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A series of memantine based salts with various aromatic and aliphatic carboxylic acids: Crystallographic analysis, Hirshfeld surfaces and dissolution study

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ABSTRACT

Memantine.HCl (MEM.HCl), an adamantane based amine is a clinically useful drug for the treatment of various neurological disorders. Surprisingly, applications of MEM salts/cocrystals in crystal engineering, as a supramolecular motif, are rarely reported in literature, in spite of opportunity that MEM salts (primary ammonium monocarboxylate, PAM and primary ammonium dicarboxylate, PAD) provide to study the reliability and stability of various non-bonded interactions such as C–H···O, C–H···N, van der Waals, etc. in presence of strong ionic hydrogen bonds (N^+ –H…O^-, O–H··· O, etc.). In the present study, a new series of 12 salts with MEM and varied carboxylic acid backbones (aliphatic and aromatic) were synthesized and characterized by various physicochemical techniques such as IR, NMR and single crystal X-ray studies. The focus was also directed to understand the supramolecular synthons present in these salts and establish a structure-property relationship among them. Qualitative (graph set analysis) and quantitative (Hirshfeld surface analyses) approaches were also employed to analyse all the single crystal structures of salts (**1A-1K**) to gain an insight regarding the supramolecular assemblies formed and some subtle variation in the well-established PAM and PAD supramolecular synthons. Additionally, all the synthesized salts were subjected to solubility studies in water and compared with the standard MEM. HCl salt. All synthesized salts displayed a range of solubility in water from high to medium to low as compared with MEM. HCl salt. Efforts were also directed to understand the possible cause of high and low solubility of newly synthesized MEM salts in water with respect to the carboxylic acid backbone, ratio of acid/amine (present in salts) and the supramolecular synthons present in the single crystal structures. Moreover, supramolecular isomerism of 1D PAM to 0D PAM, with bulky group substituted carboxylic acid (pivalic acid and 4-methylbenzoic acid), suggests bright future prospects of designing new materials from crystal engineering point of view.

1. Introduction

Over the years, crystal engineering [1–3] has emerged as one of the fastest growing areas in research because of its applications in drugs and pharmaceuticals (polymorphs, pseudo-polymorphs), organic electronics, optical devices, molecular machinery, and many more [3,4]. The field of crystal engineering (or solid-state supramolecular synthesis) deals with the understanding of intermolecular and intramolecular interactions (present in a structure) in the context of crystal packing and applying the understanding to design the pre-desired crystal structures with specific physical or chemical properties [5]. In the recent years, transformation of APIs from their original form into co-crystals has gained a lot of interest. A salt/co-crystal of an API is expected to show modified physical and chemical properties than the pure compounds, which enables us to improve the bioavailability of the drug, thus creating an attractive route for drug development [6]. As a result, crystal engineering approach proved to be quite fruitful in modifying the properties of drugs, viz. solubility, dissolution rate, bioavailability, melting point, stability and compressibility [7–19].

We have been working in the area of design, synthesis and application of new Low Molecular mass Gelators (LMOGs) [20,21], using crystal engineering approach, since a decade. Recently, we got interested in physicochemical alteration of a known drug

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Design, synthesis, and application of a new series of organogelator using crystal engineering approach and solvent parameter study: A synergetic approach

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ABSTRACT

A new series of organic salts (**A1B1-A1B6**) based on pivalic acid and primary amine (alicyclic, aromatic, aliphatic) has been designed and synthesized for its potential organogelation behavior. A simple strategy of synthesizing 1-D hydrogen bonded network of PAM (primary ammonium monocarboxylate) leads to the discovery of five new gelators. All the synthesized salts (gelator/non-gelator) were subjected to single crystal X-ray studies to support the hypothesis that 1-D hydrogen bonded networks favor gelation. A detailed study of solvent parameters like dielectric constants, Kamlet-Taft parameters, Hansen parameters, etc. was carried out to get an insight into the role of solvents on the thermal stability and gelation performance of these salts. Organogelation behavior of Salts (**A1B1-A1B5**) is found to be dependent upon bulk solvent properties such as dielectric constant (ε), polarity index (P') and a strong correlation between multi-component solvent parameters such as (β) and polar cohesive energy (δ_p) is observed. Gel network of salt **A1B3** (in Acetonitrile solvent) has been used as a template for synthesis of silver nano particles owing to its rectangular hollow xerogel fibers.

1. Introduction

'Supramolecular gel', a non-covalently bonded colloidal system, contains nano-scale molecular assembly of solutes capable of immobilizing solvents [1–4]. Supramolecular gels are invariably correlated with low molecular weight organo gelators (LMOGs) comprising of small (molecular weight <3000) compounds, which can form self-assembled fibrilar networks (SAFiNs) through various non-covalent interactions such as hydrogen bonding, van der Waals interaction, π-π interaction, hydrophobic interactions, etc. resulting in the gelation of solvent (aqueous/organic). Last decades have seen an enormous rise in the research revolving around thermo-reversible multicomponent LMOGs owing to their innumerable applications like templating agents, smart materials, optoelectronic materials, pollutant removal, reusable catalysts, to name a few [5–7].

Multicomponent supramolecular gelators [8–10], a member of the vast family of LMOGs, represent a special position in the ever-growing list of compounds displaying gelation properties, mainly due to: (i) simplicity of the system to understand the mechanism of gelation, especially, when the number of non-bonded contacts are limited (ii) multiple functionalities can be envisaged in a single system by suitable choice of individual components and (iii) crystal engineering approach can be applied successfully to design a new two-component gelator.

In recent years, crystal engineering has been proved to be an inevitable tool for designing new gelators, using the concept of supramolecular synthons [11,12]. Crystal engineering strategy can help us to design a molecule with a preferential 1-D hydrogen bonding network, a prerequisite for supramolecular gelation. Understandably, the anisotropic growth of molecular assemblies results in the formation of a continuous network of ribbons, fibers, rods, tubes, etc. [13–15] which further entangle among themselves through weak non-covalent interactions forming a three-dimensional network, thereby trapping bulk solvents, as a result of capillary forces and surface tension.

Inspired by our recent success with organic salts, namely 2-aminothiazole containing salts [16] (supramolecular gelation study) and memantine based salts [17] (crystal engineering study), we decided to work with simple two-component systems possessing the potential to show supramolecular gelation. Surprisingly, a simple acid molecule of tert-butyl carboxylic acid (pivalic acid), which lacks long aliphatic chain, but has multiple methyl groups that can induce steric hindrance and may contribute to various weak non-bonded interactions such as C-H…O, C-H…N, C-H…π, etc. has never been considered for supramolecular gelation studies. However, few pivalic acid salts have been reported in the literature due to its interesting hydrogen bonded network, and surprisingly, their gelation property was never explored [18].

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A series of multifunctional pivalamide based Low Molecular Mass Gelators (LMOGs) with potential applications in oil-spill remediation and toxic dye removal

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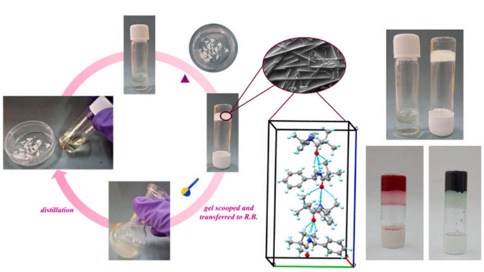
GRAPHICAL ABSTRACT



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ABSTRACT

Designing new Low molecular weight gelators (LMOGs) which can congeal organic/aqueous solvents is a daunting task, especially those capable of selective organogelation in presence of oil/water systems. Phase selective organogelation (PSOG) offers various advantages over conventional methods for oil spill remediation, viz. programmability, responsiveness and biocompatibility. Molecules with multiple fragments such as one-dimensional hydrogen bonding groups, terminal bulky group and a variable organic moiety (aromatic, aliphatic, alicyclic) appear to be good candidates for design of new LMOGs. In this work, a new series of pivalic acid based amides (**1A–13A**) having aromatic, aliphatic and alicyclic backbones were synthesized and characterized by various physicochemical methods. All the compounds were exploited for their ability to congeal various organic solvents including crude oil fractions, fuels and oils. Out of 13 newly synthesized compounds, six turned out to be excellent organogelators. Multifunctional properties of these compounds were observed such as selective gelation of aliphatic solvents in presence of water and removal of dyes from aqueous medium with good efficiencies. A detailed study is undertaken to establish the cause of gelation/non-gelation of solvents based on structure-property correlation using single-crystal X-ray diffraction, powder X-ray diffraction, Hirshfeld surface analysis, etc. Moreover, these compounds represent a class of one of the smallest molecules explored for the application of phase selective organogelation of fuel for containing oil-spills and dye adsorbing materials for water pollution control.

Abbreviations: PSOG, phase selective organo-gelation; MGC, minimum gelator concentration; LMOG, low molecular weight organo-gelator.

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Design and synthesis of novel heterocyclic pivalamide ligands and their copper(II) complexes: Structure, BSA/DNA interactions and SOD *synzyme* activity

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BSA binding studies

A B S T R A C T

Four new heterocyclic pivalamide based ligands (**L1-L4**) and their respective mononuclear copper(II) complexes (**C1** = [Cu(N-(thiazol-2-yl)pivalamide)$_2$], **C2** = [Cu(N-(5-methylthiazol-2-yl)pivalamide)$_2$], **C3** = [Cu(N-(benzothiazol-2-yl)pivalamide)$_2$], **C4** = [Cu(N-(benzoimidazol-2-yl)pivalamide)$_2$]) were synthesized to serve as low molecular weight SOD mimics. The complexes were characterized by single crystal XRD, Hirshfeld surface analysis, FT-IR, UV–vis, EPR and ESI-MS studies. **C1** crystallizes out in a triclinic system with P-1 space group, while **C2** and **C4** belong to $P2_1/c$ and $P2_1/n$ space groups respectively, from monoclinic system. The crystal structures indicate nearly square planar geometry where mononuclear copper(II) metal ions have coordinated with O and N donor atoms of the pivalamide ligands in *trans* fashion. All the complexes can scavenge superoxide concentration at low concentrations, in the order **C2** < **C3** < **C1** < **C4**. The interaction of all the complexes with BSA (bovine serum albumin) protein investigated using fluorescence titration method indicated a static quenching mechanism (K_{BSA} values of the order 10^5 M^{-1}). The ability of the complexes to bind with calf thymus DNA were also evaluated using absorption and fluorescence titration methods and an intercalative interaction mode of the complexes with DNA was established (K_b values of the order 10^4 M^{-1}). The complexes have a strong ability to cleave supercoiled plasmid DNA.

1. Introduction

Supramolecular chemistry is the study of non-covalent interactions in organic solids, metal complexes and organometallic compounds. In coordination chemistry, the binding of bioactive molecules to their bioactive targets occurs primarily through supramolecular interactions. With decades of dedicated work in the design and synthesis of novel supramolecular architectures, supramolecular synthesis of multi-functional systems has evolved and brought us closer to develop such systems for the betterment of mankind. The key is to gain control over supramolecular assemblies, which can contribute to development of host–guest assemblies, target selective drug delivery, biosensors, tissue engineering, etc. [1].

Thiazole containing compounds are widely known for their exclusive biological properties like anti-protozoal, anti-convulsant, anti-diabetic, anti-inflammatory, anti-tumor, antiviral, and many more because of the presence of –N=C–S– group. Thiazole based metal complexes have been widely studied in the past for their promising anti-fungal, anti-bacterial and cytotoxic behavior [2–5]. This inspired us to investigate the properties of synthesized complexes for their newer biological activities.

Redox-active transition metal ions in a coordination environment make good candidates for biological catalytic activity in redox reactions [6,7]. Specially, copper(II) containing coordination complexes possess redox potentials similar to those of reactive oxygen species, and hence, can be best utilized in catalyzing the dismutation of superoxide anion (a product of oxygen metabolism in the living systems). This superoxide ion can be a mediator of reperfusion diseases such as myocardial infarction (stroke), initiate inflammatory processes associated with diseases like arthritis, even cause oxidative injury to the tissues which can lead to various neurological disorders like Parkinson's and Alzheimer's [8]. Naturally occurring superoxide dismutases (SOD) in living

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