PROCEEDINGS OF UGC-SPONSORED NATIONAL SEMINAR

ON

"*RECENT DEVELOPMENT IN BIO-ACTIVE MOLECULES*"

(RDBAM-2016)

4th-5th August, 2016

Edited by

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Organized by

Department of Chemistry

Haldia Government College, Haldia

West Bengal 721657, India

In Collaboration with

Department of Chemistry

Vivekananda Mission Mahavidyalaya, Chaitanyapur

West Bengal 721645, India

Sponsored by

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VIDYASAGAR UNIVERSITY

Professor Ranjan Chakrabarti
Vice-Chancellor

Date: 28.07.2016

MESSAGE

I am happy to learn that the Department of Chemistry, Haldia Government College, Haldia, Purba Medinipur is going to organize a UGC-sponsored Two-day National Seminar on *Recent Development in Bio-Active Molecules (RDBAM-2016)*, in collaboration with Vivekananda Mission Mahavidyalaya, Chaitanyapur, Haldia, Purba Medinipur to be held during August 4 – 5, 2016.

I commend the endeavour of the organizers and convey my best wishes for the success of the programme.

(Professor Ranjan Chakrabarti)

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& President of RDBAM-2016
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From :- The Principal, Haldia Govt. College
Purba Medinipur

To :

Message from the Desk of the Officer-In-Charge

Bioactive molecules are molecules that are pharmacologically active derived from natural sources and through chemical synthesis. Over the years many of such molecules have been discovered through bio prospective endeavours. The search for bioactive molecules has been an ongoing task of the scientists and researchers. The development in the field has seen numerous advancements both in its science as well as techniques and enabling technologies that have been driving the pace of discovery and synthesis. The recent progresses in bioinformatics, chemical genetics and computational biology have changed the way and direction in which bioactive molecules are classified and discovered. Advances in these areas together with combinatorial chemistry, have transformed the landscape of modern scientific discovery of bioactive molecules.

Considering the development of research in bio-active molecules the Department of Chemistry of Haldia Government College has taken a bold attempt to organize two-day UGC sponsored National Seminar on "Recent Development in Bio-Active Molecules "in collaboration with the Department of Chemistry, Vivekananda Mission Mahavidyalaya, Chaitanyapur focusing on various thrust areas of chemistry and its application in biology. The whole academic discussions, exchange of views and ideas will certainly make the programme a grand success.

I really appreciate the approach in the form of a seminar and studiously intend the seminar to be a most perfect performed one. I convey my best wishes and heartiest thanks to all concerned.

With warm regards

28/07/16

Dr. Pijush Kanti Tripathi
Officer-in-Charge
Haldia Govt. College.

MESSAGE

The Department of Chemistry at Haldia Government College have started regular M.Sc. programme under the affiliation of Vidyasagar University from last year. Many of these brilliant post-graduate students are very much interested in research programme in future. Being a teacher, we want to create a proper environment so that these students can have an idea about the field of research activities going on in different institutes/laboratories throughout the country. Moreover, through this seminar the students will get a platform to interact with the scientists and professors which will help them a lot in future.

Being a researcher from an interdisciplinary field, I have seen that lack of co-ordination and collaboration among different research groups spoil months and years in order to get some simple experimental data. In spite of an excellent innovative idea, young scientists especially researchers from colleges and universities are often faced problem in obtaining analytical data's, bio-activity study related data's which restrict them in publishing their research work in high impact journals. This seminar will be a milieu of synthetic chemists, analytical chemists, biologists and chemical biologists from all over the country and will create an ideal platform to make a bridge among these groups. We are very hopeful that people will be able to share their thoughts, innovative ideas, knowledge, and challenges which will create new pathways, ideas and thus enabling more advance research and high impact publication.

Towards organizing the seminar on behalf of the organizing committee I want to express my sincere gratitude and thanks to Higher Education Department, Govt. of West Bengal and Haldia Govt. College for allowing to organize the seminar. I want to thank University Grants Commission, New Delhi for providing the financial support. My sincere thanks to Honourable Vice-Chancellor, Vidyasagar University for his generous support towards organizing the seminar. I want to thank Officer-in-Charge, Haldia Government College for his valuable suggestions, encouragement, support and endless help towards the successful completion of the seminar. My sincere thank to all teaching and non-teaching staff of Haldia Govt. College for their constant encourage and support. I want to thank my departmental colleagues for their endless effort. I am grateful to all resource persons and distinguished invited speakers who have made their time within their very busy time schedule and came to our college. I welcome all teachers from different colleges, institutes and research scholars from various organizations, students from different institute and all other participants. Finally I want to thank from my heart to my beloved students for their enthusiasm and without this we could not arrange this big event.

I am so honored to be the convener for the RDBAM 2016 and welcome you all to Haldia Govt. College to have a great time and entertainment.

With warm regards,

Dipankar Pramanik

Convener

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Department of Chemistry was started since the inception of the college. Along with the undergraduate courses (Honours & General), the department currently offers regular two year (4-Semester) M.Sc. degree in Chemistry. The department also offers two year M.Sc. program in distance mode (Directed Distance Education under Vidyasagar University). The department has a team of highly qualified, experienced and dedicated faculty members engaged in teaching and research activities. The department has very good infrastructure and well equipped research laboratory with sophisticated instruments like UV-Vis spectrophotometer, Fluorescence spectrofluorimeter, Polarimeter and many other types of equipment.

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CONTENTS

Synthesis, Crystal Structure, Spectroscopic Studies and Supramolecular Facets of Unnatural Coordination Mode of Cobalt(II) Complex

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Abstract:

The complexation behaviour of pyridine derived ligand pyridine-2,6-dicarboxylic acid (HL) towards particular 3d transition metal ion of group 9 is reported by the synthesis and characterization of mononuclear cobalt complex $[Co^{II}(L)_2(H_2O)_3]$ (**1**). In the complex **1**, the half of the deprotonated uninegative tridentate ligand serves as ONO donor where one pyridine ring N atom, one carboxylate O atom and one carboxyl group O atom of carboxylic acidare coordinatively active. In complex **1**, metal ion has distorted octahedral geometry.The complex is characterized by X-ray crystallography and spectral analysis. In addition, the complex molecule gains extra stability by H-bonding, lp(lone pair)●●●π and π●●●π interactions. The CSD search results to represent the unprecedented type of coordination of the said ligand.

***Keywords*:** Pyridine based ligand/Cobalt(II) complex/ X-ray crystal structure/ Supramolecular interactions.

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1. Introduction

The design and construction of metal complexes with unique structural motifs offer infinite opportunities for the design of compounds with bioactivity and unique chemical and physical properties has attracted extensive interest in supramolecular chemistry and materials chemistry [1–5]. In general, the nature of the metal ion with its particular oxidation state and number of bound different ligands and isomers of the metal complex can all exert a critical influence on the biological activity [6]. Metal complexes with pyridine dicarboxylic acids as a ligand have been found to have broad biological activities and different chemical reactivity and, also shows extensive application in medicine and acts as electron carriers in model biological systems as explicit molecular tools in DNA cleavage and as NO scavengers [7].

Crystal engineering is based on the understanding of intermolecular interactions and applying them for designing new solids with desirable physical and chemical properties [8]. Consideration of non-covalent interactions such as hydrogen bonds, π●●●π stacking, C-H●●●π, and lone pair●●●π interactions between various functional groups in each molecule as well as their effects on the spatial arrangement of the crystal lattice can provide some understanding of possible structures that could be adopted [9]. Although the classification and evaluation of intermolecular interactions can be useful for creating new compounds, there is the problem of deciding which of these forces control the final structures.

In the present study, attempts have been made to prepare Co(II) complex of the pyridine derived ligand pyridine-2,6-dicarboxylic acid (HL). The ligand behaves as a tridentate ONO donor uninegative one in the complex (**Scheme 1**). Moreover, noncovalent interaction involving πaromatic clouds, namely H-bonding, π●●●π, lp●●●πhave been found to take part in crucial role in the self assembly process.A CSD search (CSD version 5.35, Nov 2013) clearly established that this is the first example of pyridine derived transition metal complex in which supramolecular interactions like H-bonding, π●●●π, lp●●●π are clearly involved (*vide infra*). Herein, we report the synthesis, characterization, X-ray crystal structures and supramolecular assembly of the molecular building blocks *via* H-bonding, π●●●π, lp●●●π interactions in new cobalt(II) complex.

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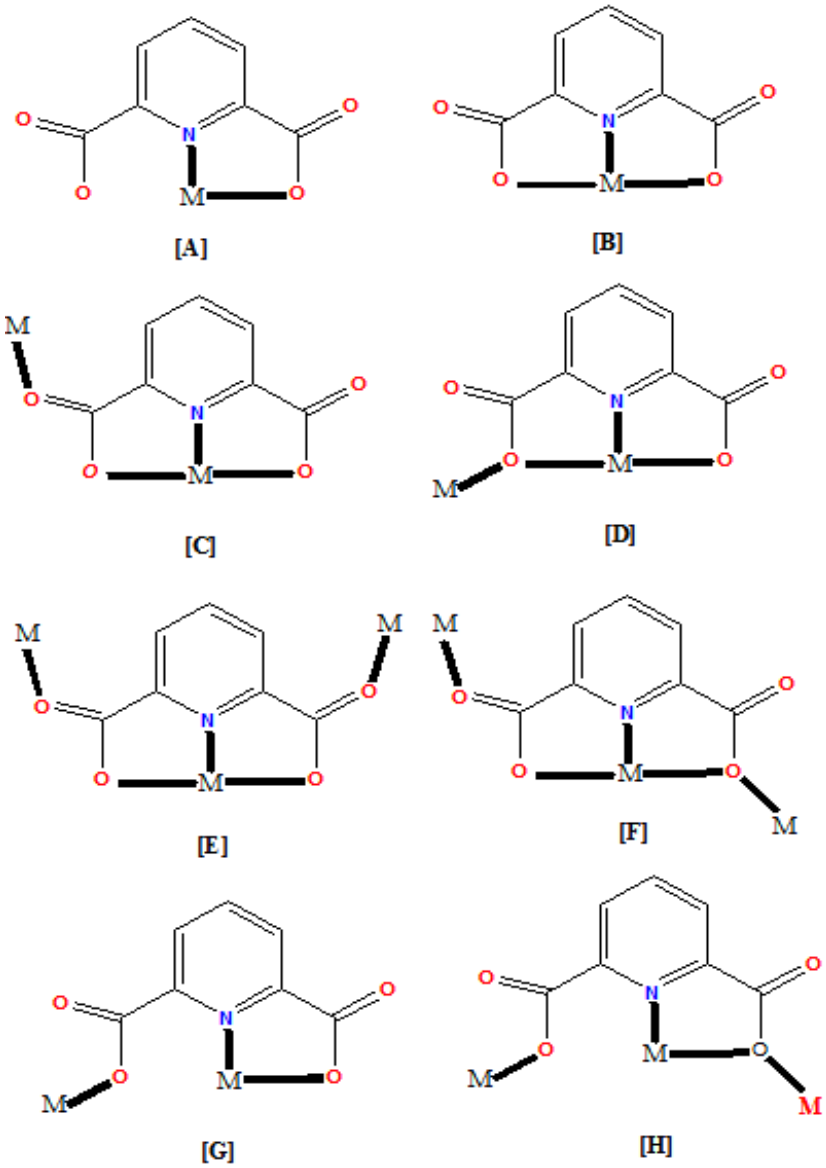

Scheme 1: Known coordination modes of ligand.

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2. Experimental section

2.1. Materials and Physical methods

All reagents and chemicals (including $Co(ClO_4)_2.6H_2O$) were of AR grade and procured from commercial sources (SD Fine Chemicals, India; and Aldrich) and used without further purification.

Caution! Although we have not encountered any problem, it should be kept in mind that perchlorate compounds of metal ions are potentially explosive in the presence of organic ligands. Only a small amount of the material should be prepared and it should be handled with care.

Elemental analyses (carbon, hydrogen and nitrogen) of the metal complex were determined with a Perkin–Elmer CHN analyzer 2400 at the Indian Association for the Cultivation of Science, Kolkata. The UV–vis spectra were recorded in a Schimadzu U-1200 spectro-photometer against appropriate reagent blank. An IR spectra (KBr pellet, 300-4000 cm^{-1}) was recorded on a Perkin-Elmer model 883 infrared spectrophotometer.

2.2. Synthesis of the complex

2.2.1. Preparation of complex $[Co^{II}(L)_2(H_2O)_3]$ (**1**)

An aqueous solution (15 ml) of $Co(ClO_4)_2.6H_2O$ (1 mmol, 0.365 g) was added dropwise to a solution of HL (2 mmol, 0.334 g) in the same solvent taken in 1:2 molar ratio with constant stirring. The solution turned pink and stirring was continued for ca. 2 h. It was left for slow evaporation at room temperature. After 3 weeks X-ray quality crystals of **1** were formed and were collected by usual technique. (Yield: 61.7%). Anal. Calc. for $C_{14}H_{11}CoN_2O_{11}$: C,37.99; H,2.48; N,6.33. Found: C,37.88; H, 2.40; N,6.34.

2.3. X-ray crystallography study

Selected crystal data for **1** is given in **Table 1** and selected metrical parameter of the complex is given in **Table 2**. For complex **1** data collections were made using Bruker SMART APEX II CCD area detector equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) source in φ and ω scan mode at 296(2) K. Cell parameters refinement and data reduction were carried out using the Bruker SMART APEX II. Cell parameters refinement and data reduction were carried out using Bruker SMART [10] and Bruker SAINT softwares for all the complexes.The structure of all the complexes were solved by conventional direct methods and refined by full-matrix least square methods using F^2 data. SHELXS-97 and SHELXL-97 programs[11]were used for structure of all the complexes solution and refinement respectively. For complex **1**, non hydrogen atoms were refined anisotropically till the convergence is attained.

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Three water hydrogen atoms were not located from difference Fourier maps, and therefore, all these hydrogen atoms were not considered in the refinement process.

Table 1

Experimental data for crystallographic analysis of **1**

Compound	**1**
Empirical formula	$C_{14}H_8CoN_2O_{11}$
Formula weight	439.15
Temperature (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.1062(13) Å b = 13.7014(18) Å c = 13.8612(18) Å α = 115.794(5)°, β = 90.004(5)°, γ = 90.230(5)°
Volume ($Å^3$)	1728.1(4)
Z	4
Density (calc)($Mg/m^{3)}$	1.688
Absorption Coefficient($mm^{-1)}$	1.058
F(000)	884
θ Range (°) for data collection	1.63 to 25.00
Index ranges	-12≤ h ≤11 -16≤ k ≤16 -16≤ l ≤16
Goodness-of-fit on F^2	1.253
Completeness to theta =25.00°	99.3 %
Independent reflections [R_{int}]	6047 [0.036]
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	6047/24/510
Reflections collected	21298
Final R indices [I > 2σ (I)]	R_1=0.0523, wR_2= 0.1758
Largest difference peak and hole ($eÅ^{-3}$)	-0.73, 1.17

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Table 2

Selected bond distance (Å) and angle (°) data for **1**

Bond Type	Distances(Å)	Angle Type	Bond Angles (°)
Co1 -O1	2.215(3)	O1 -Co1 -N1	75.01(11)
Co1 -O3	2.094(3)	O3 -Co1 -N1	77.47(11)
Co1 -O14	2.235(2)	O14 -Co1 -N2	74.82(10)
Co1 -O20	2.132(2)	O20 -Co1 -N1	102.02(9)
Co2 -O13	2.240(2)	O19 -Co2 -N6	77.03(11)
Co2 -O19	2.141(2)	O13 -Co2 -N6	74.98(10)
Co2 -O9	2.094(3)	O9 -Co2 -N5	77.26(11)
Co2 -O11	2.213(3)	O11 -Co2 -N5	75.26(11)
C14 -O2	1.275(5)		
C14 -O1	1.248(5)		
C7 -O14	1.231(4)		
C7 -O16	1.290(4)		
C8 -O4	1.245(5)		
C8 -O3	1.267(4)		
C6 -O20	1.284(5)		
C6 -O18	1.221(5)		
C22 -O10	1.239(5)		
C22 -O9	1.262(4)		
C28 -O11	1.248(5)		
C28 -O12	1.273(5)		
C21 -O15	1.287(4)		
C21 -O13	1.228(4)		
C15 -O17	1.226(5)		
C15 -O19	1.279(5)		
Co1 -N1	2.016(2)		
Co1 -N2	2.019(3)		
Co2 -N5	2.015(2)		
Co2 -N6	2.016(3)		

3. Result and discussion

*3.1. Structural description of complex**1***

The molecular structure of complex **1** with atom numbering scheme is shown in **Fig. 1**.Selected metrical parameters are listed in **Table 2**. The single crystal X-ray diffraction study reveals that complex **1** is a monomeric Co(II) complex crystallizes in P-1 space group. The Unit cell of **1** comprises of only four molecules. The molecular packing of **1** is represented in **Fig. 2**.

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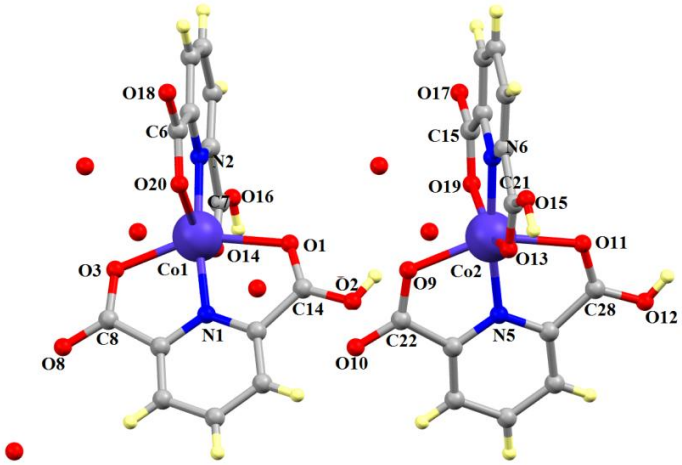

Fig. 1: The molecular view along with coordination environment of **1**.

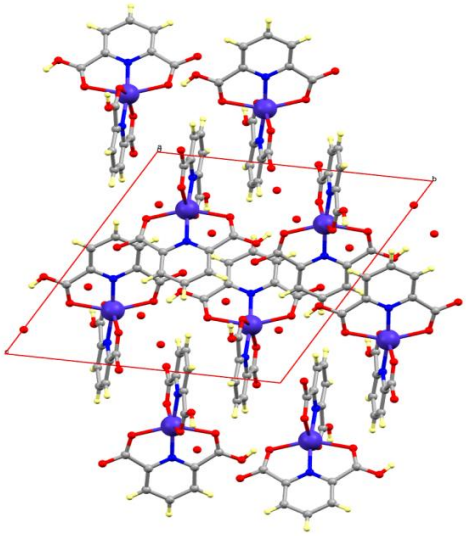

Fig. 2: The molecular packing of complex **1**.

In **1**, ligand molecule behaves as a tridentate ONO type. The central metal ion attains distorted octahedral geometry with N_2O_4 chromophore. Here for Co1, the equatorial positions are occupied by the two pyridyl nitrogen atoms N1 and N2, one carboxyl group O atom of carboxylic acid O1 and another one carboxylate oxygen atom O3 while axial positions are occupied by carboxyl group O atom of carboxylic acid O14 and another one carboxylate oxygen atom O20 and for Co2, the equatorial positions are occupied by the two pyridyl nitrogen atoms N5 and N6, one carboxyl group O atom of carboxylic acid O13 and another one carboxylate oxygen atom O19 while axial positions are occupied by carboxyl group O atom of carboxylic

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acid O11 and another one carboxylate oxygen atom O9. The average Co(II)-N and Co(II)-Obond distance falls in the range 2.016 Å and 2.170 Å respectively.From the bond angles **Table 2**, it is observed that the coordination geometry is quite far from a perfect octahedron due to the steric interactions and asymmetric nature of the ligand molecules.

The supramolecular architectures of complex **1** involve H-bonding, lp●●●π and π●●●π interactions. The structure **1** is stabilized by intermolecular hydrogen bonding (**Fig. 3**) (**Table 3**) which binds two units *via* carboxylic acid H atoms H16A, H27, H29 and H15A oxygen atoms of water molecules O21, O26, O23 and O22 respectively. A cooperative intermolecular lp●●●π interaction is responsible for the stabilization of the crystal structure of **1**. Each molecule of $[Co(HL)_2]$ is assembled by lp●●●π interactions involving the one C–O (of carboxylate group), C(15)–O(17) donor group of ligand and another pyridine ring Cg(12) (the ring centroid defined by N(6) - C(16) - C(17) - C(18) - C(19) - C(20) atoms) of symmetry -X,1-Y,-Z (**Fig. 4**) and another lp●●●π interaction involving the one C–O (of carboxylate group), C(6)-O(18) donor group of ligand and another pyridine ring Cg(6) (the ring centroid defined by N(2) - C(3) - C(2) - C(1) - C(5) - C(4) atoms) of symmetry 1-X,-Y,-Z (**Fig. 5**) (**Table 4**). The chelate ring again creates π●●●π interactions (**Fig. 6**) with the pyridine ring of symmetry related adjacent moiety. The detailed π●●●π interactions are represented in **Table 5**.

Table 3

Details of hydrogen bond distances (Å) and angles (^{o}) for **1**

D − H···A	d(D − H)	d(H●●●A)	d(D●●●A)	<(DHA)
O15 - H15A ●●● O22	0.8200	1.6900	2.499(4)	169.00
O16 - H16A ●●● O21	0.8200	1.6800	2.491(4)	169.00
O2 - H27 ●●● O26	0.8200	1.6600	2.473(5)	169.00
O12 - H29 ●●● O23	0.8200	1.6600	2.471(5)	168.00

D, donor; H, hydrogen; A, acceptor

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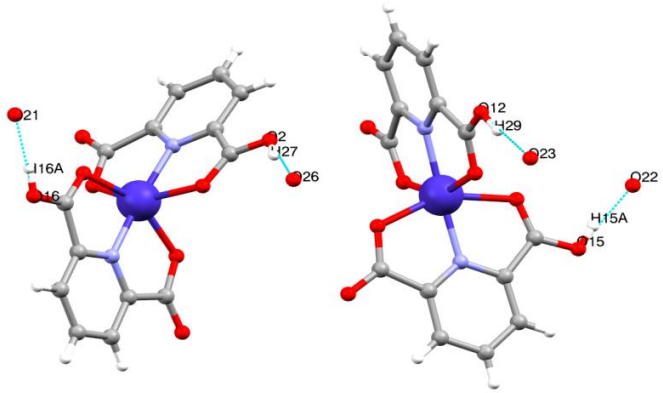

Fig. 3: H-bonding interactions in **1**.

Table 4: Geometric features (distances in Å and angles in degrees) of the lp●●●π interactions obtained for **1**

Complexes	C–H●●●Cg(Ring)	H●●●Cg (Å)	C–H●●●Cg (°)	C●●●Cg (Å)	Symmetry
Complex 1	C15 – O17●●●Cg(12)	3.298(5)	85.2(3)	3.421(5)	-X,1-Y,-Z
	C6 – O18●●●Cg(6)	3.308(5)	85.0(3)	3.425(5)	1-X,-Y,-Z

For complex **1**, Cg(12) = centre of gravity of ring [N6-C16-C17-C18-C19-C20] and Cg(6) = centre of gravity of ring [N2-C3-C2-C1-C5-C4].

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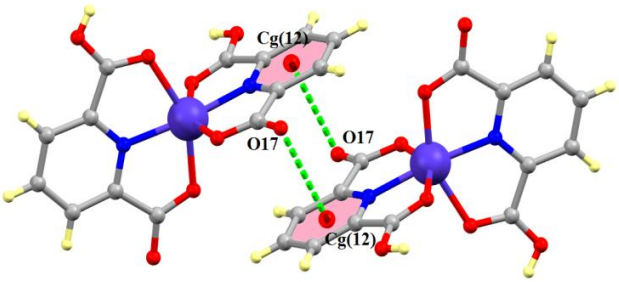

Fig. 4: lp●●●π interaction in **1**.

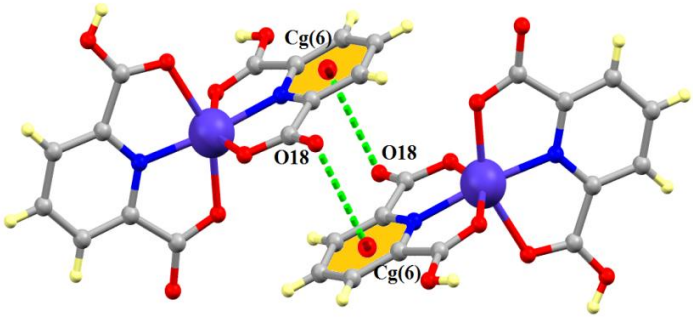

Fig. 5: lp●●●π interaction in **1**.

Table 5: Geometric features (distances in Å and angles in degrees) of the π●●●π interactions obtained for **1**.

Complex	Cg(Ring I)●●●Cg(Ring J)	Cg●●●Cg	Cg(I)●●●Perp	Cg(J)●●●Perp	α	β	γ	Symmetry
Complex 1	Cg(1)●●●Cg(5)	3.947(2)	3.474	3.407	2.16	30.33	28.33	1-X,1-Y,1-Z
	Cg(4)●●●Cg(6)	3.941(2)	3.311	3.300	0.52	33.12	32.82	1-X,-Y,-Z
	Cg(8)●●●Cg(11)	3.964(2)	3.486	3.418	2.13	30.41	28.42	-X,2-Y,1-Z
	Cg(10)●●●Cg(12)	3.946(2)	3.305	3.293	0.49	33.43	33.11	-X,1-Y,-Z

α = Dihedral angle between ring I and ring J (°); β= Cg(I)-->Cg(J) or Cg(I)-->Me vector and normal to plane I (°); γ = Cg(I)-->Cg(J) vector and normal to plane J (°);Cg-Cg = Distance between ring Centroids (Å); CgI----Perp = Perpendicular distance of Cg(I) on ring J (Å); CgJ----Perp = Perpendicular distance of Cg(J) on ring I (Å); Cg(1) = centre of gravity of ring [Co1-O1-C14-C13-N1]; Cg(4) = centre of gravity of ring [Co1-O20-C6-C4-N2], Cg(5) = centre of gravity of ring [N1-C9-C10-C11-C12-C13], Cg(6) = centre of gravity of ring [N2-C3-C2-C1-C5-C4], Cg(8) = centre of gravity of ring [Co2-O11-C28-C27-N5], Cg(10) = centre of gravity of ring [Co2-O19-C15-C16-N6], Cg(11) = centre of gravity of ring [N5-C23-C24-C25-C26-C27] and Cg(12) = centre of gravity of ring [N6-C16-C17-C18-C19-C20].

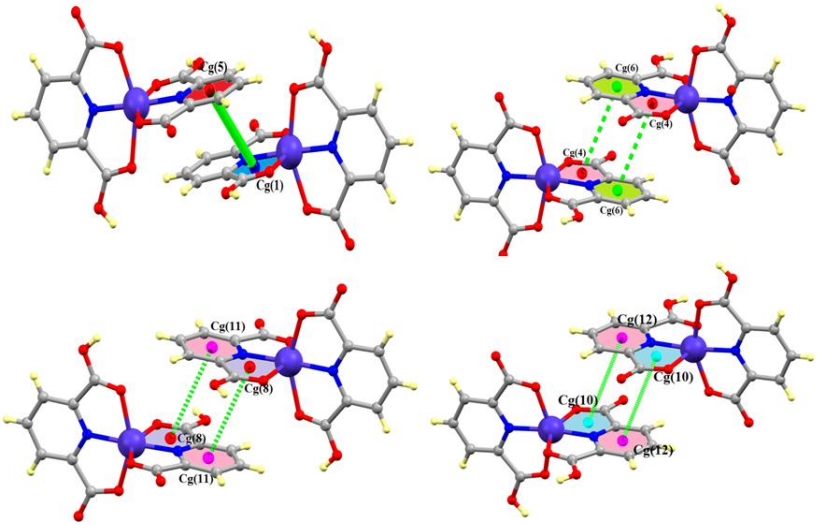

Fig. 6: Different types of π ●●●π interactions involved in **1**.

3.2. IR and UV-vis spectrophotometric study

A comparative study of the IR spectral data of the reported complexes with that of the uncoordinated ligand gives supportive evidences towards better understanding of the coordinating behaviour of the ligand molecule. The strong $\nu_{C=N}$ bands occurring at 1610 cm^{-1} is shifted considerably towards lower frequencies compared to that of the free ligands (1625 cm^{-1}), indicating the coordination of the azomethine nitrogen atom. The presence of a band at ca. 1680 cm^{-1} is assignable to νM–CO (here M stands for the corresponding metal ion). The another peak at 3100 cm^{-1} is responsible for νOH of -COOH of ligand.

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The electronic spectrum of $1x10^{-4}$ (M) solution of complex **1** in dimethyl formamide (DMF) shows two bands in the region 270-350 nm assigned to intraligand π-π* transitions [12]. Low intensity absorption bands observed at 442-699 nm are due to d-d electronic transitions central metal ions and the low energy absorption is due to the presence of carboxylic group that result in low π*-orbital energy level.

3.3. CSD study

We have performed several searches in the Cambridge Structural Database in order to demonstrate that the structure reported herein is rare and scarcely found in the literature. The CSD search (CSD version 5.35, Nov 2013) accounting 238 hits, out of which nobody can report the unprecedented type of coordination of the said ligand along with the structurally representation of the supramolecular lp●●●π and π●●●π interactions. In conjunction, the title compound synthesized and described herein and the CSD search results to represent clear examples where this previously unnoticed lp●●●π and π●●●π interactions play a relevant role in the crystal packing.

4. Conclusions

Apyridine based ligand HL has been used to synthesize a mononuclear Co(II) complex with Co(II) perchlorate as the metal salt. It has been synthesized and characterized by X-ray crystallography analysis and spectral studies. In the complex **1**, the deprotonated uninegative tridentate ligand acts as a ONO type. The supramolecular architecture of complex **1** involves H-bonding, lp●●●π and π●●●π interactions to play a significant role in the crystal packing. The CSD search represents clear examples where previously unnoticed abnormal coordination mode of pyridine-2,6-dicarboxylic acid (HL) towards transition metal atom.

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Appendix A. Supplementary data

CCDC 1479338 contains the supplementary crystallographic data for **1**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, 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.

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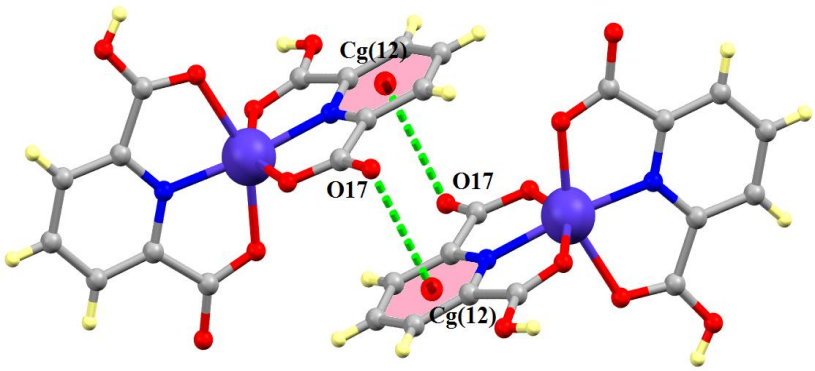

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Biological and Biomedical Applications of Supramolecular Interactions

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INTRODUCTION

Supramolecular chemistry is one of the most popular and fastest growing areas of experimental chemistry and it seems set to remain that way for the foreseeable future. The term 'supramolecular' has its origin in 1903 according to Webster's Dictionary but was first applied in the modern sense by Jean-Marie Lehn in 1978 as the 'chemistry of molecular assemblies and of the intermolecular bond'.[1]Supramolecular chemistry refers to the area of chemistry beyond the simple individual molecules and focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components. Traditional organic synthesis involves the making and breaking of covalent bonds to construct a desired molecule. In contrast, supramolecular chemistry utilizes far weaker and reversible noncovalent interactions, such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π–π interactions, and/or electrostatic effects to assemble molecules into multimolecular complexes. Important concepts that have been demonstrated by supramolecular chemistry include host-guest chemistry, self-assembly, and molecular recognition, mechanically-interlocked molecular architectures and dynamic covalent chemistry.[2] Supramolecular chemistry gives ample opportunity in manipulating molecules or supramolecular building blocks at a molecular level, allowing the "bottom-up" method to control the sizes and morphologies of the supramolecular networks. Especially, the design of nano sized supramolecular materials with uniform size has become a hot research topic, because nanomedicines have some potential biomedical applications. Designing of various supramolecular networks will provide a variety of novel diagnostic and therapeutic platforms toward applications in nanomedicine.[3] As a result of the above-mentioned advantages along with good biocompatibility or low toxicity of certain molecules and materials used, supramolecular systems have been widely utilized in the biological field.[4–9] Yoon and Jang reviewed polymeric supramolecular systems developed for drug delivery, which include polymeric micelles, vesicles, and polymeric hydrogels.[9] Zhao and coauthors summarized the recent research progress of self-assembly systems for the fabrication and application of bioinspired materials from the view of biomimetic chemistry.[7] Among various noncovalent interactions under the definition of supramolecular chemistry, host−guest interaction based on macrocyclic molecules is a very important phenomenon that has been extensively investigated. Through such host−guest inclusion, two or more chemical moieties can be

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integrated together in a facile and reversible manner, providing vast possibilities for the construction of novel supramolecular structures. During the past few decades, a series of macrocyclic molecules and their derivatives have been developed, including calixarenes (CAs), crown ethers, cyclodextrins (CDs), cyclophanes, cucurbit[n]urils (CBs), pillar[n]arenes, and so on. These macrocyclic molecules are regarded as the hosts, possessing the cavities to encapsulate the guests. The specific biomedical applications of the host−guest systems discussed contain several leading directions, that is, drug delivery, gene delivery, drug/gene codelivery, bioimaging, and photodynamic therapy (PDT).

WEAK INTERACTIONS AND THEIR BIOLOGICAL APPLICATIONS:

The chemistry of noncovalent interactions is a highly active interdisciplinary field with significant inference in biology, chemistry, physics and engineering.[10] Recently developed branch of supramolecular chemistry has revealed novel types of noncovalent forces. Chemical interactions between a protein and a drug, or a catalyst and its substrate, self-assembly of nanomaterials,[11] and even some chemical reactions[12] are dominated by noncovalent interactions. These types of interactions involve hydrogen bonding, dipole-dipole interactions, steric repulsion and London dispersion forces.[13] In modern chemistry, a new type of noncovalent interaction involving aromatic rings has drawn considerable attention because aromatic rings are ubiquitous in biological systems.[14,15] Interactions of the type anion···π, cation···π, lone pair···π, π···π and C–H···π have attracted considerable attention in the last two decades. These interactions are also acknowledged as supramolecular interactions. Recently some new types of supramolecular forces emerges like $\pi^{+}\cdots\pi$, $\pi^{+}\cdots\pi^{+}$, $\pi^{-}\cdots\pi^{-}$,salt bridge···π and lone pair···salt bridge which also become a matter of discussion.

Over the last five years a substantial research effort has been invested by our group on weak intermolecular interactions present in small synthetic inorganic–organic hybrid crystals to understand their remarkable potentiality to govern molecular packing and hence the crystal structures and bulk properties. An essentially unexplored noncovalent interaction involving aromatic rings is re–defined and described: the salt-bridge–π interaction. It consists of the stacking interaction between an aromatic ring and a planar salt-bridge. We also report the synthesis and X-ray characterization of one Cu(II) malonate complex with protonated 2-aminopyridine as the auxiliary ligand, which is acting as the counter cation, namely, $\{(C_5H_7N_2)_6[Cu(C_3H_2O_4)_2(H_2O)_2][Cu(C_3H_2O_4)_2](PF_6)_2\}_n$**(1)** [$C_5H_7N_2$ = protonated 2-aminopyridine, $C_3H_4O_4$ = malonic acid][16] where this type of interaction is observed. Other weak forces like hydrogen bonding, π···π stackingand anion···πinteractions were also found to be responsible for the overall stabilisation of the complex **1**. Interestingly, an extended supramolecular network of the type sb–π / π–π / π–π /π–anion (Fig. 1) has been observed in the solid state structure of complex **1**.

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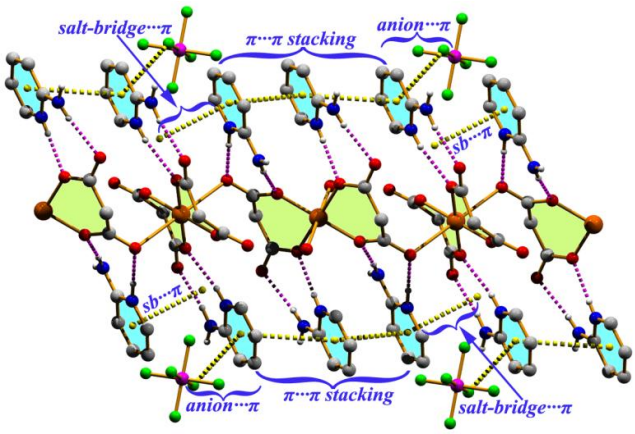

Fig. 1. Supramolecular network in **1**, generated through cooperative Salt-bridge···π / π···π / π···π /π···anion interactions.

Moreover, A Cu(II)–malonate complex system with formula $\{(C_5H_6N_2Cl)_{12}[Cu(1)(C_3H_2O_4)_2][Cu(2)(C_3H_2O_4)_2(H_2O)_2][Cu(4)(C_3H_2O_4)_2][Cu(3)(C_3H_2O_4)_2(H_2O)_2](ClO_4)_4\}_n$(**2**) [$C_5H_6N_2$ Cl = protonated 2-Amino-5-chloropyridine, $C_3H_4O_4$ = malonic acid, ClO_4^- = perchlorate][17]has been synthesized from purely aqueous media simple by mixing the reactants in their stoichiometric ratio and its crystal structure has been determined by single-crystal X-ray diffraction. A multitude of salt bridges are formed in this structure connecting the protonated 2-amino-5-chloropyridines and the malonate ligands of the polymeric polyanion. Examining this characteristic of the solid state architecture, we noticed several salt-bridge (sb)···□ interactions and an unex one pair (lp) of one malonate oxygen atom and a planar salt-bridge (Fig. 2). The combination of this interaction with various other weak intermolecular forces results in a remarkably extended supramolecular network combining a wide variety of interactions involving π–systems (Cl···π, π···π) and salt bridges(sb···π and lp···sb). We describe the energetic and geometric features of this lone pair – salt-bridge interaction and explore its impact on the resultant supramolecular organisation using theoretical DFT-D3 calculations.

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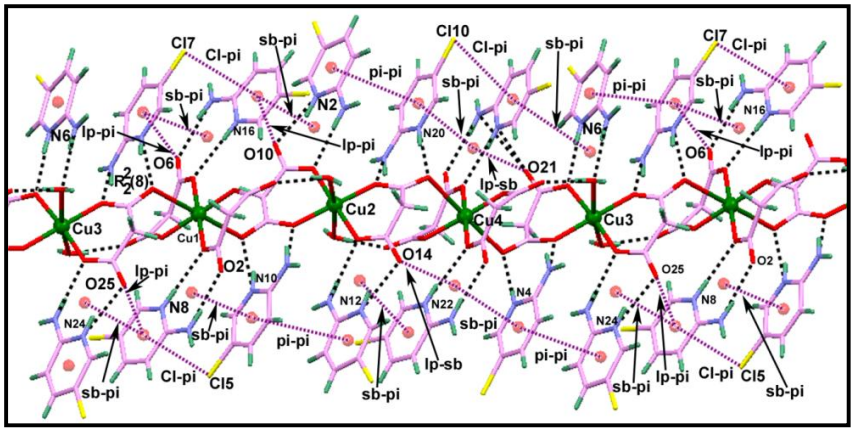

Fig. 2. Supramolecular network of the weak forces in **2.**Viewed along *b* axis. Color code: Cu, green; O, red; N, blue; C, light purple; Hydrogen, aquamarine; Chlorine, yellow.

Our interest in these fundamental noncovalent interactions stems from the desire to better understand the basic nature and their decisive role in molecular packing, since they have several implications in various fields, including amazing biological systems.

Hydrogen bonding plays an important role in determining the three-dimensional structures adopted by proteins and nucleic acids. In these macromolecules, bonding between parts of the same macromolecule cause it to fold into a specific shape, which helps in determining the molecule's physiological or biochemical role. Nature's ultimate example of a self-assembled hydrogen bonded array is of course the double helix of DNA which is formed by complementary hydrogen bonding between cytosine (C) and guanine (G), and adenine (A) and thymine (T) base pairs (Fig. 3),[18] which link one complementary strand to the other and permit replication.

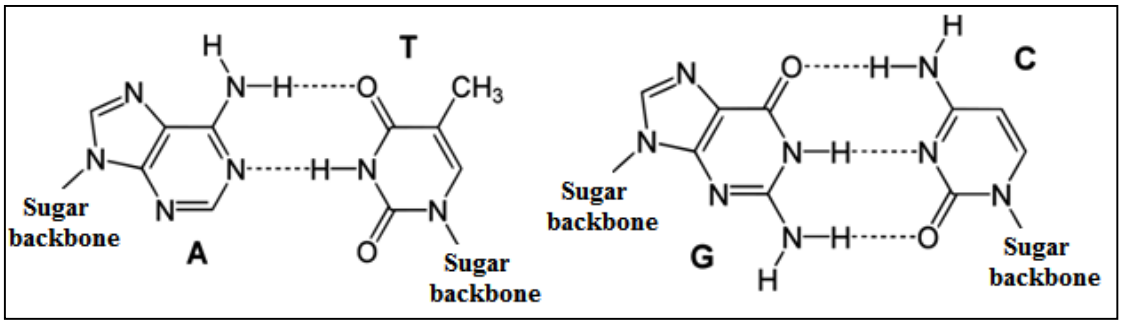

Fig. 3. Watson-Crick hydrogen bonding in DNA.

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In proteins, the peptide linkage forms primary structure, which is actually the elimination of a molecule of water from two same or different amino acids. Within the long protein chains there are regions in which the chains are organized into regular structures known as alpha-helices (alpha-helixes) and beta-pleated sheets. These are the secondary structures in proteins.[19] These secondary structures are held together by hydrogen bonds. These hydrogen bonds are formed between one of the lone pairs on an oxygen atom and the hydrogen attached to a nitrogen atom (Fig. 4).

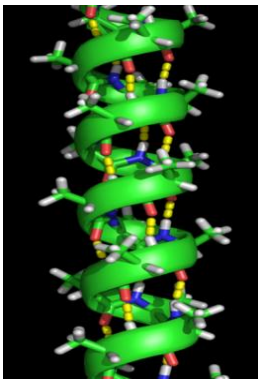

Fig. 4. An alpha-helix with hydrogen bonds (yellow dots).

Dennis A. Dougherty is one of the pioneers in establishing cation···π interactions in chemical and biological fields. He also proved that within a protein, cation···π interactions could occur between the cationic side chains of either lysine (Lys, K) or arginine (Arg, R) and the aromatic side chains of phenylalanine (Phe, F), tyrosine (Tyr, Y) or tryptophan (Trp, W).[20] Lately R. Wu and T. B. McMahon investigated theoretically the binding energies and the strengths of cation···πinteractions between Phenylalanine, Tyrosine and Tryptophane with NH_4^+, Na^+ or $CH_3NH_3^+$187.[21]

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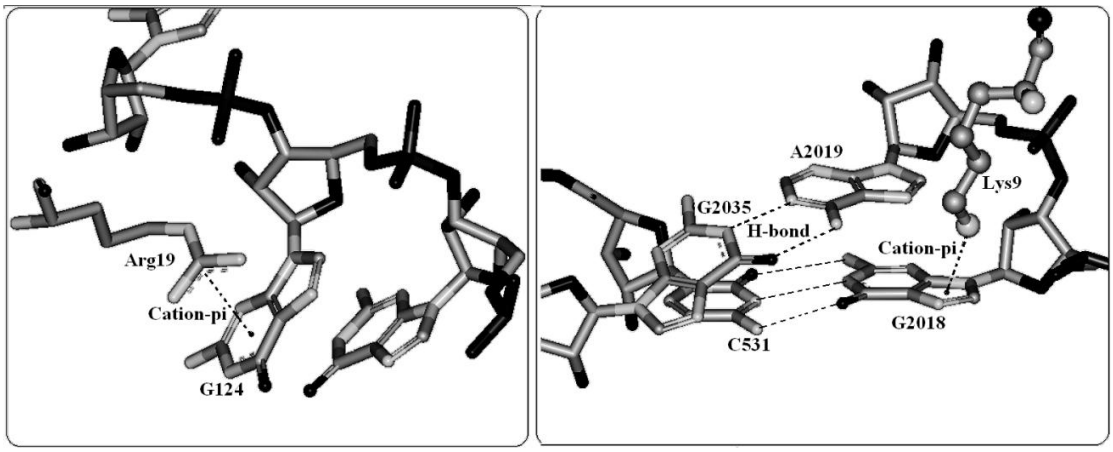

Fig. 5. Cation···π interactions involving unpaired and paired bases. (a) The cation···π interaction between Arg19 of chain 7 and G124 of chain A in protein–RNA complex 2j01. (b) The cation···π interaction between Lys9 of chain 5 and G2018 (paired with C531) of chain A in protein–RNA complex 2j01.[22]

Lone pair···π interaction is one of the most important supramolecular interactions recognized by the scientific community.Egli and co-workers have extended this concept of lone pair–π (lp–π) interaction.[23] They reported two distinct cases of lp–π interactions in biomacromolecules: (a) the stabilization of the structure of *Z*-DNA[24,25] and (b) H_2O-π interactions within a ribosomal frame-shifting RNA pseudoknot.[26] Indeed, lp–π interactions play a key role for the stabilization of biological macromolecules, as well as for the binding of inhibitors in the binding pocket of biochemical receptors.[27]

Though the role of anion–π interactions in chemical processes is being progressively acknowledged,[28–33] their involvement in biological processes has been scarcely reported. Recently, Lucas and co-workers present a large-scale PDB analysis of the occurrence of anion– π interactions in proteins and nucleic acids. Moreover, to gain insight into the role of anion– π interactions in the stabilization of macromolecular complexes, inter-chain recognition has also been a subject of study, primarily for proteins. In addition they have gone a step further by considering the existence of cooperativity effects through the inclusion of a second noncovalent interaction, i.e. π -stacking, T-shaped, or cation– π interactions to form anion– π –π and anion– π –cation triads.[34] They observed different kinds of anion–π interactions in biological systems. (Fig. 6).

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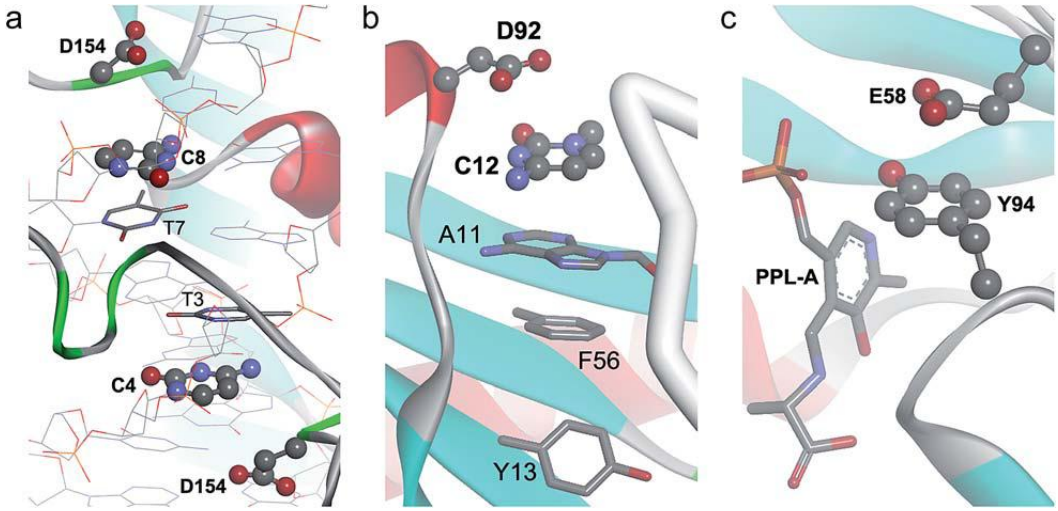

Fig. 6. Binary anion–π interactions in biological systems. (a) Postreactive state of endonuclease BamHI complexed to DNA (PDB code 3BAM), where Asp– π interactions are shown. (b) C-terminal domain of human protein U1A bound to RNA (PDB code 1URN), where the Asp92– π interaction is shown. (c) Active site of the complex of pyridoxal- 50-phosphate-dependent catalytic antibody 15A9 with a phosphopyridoxyl- L-alanine (PPL-A) substrate analogue (PDB code 1WC7), where the Glu58– π interaction is shown.

BIOMEDICAL APPLICATIONS:

Drug Delivery

Although several anti cancer drugs have been already developed, the efficacy of cancer treatment is significantly low due to the unavailability of efficient drug delivery strategies. For example, hydrophobic drugs have limited applications in biological environment due to their low solubility in aqueous solutions. Moreover, nontargeted drug delivery might cause unwanted damage to healthy or normal tissues instead of focusing on cancerous tumor sites. The cancer cell membrane naturally sets up the last barrier for anticancer drug delivery into cancer cells. As a result modified drug delivery systems are required for the development of anticancer drug solubility in aqueous environment, targeted drug delivery into tumor sites, and effective internalization into cancer cells. Supramolecular strategies have been directed to achieve these goals in drug delivery.[35]

Gene Delivery

Over the past few years Gene therapy has attracted increasing interest in since. The success of gene delivery strongly depends on the gene carriers. Due to toxicity issue, immunogenicity, and

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low scaled-up capability traditional viral delivery has not been implemented. Therefore, a huge modification is required for the development of nonviral gene delivery systems to overcome these drawbacks[36]Now a days, a substantial effort has been given to apply supramolecular chemistry for the prospect of gene delivery and becoming a hot research topic in biomedical field.[37,38] Simple cationic macrocyclic molecules, like star-shaped derivatives or amphiphilic macrocyclic molecules, were utilized to condense nucleic acid by electrostatic interaction.[39,40,41−48] Cell penetrating peptide conjugated macrocyclic molecules were fabricated to enhance the cellular uptake and DNA delivery efficacy.[49] Researchers also chemically conjugated macrocyclic molecules onto cationic polymer chains to enhance the gene delivery efficacy, while decreasing the toxicity of the cationic polymers.[50,51] Supramolecular micelles constructed by amphiphilic macrocyclic molecules were used to encapsulate genes by supramolecular self-assembly for accomplishing the gene delivery.[52,53−57] In addition, targeting ligand folic acid was conjugated onto such micelles to realize targeted gene delivery.[58]

CONCLUSIONS

With the advancement of supramolecular chemistry, it has been extensively applied in different research fields. During the past few years, lots of efforts have been dedicated for the progress of biological and biomedical applications of supramolecular systems based on noncovalent interactions, including hydrogen-bonding interaction, electrostatic interaction, van der Waals forces, hydrophobic/hydrophilic interaction, host−guest interaction, and so forth. Along with the improvement of supramolecular chemistry and new functionalization techniques, the host−guest complexes having weak noncovalent interactions and multifunctional properties have shown great potentials for biomedical applications. We can expect that in near future these newly explored interactions like saltbridge-π and lonepair–saltbridge will play a pivotal role in biological as well as in biomedical field.

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