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Imidazolium tagged acridines: Synthesis, characterization and applications in DNA binding and anti-microbial activities

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ABSTRACT

New water soluble 4,5-bis imidazolium tagged acridines have been synthesized and structurally characterized by multinuclear NMR and single crystal X-ray diffraction techniques. The DNA binding and anti-microbial activities of these acridine derivatives were investigated by fluorescence and far-UV circular dichroism studies.

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1. Introduction

The fluorescent tagged imidazolium salts have asserted significant attention for examining biological processes as these can be traced using fluorescent technique [1–5]. Using fluorophore as a key tool, the imidazolium salts offer excellent performance. As a result the fascinating features of fluorophores can be combined with typical properties of imidazolium salts. For example, anthracene tagged imidazolium-based sensors have been extensively examined to probe various biologically important anions including phosphates, ATP, nucleotides and DNA [1,3,4]. In contrast to anthracene imidazolium derivatives, acridine imidazolium derivatives are rare. The first acridine imidazolium derivative, 5-bis(N-butyl-imidazoliummethyl)acridine was developed for pyrophosphate and dihydrogen phosphate identification in dimethyl sulfoxide [6]. Recently, the tweezer-like acridine-based bifunctional imidazolium fluorescent sensor for $H_2PO_4^-$ and HSO_4^- in acetonitrile was developed [7]. By extending this approach, fluorescence responsive acridine-based macrocyclic imidazolium toward $H_2PO_4^-$ was reported in acetonitrile [8]. Notably, acridine tagged imidazolium-based fluorescent sensors have never been tested for DNA binding. Besides, these recent efforts have not answered the critical questions necessary to clearly realize the role of acridine moiety in acridine imidazolium derivatives. For example, (i) do acridine imidazolium derivatives interact with DNA, (ii) sensitivity ratio of acridine imidazolium receptors vs anthracene imidazolium receptors with DNA, (iii) key role of acridine in the biological process, (iv) applications of water soluble acridine imidazolium receptors in biological activities? In order to address these above challenges, in this paper we report the new water soluble acridine imidazolium receptors and their applications in DNA binding and anti-microbial activities.

2. Experimental

2.1. The material and methods

All manipulations were carried out under argon atmosphere in a glove box using standard Schlenk techniques. The solvents were purchased from commercial sources and purified according to

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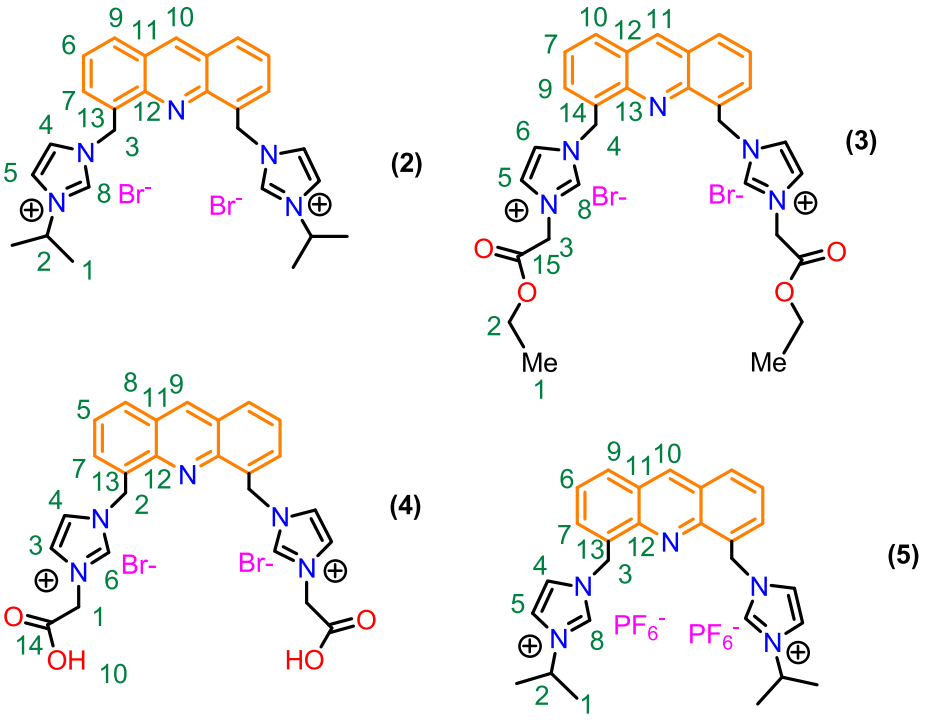

Scheme 1. NMR labelling of **2**–**5**.

standard procedures and freshly distilled under argon atmosphere prior to use [9]. 4,5-bis-bromomethylacridine (**1**) was prepared as reported [8]. [4,5-bis{(N-isopropylimidazolium)methyl}acridine] dibromide (**2**), [4,5-bis{(N-ethoxycarbonyl methyl imidazolium) methyl}acridine] dibromide (**3**), [4,5-bis{(N-carboxy methyl imidazolium)methyl}acridine] dibromide (**4**) and [4,5-bis{(N-isopropylimidazolium)methyl}acridine] hexafluorophosphate (**5**) ware synthesized by modified procedures [10]. Potassium hexafluorophosphate (Aldrich), Acridine (Alfa aesar), Bromomethyl methylether (Alfa aesar) and Imidazole (Merck) were purchased from commercial sources. Calf thymus DNA (CT-DNA) was purchased from Sigma–Aldrich, USA. 10 mg/mL solution of CT-DNA was prepared in Tris–EDTA (TE) buffer (10 mM TrisHCl buffer pH 8.0 with 1 mM EDTA) by gradual mixing overnight at 4 °C. The CT-DNA solution was further sonicated on ice to produce shorter DNA fragments and their molecular weight was determined by agarose gel electrophoresis. Average molecular weight of the generated fragments was ~10 kb. Aliquots of CT-DNA solution (50 μL) were stored at −20 °C until further use. Before use, CT-DNA aliquots were thawed on ice. Salmon sperm DNA (10 mg/mL) was purchased from Invitrogen. Bovine Serum Albumin (BSA), Tris base, EDTA were from Sigma, USA. dNTP (dNTP = deoxy nucleoside tri phosphate) mixture (equimolar mixture of nucleotides dATP, dTTP, dCTP & dGTP) was also from Sigma. PVDF Membrane filter of 0.2 μM pore size was from Millipore USA.

FT-IR measurements (neat) were carried out on a Bruker Alpha-P Fourier transformation spectrometer. The UV–vis spectra were measured on a T90+ UV–visible spectrophotometer. NMR spectra were recorded on Bruker Ultrashield-400 spectrometer at 25 °C unless otherwise stated (see Scheme 1). Chemical shifts are given relative to Me_4Si and were reference to the solvent resonances as internal standards. The crystal structures of **2** and **5** were measured on an Oxford Supernova diffractometer. Single crystal were mounted on an Xcalibur Goniometer equipped with Eos CCD detector. Crystals of **2** were obtained from **2** in DMSO at 25 °C and crystals of **5** were obtained from 50% mixture of acetonitrile and methanol solution of **5**. The suitable single crystals for X-ray structural analysis were mounted at 298 K in inert oil. Using Olex2 [11], the structure was solved with the ShelXS [12] structure solution program using Direct Methods and refined with the olex2.refine refinement package using Gauss-Newton minimization.[‡] Absorption corrections were performed on the basis of multi-scans.

Non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in the refinement in calculated positions riding on their carrier atoms. No restraint has been made for any of the compounds. **2** showed the solvent accessible void volume and stacked the R-factor higher. Severely disordered solvent molecules were occupied into the voids and unable to identify the molecular structure clearly. The MASK procedure was implemented in all three structures using *OLEX2* program and removed the void volumes caused by disordered solvent molecules (presumably water molecules). Only the atoms used in the final model are reported in the chemical formula and related values for these structures. The refinement without SQUEEZE procedure clearly showed severely disordered isolated solvent molecules with void volume of 424 $Å^3$ (27% from the total volume of the unit cell). Instead of PLATON SQUEEZE, a solvent masking procedure was implemented in *OLEX2* to remove the electronic contribution from disordered solvent molecules (presumably acetonitrile molecule). CCDC 1414072–1414073 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

2.2. Synthesis of **2**

A mixture of **1** (1.00 g, 2.73 mmol) and *iso*propyl imidazole (1.20 g, 10.89 mmol) in acetonitrile (8 mL) was refluxed for 3 days under N_2 atmosphere. The solvent was evaporated under vacuum then the resulting solid was washed with acetone for several times.

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