Inorganica Chimica Acta 390 (2012) 95–104

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Synthesis, structure, DNA binding and photonuclease activity of a nickel(II) complex with a *N*,*N*′-Bis(salicylidene)-9-(3,4-diaminophenyl)acridine ligand

Mariappan Mariappan [a,*], Masahiko Suenaga [b], Abhik Mukhopadhyay [c], Bhaskar G. Maiya [a,1]

[a] School of Chemistry, University of Hyderabad, Hyderabad 500 046, India
[b] Dept. of Chemistry, Faculty of Sciences, Kyushu University, Japan
[c] Departamento Quimica, Faculdade de Ciencias e Tecnologia, Universidade Nova de Lisboa, Portugal

ARTICLE INFO

Article history:
Received 4 October 2011
Received in revised form 6 April 2012
Accepted 10 April 2012
Available online 20 April 2012

Keywords:
Salen
Nickel
Acridine
Electrophoresis
DNA binding
Oxone

ABSTRACT

A new class of salen functionalized novel ligand *N*,*N*′-Bis(salicylidene)-9-(3,4-diaminophenyl)acridine, H_2daasal (two potential intercalators, salen and acridine, which are linked together via C–C bond) and its metal complex [Ni(daasal)] have been synthesized and characterized by X-ray diffraction, elemental analysis, UV–Vis, IR, ^{1}H NMR, MALDI-TOF mass spectrometry and cyclic voltammetry methods. From the crystal structure, the salphen moiety is not coplanar with the acridine ring, having a dihedral angle of 68° and 76° in both H_2daasal and [Ni(daasal)], respectively. [Ni(daasal)] shows a reversible oxidation cyclic voltammetric response near 1.03 V versus SCE in CH_3CN (0.1 M TBAP) assignable to the Ni(II)/Ni(III) couple. The interaction of these compounds with calf-thymus (CT) DNA was examined using spectroscopic and viscosity measurements. These studies reveal that both compounds bind to CT DNA via an intercalative mode. Molecular-modeling studies also support an intercalative mode of binding to the model duplex d(CGCAATTGCG)$_2$ possibly from the major groove with a slight preference for GC rich region. Additionally, [Ni(daasal)] promotes the cleavage of plasmid pBR322 DNA upon irradiation under terminal oxidant Oxone.

1. Introduction

Transition metal complexes have shown considerable attention as catalysts due to their DNA binding and cleavage properties [1,2] and ability to probe electron-transfer reactions involving metalloproteins [3]. These metal complexes can interact non-covalently with nucleic acids by intercalation, groove binding or external electrostatic binding [4]. Among the above interactions, the intercalative interaction of the ligands with the DNA are very interesting since many anti-cancer drugs and antibiotics show their biological activities through DNA intercalation [5,6]. Nickel is recognized as an essential trace element for bacteria, plants, animals and humans, though the role of this metal in animal biochemistry is still not well defined. Schiff bases are potential anti-cancer drugs with anti-cancer activity increasing when they complex with metal ions [7]. Among the Schiff bases are salicylidene-ethylendiamines, commonly known as salens, which can form stable complexes with a variety of transition metals. These metal Schiff base complexes have been developed as catalyst for the oxygen sensing [8a], epoxidation of olefins [8b–d] and nucleic acid reagents to induce specific damages in DNA and RNA [2]. Nickel(II) complexes using salen as a ligand (where salen = ethylenediamine-*N*,*N*′-bis(salicylaldimine)) are well suited for covalent modification of DNA since the Ni(III)/Ni(II) couple often lies near the redox potential of the ligand, at ca. 1 V versus SCE [9]. Moreover Ni(salen) complexes disclose their antitumor activity via DNA adduct formation and double strand breaks, promoting selective oxidation of Z-DNA [9,10].

Acridine and its derivatives are typical intercalative agent for DNA and are active in antitumor treatment and chemotherapy [11]. These compounds besides showing therapeutic and antitumor activities [12–16], have also interesting photophysical and photochemical properties [17–19]. Many efforts have so far been made to enhance the reactivity of the metal complexes cleaving DNA. Among those, one is the conjunction of metal complexes and intercalating groups to increase the DNA affinity of the cleaving agents [13,20,21]. We therefore decided to synthesize a novel complex containing both Ni(salen) and acridine (potential intercalators) subunits in their architecture. This paper presents the synthesis, characterization, crystal structure, DNA binding and photocleavage properties of H_2daasal and [Ni(daasal)] where H_2daasal is *N*,*N*′-Bis(salicylidene)-9-(3,4-diaminophenyl)acridine – a salen based ligand that incorporates an acridine chromophore in its architecture.

* Corresponding author. Present addresses: Dept. of Chemistry and Nano science, Ewha Womans University, Seoul, Republic of Korea, Dept. of Bioinspired Science, Ewha Womans University, Seoul, Republic of Korea. Tel.: +82 23 2773107; fax: +82 23 2774441.
E-mail address: tmmari@yahoo.com (M. Mariappan).
[1] Deceased.

0020-1693/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ica.2012.04.016

2. Experimental

2.1. Materials

Acridine, salicylaldehyde, tetrabutylammonium perchlorate (TBAP) and deuterated solvents were obtained from Aldrich Chemical Co. (USA). The metal salts used were acquired from either Aldrich Chemical Co. (USA) or Acros Organics (Belgium). The remaining chemicals, reagents and solvents utilized in this study were procured at their highest available purity from B.D.H (India). Calf-thymus DNA (CT DNA) was obtained from Sigma (USA), agarose (molecular biology grade). Ethidium bromide was purchased from Bio-Rad Laboratories Inc. (USA). Supercoiled pBR 322 DNA (CsCl purified) was obtained from Bangalore Genie (India) and was used as received. All the solvents utilized for spectroscopic and electrochemical studies were rigorously purified before use following standard procedures [22]. Deionized, triply distilled water was used for preparing various buffers. 9-(3,4-Diaminophenyl)acridine (daa) was synthesized by previously reported procedures [23]. The synthetic route for the ligand H_2daasal and its Ni(II) complex [Ni(daasal)] are shown in Scheme 1.

2.1.1. Synthesis of N,N′-Bis(salicylidene)-9-(3,4-diaminophenyl)acridine (H_2daasal)

9-(3,4-Diaminophenyl)acridine (0.19 g, 0.67 mmol) and salicylaldehyde (1.68 mmol, 0.17 mL of 99%) were taken in 40 mL methanol and triethyl orthoformate (0.2 mL) was added into it. The reaction mixture was refluxed for 4 h and was allowed to cool to room temperature. The resulting yellow precipitate was filtered and was recrystallized from a mixture of DMF–diethyl ether (1:3, v/v). Yield = 0.26 g (78%). Analytical data: Calc. $C_{33}H_{23}N_3O_2$: C, 80.31; H, 4.67; N, 8.51; Found: C, 80.18; H, 4.74; N, 8.42%; IR: ν_{max} (KBr, cm^{-1}): 3443 (O–H stretching), 3047 (C–H, aromatic), 1614 (C=N). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): 13.05 (s, 1H), 13.01 (s, 1H), 8.84 (s, 1H), 8.70 (s, 1H), 8.34 (d, J = 8.5 Hz, 2H), 7.84 (t, 4H), 7.51 (m, 6H), 7.46 (s, 1H), 7.31 (d, J = 8 Hz, 2H), 7.12 (dd, J_1 = 7.9, J_2 = 7.9 Hz, 2H), 6.96 (t, 1H), 6.90 (t, 1H); MALDI-TOF (m/z): 495 [M^+].

2.1.2. Synthesis of N,N′-Bis(salicylidene)-9-(3,4-diaminophenyl)acridine-Nickel(II) [Ni(daasal)]

A mixture of ligand H_2daasal (0.31 g, 0.63 mmol) and $NiCl_2{\cdot}6H_2O$ (0.10 g, 0.42 mmol) was dissolved in ethanol (35 mL). The reaction mixture was refluxed for 2 h. The resulting dark reddish-orange precipitate was filtered and was recrystallized from DMF. Yield = 0.17 g (72%). Analytical data: Calc. $C_{33}H_{21}N_3O_2Ni$: C, 72.04; H, 3.82; N, 7.64; Found: C, 71.93; H, 3.74; N, 7.71%; IR: ν_{max} (KBr, cm^{-1}): 3049 (C–H aromatic), 1608 (C=N). ^{1}H NMR ($(CD_3)_2SO$, 400 MHz, TMS): 9.35 (s, 1H), 9.08 (d, J = 18.5 Hz, 1H), 8.91 (s, 1H), 8.41 (t, 2H), 8.38 (s, 1H), 8.26 (m, 3H), 7.89 (m, 3H), 7.65 (m, 5H), 7.04 (dd, J_1 = 16, J_2 = 16 Hz, 2H), 6.91 (t, 1H), 6.63 (t, 1H); MALDI-TOF (m/z): 550 [M^+].

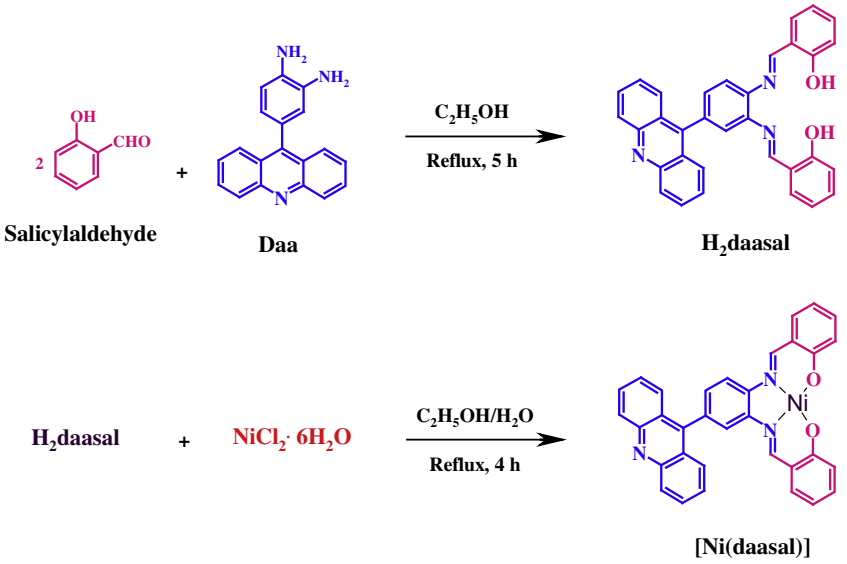
2.2. X-ray crystallography

Slow evaporation of a DMF solution of H_2daasal and a DMF–diethyl ether (1:3) solution of [Ni(daasal)] provided single crystals of the respective compounds. X-ray diffraction data was collected at 293 K on a Bruker Nonius Smart Apex CCD detector diffractometer equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073 Å) operated at 1750 W power (50 kV, 35 mA). The detector was placed at a distance of 6.003 cm from the crystal. A total of 2400 frames were collected with a scan width of 0.3° in ω and an exposure time of 30 s/frame. The frames were integrated using a Bruker SAINT Software package with a narrow-frame integration algorithm [24]. Data was corrected for absorption effects using the multi-scan technique (SADABS). All non-hydrogen atoms were found using the direct method analysis in SHELXTL [25]. After several cycles of refinement, the positions of the hydrogen atoms were calculated and added to the refinement process. The ORTEX6a [26] and the PLATON [27] packages were used for molecular graphics. Physical methods, DNA experimental details and computational methods are given in the Supporting information.

3. Results and discussion

3.1. Syntheses

Syntheses of H_2daasal and [Ni(daasal)] are illustrated in Scheme 1. H_2daasal was prepared by the condensation of 9-(3,4-diaminophenyl)acridine [23] and salicylaldehyde (1:2.5 mol ratio) in methanol. The Ni(II) complex was prepared by reacting H_2daasal (1.5 mmol) with $NiCl_2{\cdot}6H_2O$ (1 mmol) in C_2H_5OH. Each synthetic step involved is straightforward and provided good yields. Both



Scheme 1. Synthesis of ligand H_2daasal and its complex [Ni(daasal)].