostat/galvanostat (Radiometer Analytical SAS, France) with a 15 mL three-electrode electrochemical cell (which comprises a glassy carbon (GC) working electrode (geometric area: 0.07 cm^2), a platinum wire counter electrode and an Hg/Hg_2Cl_2 paste-coated wire reference electrode). At 298 K, a voltammogram of 6 mM of anthranilic acid in a 0.1 M phosphate buffer solution (KH_2PO_4/K_2HPO_4, pH 7.2) was recorded without the addition of DNA. Another voltammogram was recorded with incremental DNA addition under the same conditions. Quantitative UV-visible spectroscopic measurements were made on a Shimadzu 1800 (Japan) spectrometer. First measurements of the spectral response of 1 mM Aa in 0.1 M phosphate buffer solution (KH_2PO_4/K_2HPO_4, pH 7.2) were performed at 298 K, followed by measurements with increasing DNA concentration.

Results and discussion

Voltametric DNA interaction study

Binding constant and binding free energy

Determination of binding constant and binding free energy of anthranilic acid and the reference drug cisplatin with DNA was done by recording the voltammograms of the ligand anthranilic acid and cisplatin in 0.1 M aqueous phosphate buffer solution at pH 7.2. The cyclic voltammograms of anthranilic acid and cisplatin show an oxidation maximum at 0.934 and 1.129 V, respectively. When an amount of DNA solution was added, there was a decrease in the anodic peak current with a positive shift in oxidation peak potential (Figure 2).

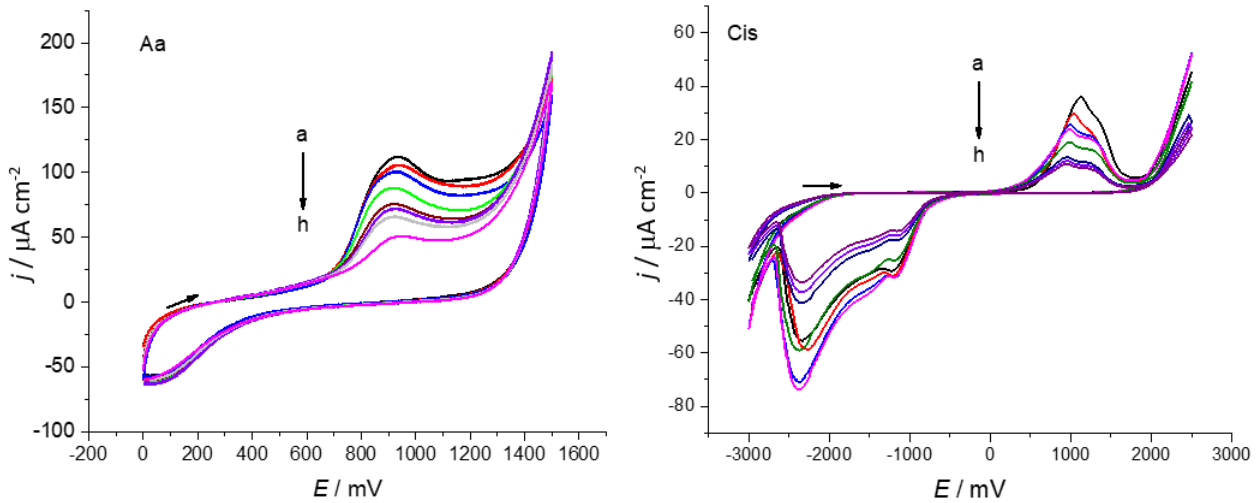


Figure 2. *Cyclic voltammograms of 6 mM Aa and 4 mM Cis in 0.1 M buffer phosphate solution recorded at 0.1 V s^{-1} potential sweep rate on GC disk electrode at 298 K in the absence of DNA (a) and presence of 1 µM (b), 2 µM (c), 4 µM (d), 7 µM (e), 8 µM (f), 10 µM (g), and 18 µM DNA (h)*

The decrease of the anodic peak current density for ligand Aa on its binding with DNA forms the basis of the calculation of the binding constant. The respective shifts in peak potential values offer information regarding the mode of interaction-intercalation, groove binding or electrostatic association between the ligand and DNA [22,23].

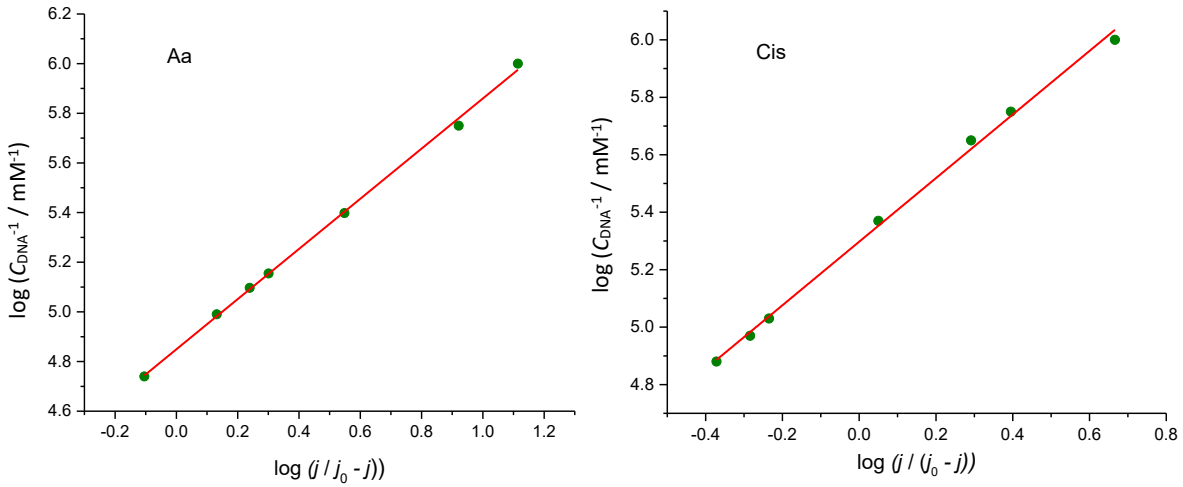


Figure 3. *Plots of log (C_{DNA}^{-1}) vs. log (j/j_0-j) used to calculate the binding constant of ligand Aa and the reference drug Cis with DNA*

The binding constants of the investigated compound and the reference drug Cis were calculated from the decrease in the anodic peak current density of Aa-DNA and Cis-DNA adducts relative to free Aa and Cis, respectively, using Equation (1) [24]:

$$\log\left(\frac{1}{C_{\mathrm{DNA}}}\right)=\log K+\log\frac{j}{j_0-j} \quad (1)$$

where K is the binding constant, j and j_0 are the anodic peak current densities in the presence and absence of DNA, and C_{DNA} is the DNA concentration. Linear equations were obtained from the plot of log(C_{DNA}^{-1}) *vs*. log(j/(j_0-j)) (Figure 3) for Aa and the reference drug Cis with a linear correlation coefficient of 0.998 and 0.997, respectively. This suggested that the binding number was 1, thus, the inclusion complexes interacted with DNA to form a 1:1 association complex. The values of the binding free energy of the ligand Aa and the reference drug Cis with DNA were obtained using binding constants obtained from the y-intercept of the linear equation, and their values were found to be -26.85 and -29.30 kJ.mol^{-1} respectively, as shown in Table 1. The standard errors for the Gibbs free energy changes were calculated from the regression analysis of the binding constant equations and are included in Table 1. These reflect the experimental uncertainty associated with the linear fits and propagation of error through the thermodynamic relationships.

Table 1. *The linear equations of log (C_{DNA}^{-1})* vs. *log (j/(j_0-j), binding constant, and binding free energy values of Aa-DNA and Cis-DNA obtained from CV data at pH 7.2 and* T *= 298 K*

Adduct	Equation	R^2	K / M^{-1}	-ΔG ± SD / kJ mol^{-1}
Aa-DNA	y = 1.01034x + 4.84926	0.998	7.08×10^4	26.85 ± 0.04
Cis-DNA	y = 1.10666x + 5.29746	0.997	19.49×10^4	29.30 ± 0.06

We found that the binding constant of Aa was 8.52×10^4 M^{-1}, a bit lower than that of Cis (19.49×10^4 M^{-1}). This finding implies that they have very different pathways in which they interact. They also show that UV-visible spectroscopy indicates a hypochromicity at 324 nm for Aa. This is probably due to groove binding, while covalent DNA interactions result in different signal modulations in the retina [25-27]. The observed binding site sizes further support our conclusions. Aa holds 5.76 base pairs, compared with 0.56 base pairs for Cis, thus providing evidence of its similar mechanism of interaction [28,29].

Binding site size

The binding site size (*s*) was calculated based on equation (2) [30,31]:

$$\frac{c_b}{c_f} = K\left(\frac{\text{free base pairs}}{s}\right) \quad (2)$$

where *s* is the size of the binding site in base pair terms, *K* is the binding constant, C_f is the concentration of the free compound and C_b is the concentration of the DNA-bound compound. Since the concentration of a DNA base pair is given in terms of nucleotide phosphate, the concentration of the DNA base pair will be expressed as $C_{DNA}/2$ and so, Equation (2) can be written as Equation (3),

$$\frac{c_b}{c_f} = K\frac{c_{DNA}}{2s} \quad (3)$$

The C_b/C_f ratio is equal to $(j_0\text{-}j)/j$ [23], which are the values of experimental peak current densities. The plots of C_b/C_f versus C_{DNA} are shown in Figure 4.

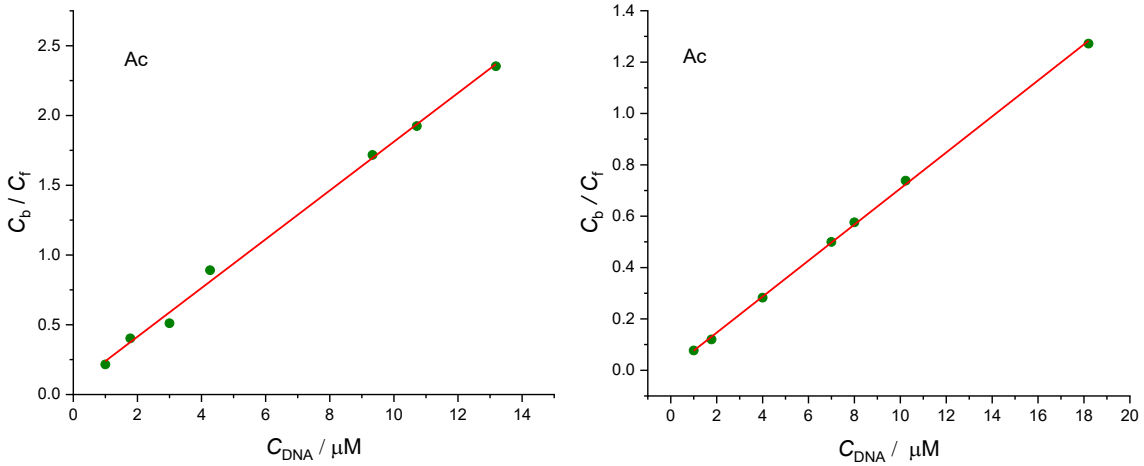


Figure 4. *Plots of C_b/C_f versus C_{DNA} for Aa and Cis, used for the calculation of binding site size*

The equations derived from the least squares fitting over the concentration studied range for Aa and the reference drug Cis are presented in Table 2, where $y = C_b/C_f$ and x = concentration of the compound, in μM.

Table 2. *Values of binding site size obtained using the plot of C_b/C_f versus C_{DNA}*

Adduct	Equation	R^2	s ± SD / base pair
Aa-DNA	$y = 0.17474x + 0.06453$	0.986	5.76 ± 0.05
Cis-DNA	$y = 0.07016x + 0.00615$	0.984	0.56 ± 0.3

The small values of binding site size further suggest that Aa and Cis interact electrostatically with DNA.

Generally, binding site sizes of 1 to 3 base pairs suggest intercalation, while values between 4 and 6 are more consistent with groove binding or non-specific hydrophobic interaction [32-33]. Very small values (*e.g.*, less than 1) may reflect highly localized, electrostatic or covalent binding, such as observed with Cis [34].

Diffusion coefficients

The diffusion coefficient is a parameter that further confirms the interaction of Aa and Cis with DNA, free Aa and Cis diffuse more rapidly in solution than their corresponding adducts Aa-DNA and Cis-DNA. These can be attributed to the high molecular weight of the formed adducts.

Figure 5 shows the electrochemical behaviour of the compound Aa and the reference drug Cis at different scan rates. The voltammograms displayed clear, stable anodic peaks. The diffusion coefficients of the free and DNA-bound form of Aa and Cis were determined using the Randles-Ševčik Equation (4) [35].

$$i = 2.69 \times 10^5 n^{3/2} SCD^{1/2} v^{1/2} \quad (4)$$

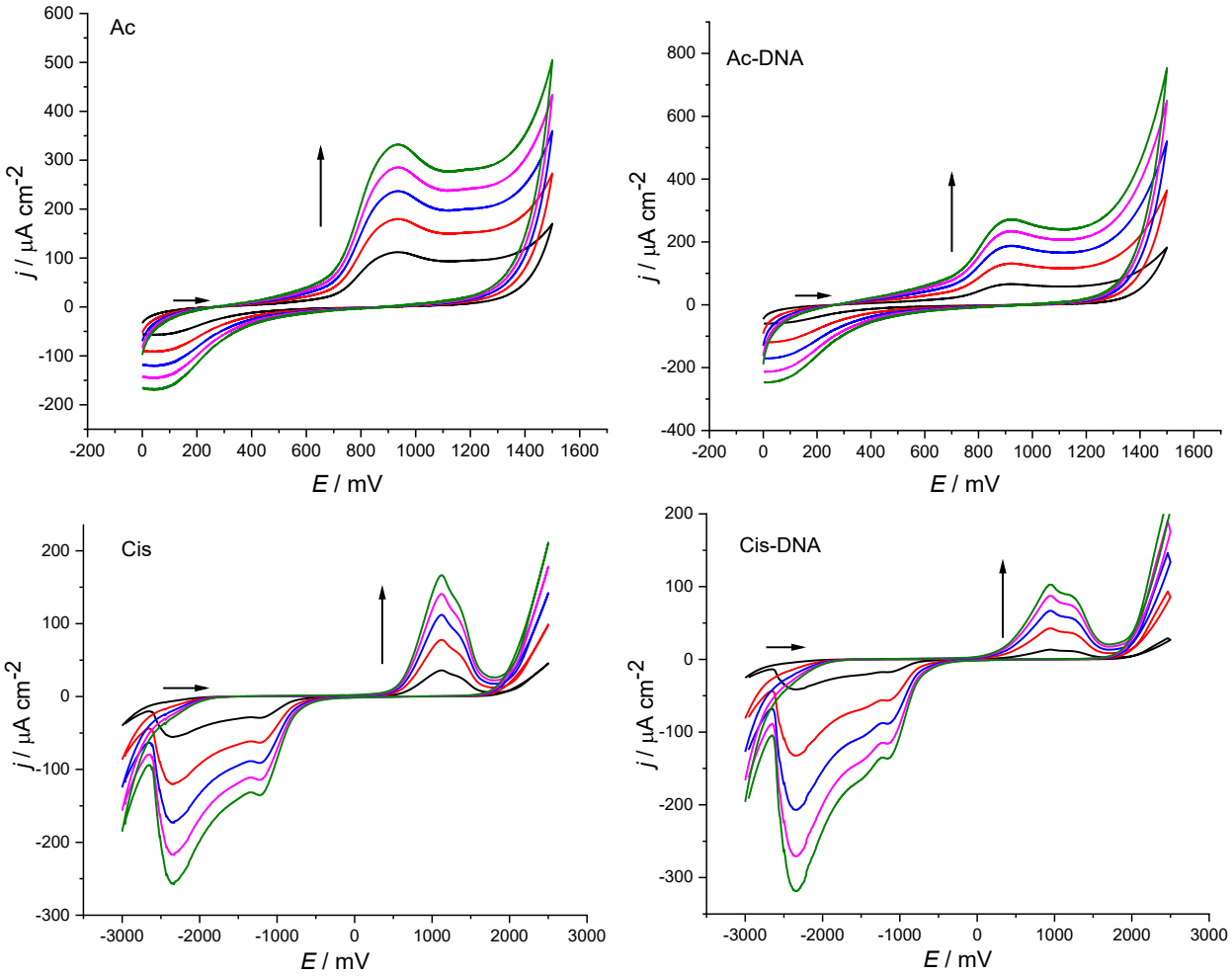


Figure 5. *Cyclic voltametric behaviour of Aa and Cis on GC disk electrode in the absence and in the presence of 8 µM of DNA in 0.1 M buffer phosphate solution at scan rates of 0.5, 0.4, 0.3, 0.2 and 0.1 V s^{-1} with supporting electrolyte 0.1 M Bu_4NBF_4. The vertical arrowhead indicates increasing scan rate*

In equation (4) i / A represents the anodic peak current, n is the number of electrons participated in the oxidation process, S / cm^2 is the surface of the working electrode, C / mol cm^{-3} is the concentration of the electroactive compounds, D / cm^2 s^{-1} is the diffusion coefficient, and v / V s^{-1} is the scan rate. The plots of anodic peak current density vs. the square root of scan rate (Figure 6) suggest that the oxidation reaction is diffusion-controlled. Diffusion coefficients of the free and DNA-bound compounds were calculated from the slopes of the linear regression of the plots of the square root of the scan rate versus the anodic peak current. The lower diffusion coefficients of the bound compounds compared to the free ones further confirm the interaction between the studied compounds and DNA (Table 3).

The diffusion coefficients of the Aa-DNA and Cis-DNA adducts are lower than those for the free Aa and Cis, indicating the formation of a high molecular weight complex that diffuses slowly towards the electrode.

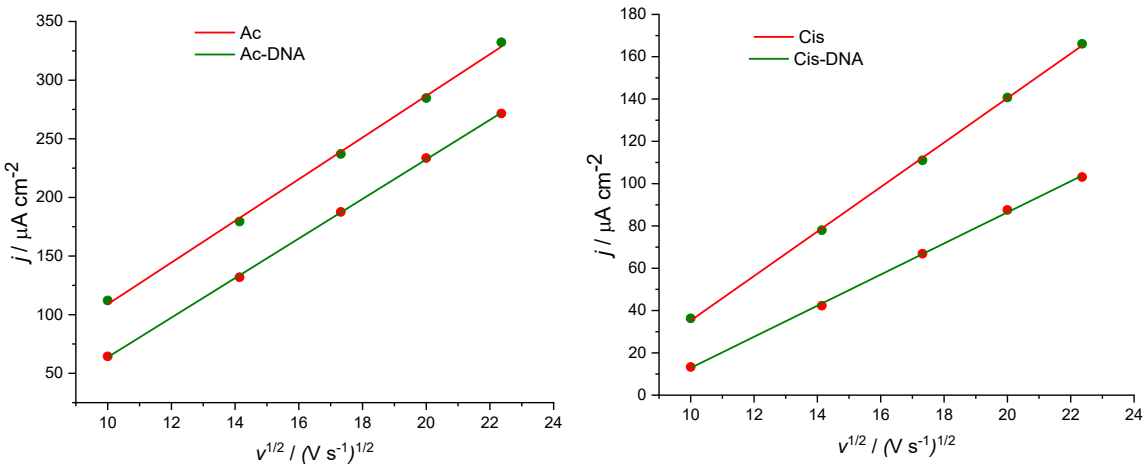


Figure 6. *Plots of the anodic peak current density vs. square root of scan rate of Aa and Cis in the absence and in presence of 8 µM of DNA under the experimental conditions given with Figure 5*

Table 3. *Diffusion coefficient values of the free and DNA bound form of Aa and Cis*

Compound	Equation	R^2	D / cm^2 s^{-1}
Aa	$y = 17.7691x - 68.7864$	0.998	3.27×10^{-7}
Aa-DNA	$y = 16.8654x - 104.9029$	0.999	2.95×10^{-7}
Cis	$y = 10.5162x - 69.8763$	0.999	1.50×10^{-7}
Cis-DNA	$y = 7.3560x - 60.69307$	0.999	0.73×10^{-7}

Absorption spectroscopic DNA interaction study

The interaction of Aa with DNA was also studied by UV-visible spectroscopic titration, and the purpose of this study was to validate the results obtained from cyclic voltammetry assays. The experiments were carried out in a 0.1 M buffer phosphate solution of pH 7.2. Incremental portions of DNA solution from 0.5 to 2.8 µM were added to a solution of 1 mM of Aa in the same solution. The obtained mixture was scanned in the range of 280 to 400 nm. DNA do not show any absorption at this wavelength, a strong peak which appeared at 324.3 nm, which involves excitation of a non-bonding electron (*n*) from the carbonyl or amine group to an antibonding π* orbital, lowered in intensity upon continuous addition of DNA (Figure 7).

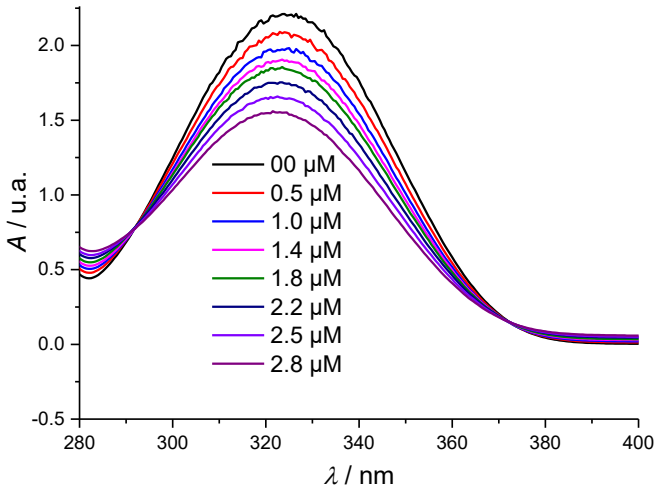


Figure 7. *Absorbance spectra of Aa-DNA adduct*

The binding constants *K* were evaluated from the absorption data according to the Benesi-Hildebrand Equation (5) [36]:

$$\frac{A_0}{A-A_0}=\frac{\varepsilon_f}{\varepsilon_b-\varepsilon_f}+\frac{\varepsilon_f}{\varepsilon_b-\varepsilon_f}\frac{1}{KC_{DNA}} \quad (5)$$

where A_0 and A are the absorbance of the ligands and their adducts with DNA, respectively, while ε_f and ε_b are their respective extinction coefficients. A plot of A_0 / (A - A_0) versus C_{DNA}^{-1} gave a slope of (ε_f / (ε_b -ε_f)) K^{-1} and an intercept at the y-axis equal to ε_f / (ε_b -ε_f), where K is the ratio of the y intercept to the slope (Figure 8). The value has been determined to be 7.82×10^4 M^{-1} for Aa-DNA. The corresponding free binding energy calculated using the equation ΔG = -nRT ln$K$ was equal to -27.9 kJ mol^{-1}, this value is in close agreement with that obtained from cyclic voltammetry experiments.

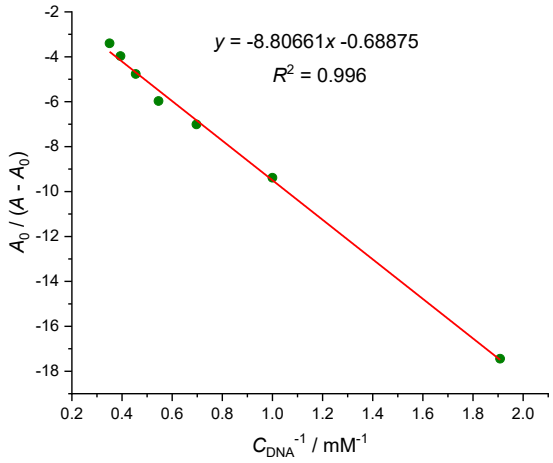


***Figure 8**. Plots of $A_0/(A_0-A)$ vs. C_{DNA}^{-1} used to calculate the binding constant of ligand Aa interacting with DNA*

Conclusions

In the present work, we examined the interaction of anthranilic acid (Aa) with DNA using cyclic voltammetry and UV-visible spectroscopy, with cisplatin as a reference drug for comparison. The findings of the electrochemical analysis revealed a decrease in anodic peak current density as a result of DNA binding, suggesting a high degree of interaction between DNA and Aa. The shift in peak potential values gave significant information on the mode of interaction, revealing non-covalent interaction that could occur through groove binding.

The obtained binding constant (7.08×10^4 M^{-1}) and binding free energy (-26.85 kJ mol^{-1}) of Aa-DNA interaction were lower than those of the drug cisplatin, demonstrating that they have different affinities and binding mechanisms. UV-Visible spectroscopy further confirmed these results, showing hypochromicity at 324 nm for Aa upon addition of DNA, typical of groove binding, with a binding constant value of 7.82×10^4 M^{-1} and −27.9 kJ.mol^{-1} for the free energy, in good agreement with the values calculated from CV.

Moreover, the estimated size of the binding site confirms that Aa binds approximately 5.76 base pairs, and the drug cisplatin binds approximately 0.56 base pairs. This is interpreted as Aa binding DNA less specifically and with a bigger site, which points toward the groove binding idea instead of intercalation or covalent bonding.

Diffusion coefficients measured validated these results, with the free Aa and Cis possessing larger diffusion coefficients (3.27×10^{-7} and 1.50×10^{-7} cm^2 s^{-1}) than their DNA-bound adducts (2.95×10^{-7} and 0.73×10^{-7} cm^2 s^{-1}), confirming the presence of larger, slower-diffusing complexes on DNA binding.

These results enhance the knowledge of biophysical interactions between Aa and DNA, thereby paving the way for its future use in drug development and therapy promotion. The unique binding

properties of Aa indicate its potential use in the design of new DNA-binding molecules with reduced cytotoxicity relative to traditional chemotherapeutic agents.

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