Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 173 (2017) 383–389

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Tuning the constrained photophysics of a pyrazoline dye 3-naphthyl-1-phenyl-5-(4-carboxyphenyl)-2-pyrazoline inside the cyclodextrin nanocavities: A detailed insight *via* experimental and theoretical approach

Beena Varghese, Saleh N Al-Busafi, FakhrEldin O. Suliman *, Salma M.Z. Al-Kindy *

Department of Chemistry, College of Science, Sultan Qaboos University, Box 36, Al-khod 123, Oman

ARTICLE INFO

Article history:
Received 19 June 2016
Received in revised form 10 September 2016
Accepted 26 September 2016
Available online 28 September 2016

Keywords:
Pyrazoline dye
Complexation
Cyclodextrins
Fluorescence
ESIMS
NMR
Molecular modeling

ABSTRACT

The modulation in the photophysics of a pyrazoline dye 3-naphthyl-1-phenyl-5-(4-carboxyphenyl)-2-pyrazoline (NPCP), when it drifts from bulk water into the nanocages of aqueous cyclodextrin solutions was investigated. The intramolecular charge transfer (ICT) fluorescence band intensity was found to increase with a blue shift in the presence of cyclodextrins. The results from ^{1}H NMR and ^{1}H—H COSY NMR spectral analysis clearly points out the position of pyrazoline ring inside the cavity and its role in complexation process. A quantitative assessment of the emission intensity data on Benesi-Hildebrand (B-H) equation along with ESI-MS spectra reveals the probable stoichiometry of NPCP-CD complexes. Molecular docking and molecular dynamics studies were conducted for β/γ cyclodextrin associated inclusion complexes of NPCP. The results obtained by computational studies are in good relation with the data obtained through experimental methods and both ascertain the encapsulation of NPCP into cyclodextrins.

1. Introduction

The fluorescent dyes are well suited to monitor the formation of discrete host/guest complexation with macrocyclic structures which serve as molecular caskets, meanwhile the knowledge of the polarizability of macrocyclic hosts provides an insight into the photophysical properties of the entrapped fluorescent dyes. This kind of "*mutualistic relationship*" yielded a numerous supramolecular architectures of relevance to organic electronic devices, switches, sensors, materials with a nonlinear optical response, nanotubes and molecular zeolites and so forth [1–5]. Cyclodextrins (CDs) represent one of the simplest encapsulating systems characterized by truncated cone shaped cavities of hydrophobic character, able to form non-covalent inclusion complexes with a large variety of biologically and pharmaceutically potent molecules by including them in their interiors [6–10]. In fact, this type of companionship results in a beneficial modification on the photophysical characteristics of the trapped guest by enhancing the fluorescence quantum yields, fluorescence lifetimes, photostability and even bioavailability of poorly soluble drugs.

A simple review of the literature on organic conjugated systems reveals that pyrazoline derivatives have displayed remarkable interdisciplinary activities and found widespread applications in areas such as bio-labeling and functionalization, novel luminescent materials, nonlinear optics, chemical sensors, optoelectronics and in biomedicine [11–16]. Having made a list of pharmacologically active molecules with pyrazoline moiety such as azolid/tandearil (anti-inflammatory), phenazone/amidopyrene/methampyrone (analgesic and antipyretic), anturane (uricosuric) and indoxacarb (insecticidal), so far the achievements are remarkable but still the poor aqueous solubility of many pyrazoline compounds limited its pharmaceutical applications [17].

It has been realized through some studies that the reduced polarity and the restricted space provided by the CD-cavity can markedly increase the blue light emission efficiency of some pyrazoline derivatives [18–19]. The impact of cyclodextrin-based nanotechnology will likely accelerate in coming years and the nanoparticles entrapped within cyclodextrin will stimulate a lot of research interests. Indeed this is an active direction and perhaps fluorescent organic nanoparticles (FONs) with pyrazoline will dominate this field.

The pyrazoline dye 3-naphthyl-1-phenyl-5-(4-carboxyphenyl)-2-pyrazoline (NPCP) is a novel compound developed recently in our laboratory and applied successfully as a fluorescent label for amino acids and neurotransmitters analysis [11]. This dye can be further exploited to

* Corresponding authors.
E-mail addresses: fsuliman@squ.edu.om (F.O. Suliman), alkindy@squ.edu.om (S.M.Z. Al-Kindy).

http://dx.doi.org/10.1016/j.saa.2016.09.047
1386-1425/

design simple chiral separations of amines using macrocyclic systems. Therefore, investigating the interactions of macrocyclic hosts like cyclodextrins with this molecule can help rationalize the design of separation protocols for chiral amines using this dye. Moreover, considering the wide applications of pyrazoline dyes in biomedical fields, the assessment of this dye in terms of solubility and bioavailability is crucial for its biomedical applications.

In this study we are prompted to investigate the interaction between NPCP and CDs of varying cavity dimensions (α-, β- and γ-CDs) using fluorescence spectroscopy. In addition, the interaction of the guest molecule with CDs is also studied using nuclear magnetic resonance (NMR), which provides information on the detailed knowledge of the dynamics and host-guest interaction. To substantiate the experimental results, we have complemented these studies with molecular modeling simulations using docking techniques as well as molecular dynamic simulations.

2. Experimental

2.1. General

All reagents and solvents used in this study were obtained from Sigma-Aldrich Chemical Company (USA) and used without further purification.

^{1}HNMR spectra of NPCP-CDs were recorded using 700 MHz Bruker spectrometer (Bruker Corp., UK) and chemical shifts (δ_C) are quoted in parts per million (ppm) to the nearest 0.1 and 0.01 and are referenced to the solvent peak (DMSO-d_6). Two dimensional (2D) ROESY spectra were acquired using a phase sensitive pulse sequence with TPPI (time proportional phase incrementation) with a mixing time of 200 ms and recycle delay of 2 s. Data sets with 2048 complex points in t_2 and 256 complex points in t_1 were acquired with a 6443.299 Hz sweep width in both dimensions and 8 scans per slice. The NMR data have been processed using Topspin 3.2 software programme.

Mass spectra were measured with Micromass Quattro Ultima Pt (Waters Corp. MA, USA) equipped with an ESI source and operated in the negative ion mode. The solutions were introduced into the electrospray ion source (ESI) *via* a syringe pump at a flow rate of 0.02 mL/min. The other parameters were set as follows: drying gas (N_2) flow rate (7.0 L/min); drying gas temperature 300 °C; nebulizer pressure 35 psi, capillary voltage 3500 V and fragmentation voltage was 200 V. A Perkin Elmer (model LS 55) Luminescence spectrometer (Perkin Elmer, USA) were used to collect fluorescence spectra. All measurements were done repeatedly, and reproducible results were obtained. Fluorescence lifetime measurements were performed using a Time Master Fluorescence Lifetime Spectrometer (Photon Technology International, USA). Data were analysed using a nonlinear least-squares fitting programme with deconvolution method.

2.2. Molecular Modeling

Hyperchem Professional 8.09 (Hypercube Inc. www.hyper.com) and MOPAC 2012 (http://openmopac.net) were used to perform all calculations. The initial geometry of NPCP was built in Hyperchem and optimized using DFT-B3LYP method using 6-31G* basis set. On the other hand, the structures of β- and γ-cyclodextrins were obtained from the crystallographic parameters provided by the Structural Data Base System of the Cambridge crystallographic data center and optimized using PM7 semiempirical method [20].

Autodock programme (version 4.2) was used to generate the inclusion complexes by docking NPCP into the cyclodextrins nanocavities [21]. *Autodock* tools were then utilized to perform cluster analysis for all inclusion complexes generated using a cutoff of 1.0 Å root mean square deviation (RMSD) [22]. The lowest energy structures which correspond to the cluster with maximum number of conformations were obtained for NPCP-CD complex where the guest molecule enters through secondary hydroxyl rim of the CD. In both cases the pyrazoline ring was inserted into the cavity of the host while the naphthalene moiety is pushed down towards the narrow rim of the cyclodextrin.

The inclusion complexes were then placed in a water box of appropriate size containing 725 and 892 TIP3P water molecules in case of NPCP:β- and NPCP:γ-CD complexes, respectively. Molecular dynamics (MD) simulations using Amber99 force field parameters were performed for both systems. The initial geometries were minimized to RMS gradient of 1 kcal/(Å mol) to allow molecules to adjust to the potential field of solutes and to eliminate unwanted interactions. The system was then heated to 300 K for 50 ps and subsequently equilibrated using Langevin dynamics for 2000 ps. The MD simulations were run using periodic boundary conditions with a bath relaxation time of 0.1 ps. The step size used was 2 fs.

The final geometries extracted from the last 1 ns of the MD simulations trajectories were optimized by PM7 semiempirical methods using MOPAC2102 package. Moreover, using these semiempirical methods harmonic frequency calculations were performed for these geometries using statistical thermodynamics at 1 atm and 298 K to obtained thermodynamic properties of the inclusion complexes, such as enthalpy change (ΔH), entropy change (ΔS), and Gibb's free energy change (ΔG).

3. Results and Discussions

While monitoring the complexation behaviour of NPCP with CDs in aqueous medium, α-cyclodextrin failed to bring any distinctable changes on the emission profile of NPCP. On the other hand the fluorescence intensity increases with increase in both β- and γ-cyclodextrins solutions along with a noticeable shift to the lower wavelength side of the emission spectra (17 nm & 13 nm respectively) (Figs. 1 & 2). It reminds us that the molecule experiences more hydrophobic environment in a similar way when its local solvation environment changes from polar solvent water (494 nm) to non-polar solvent cyclohexane (452 nm) [23]. In NPCP an ICT emission state arises due to the lone pair of electrons on the pyrazoline ring and its delocalization to nearby naphthalene and phenyl ring thereby extending the conjugation of the system. The locally excited band is usually observed around 425 nm, however, in aqueous media is found buried under the strong emission of the ICT [23]. It is obvious that the deep inclusion of the pyrazoline fragment into the hydrophobic cage avoid the influence of hydrogen bonding from the outside water causes an increase in emission intensity in both β- and γ-cyclodextrin solutions. The appreciable modification of emission intensity further establish that when the molecule gets tightly

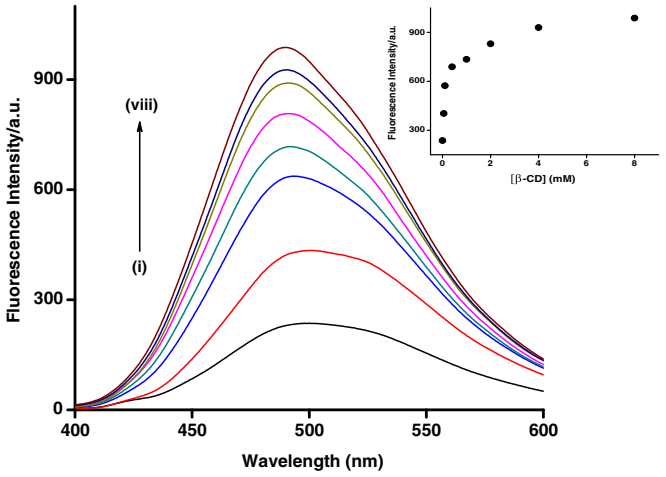

Fig. 1. Fluorescence spectra of NPCP in aqueous solution of [β-CD]: (i) 0 (ii) 0.05 (iii) 0.1 (iv) 0.4 (v) 1 (vi) 2 (vii) 4 (viii) 8 mM, respectively. Inset represents the variation of fluorescence intensity of NPCP with increasing concentration of β-CD.