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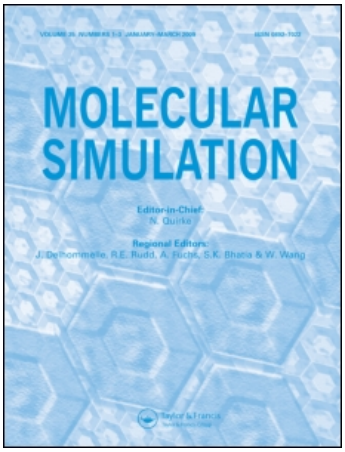

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Predictive modeling of self assembly of chromonics materials

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Predictive modeling of self assembly of chromonics materials

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This study identifies mechanisms of self-assembly of a chromonic molecule with interesting self-assembly properties. Results from molecular dynamics (MD) studies used to understand the moieties of the molecule that affect the structure are consistent with experimental observations of these self-assembled structures. Coulombic forces, with significant contributions from $\pi-\pi$ interactions drives the self-assembly of this class of materials; hydrogen bond energies are also significant.

Keywords: Chromonics; Molecular dynamics (MD); Dipole moments; Isoelectricstatic potential; Zwitterions; $\pi-\pi$ Interactions

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1. Introduction

Chromonics are a class of liquid crystal materials that are distinct from amphiphiles in that they do not show any surfactant properties. These are generally plate-like molecules consisting of aromatic rings that are bonded to each other and to hydrophilic groups at the periphery of their structures [1]. The hydrophilic groups may be charged moieties or hydrogen-bonding groups.

Examples of chromonics materials include a variety of drugs and dyes (examples in figure 1). The tendency of chromonics to aggregate into columns even in dilute systems (like amphiphiles which form micelles before they form their mesophases) is unique; even though there may be a lower aggregation concentration, no optimum aggregation size and no critical micelle concentration (CMC) is observed for these self-assemblies. In addition, there is a distinct absence of a Krafft temperature. These tendencies suggest that the mechanism of self-assembly for these molecules is distinctly different form those of amphiphilic micelles.

Micelles are formed, driven by hydrophobic interactions of amphiphiles (entropic interactions of water molecules that exclude the amphiphile molecules are critical to micellization [2]). The association of chromonic aggregates is different from micelles. It is an exothermic process; $\pi-\pi$ interactions between the aromatic rings are suspected to play an important role. Past studies [3–5, and references therein] have pointed out that for chromonics self-assemblies, entropic driving forces are small and in fact, enthalpic forces, possibly based on $\pi-\pi$ interactions between aromatic rings lead to self-assembled structures.

In this paper, molecular simulation are used to predict the behavior of a new chromonic molecule, compare these predictions with experimental data and use this study to understand the mechanisms important for the self-assembly of such a molecule.

2. The molecule

The molecule of interest is 3-{[6-(3-carboxyanilino)-4-(3-methyl-1H-imidazol-3-ium-1-yl)-1,3,5-triazin-1-ium-2-yl]amino}benzoate†, as shown in figure 2 and is used as a chloride salt. The molecule is referred to as NMI (*n*-methyl imidazol). NMI has a positively charged nitrogen center balanced with the chloride ion. In its acidic state, the molecule is not soluble in water. On increasing the basicity of the solution (using a molar equivalent of base), the molecule forms zwitterions with one of the carbonic acid groups bearing a negative charge. On further increasing the basicity (using two molar equivalents of any of the above bases), the solution turns into a liquid crystal state with a pearly white color—the exact shade is influenced by the cation used.

TEM images (figure 3) show that these molecules self assemble into long filaments. A 20% aqueous solution of NMI was further diluted with ultrapure water in a ratio of

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†Alignment structure for use in liquid crystal displays, includes layer of chromonic liquid crystalline material including chromonic material and pre-tilt additive, WO 200244802A.

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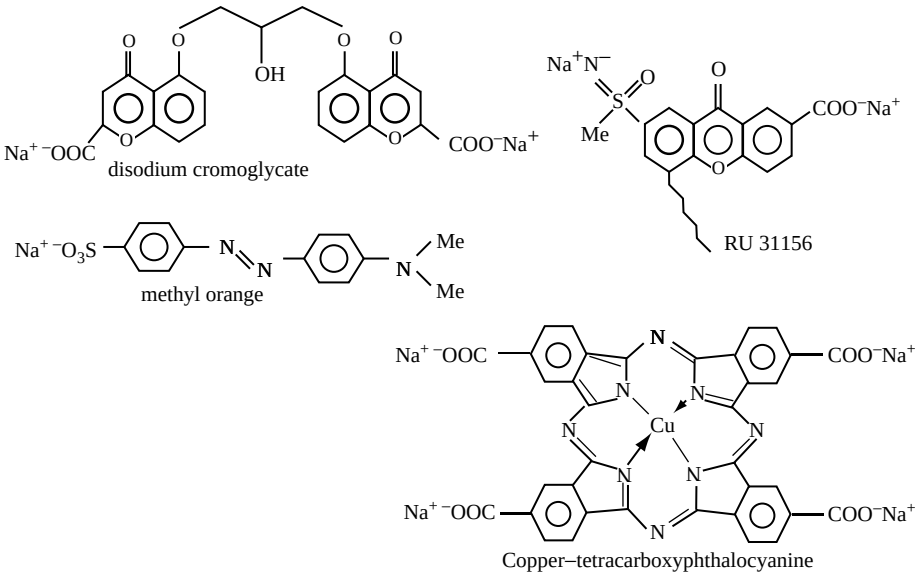

Figure 1. Molecular structures of examples of chromonics materials.

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1:20. A partial drop of this dilution was placed on a carbon/formvar lacey substrate on 200 mesh Cu TEM grid which was immediately frozen by plunging into liquid ethane at − 167°C using a Leica EMCPC instrument. This was then transferred under liquid nitrogen temperature using a Gatan 626 Cryo-Transfer holder into a Hitachi model H9000 NAR-TEM (300 kV) to be characterized while at liquid nitrogen temperature. Figure 3 shows a cryo-TEM image of a 20% (by weight) solution of NMI diluted further by 1:20 with water. Filaments that are about 30 nm in cross section are clearly visible. Given that a chromonics molecule is about 3 nm across (which also corresponds to the cross-dimension of the simulated stacks of chromonics), each filament is made up of about 10 of these stacks bundled together. In addition, one sees almost no beginnings and ends of these filaments in any given field of vision under the microscope suggesting that these filaments are indeed extremely long. It is not clear whether these long filaments are continuous stacks or they are in fact shorter stacks braided together like a coir rope is made from coconut fiber.

X-ray diffraction studies also show that these molecules self-assemble. A 30% NMI solution in water, dissolved with ammonium hydroxide was used. The sample was diluted to 5, 10, and 20% (by weight) concentration and drawn into a 1.0 mm glass capillary. Transmission X-ray data were collected with the capillary tube long dimension placed in the vertical. Figure 4 shows the transmission 2D diffraction pattern for 20% (by weight) aqueous solution of NMI. At concentrations higher than 10%, we see a peak corresponding to 3.3 Å is observed centered on the 2D data equator that corresponds to the spacing between the aromatic molecules in a stack. An additional peak centered along the 2D data meridian corresponds to 25 Å; however, this peak does not shift by changing the concentration of the NMI solution suggesting that this peak represents the cross-sectional dimension of a stack rather than the spacing between stacks. The latter would have increased with increasing dilution. No higher order structure have been observed using X-ray studies.

When 10% solutions of NMI were coated on glass slides, optical microscope images show ordered domains aligned along the coating direction. These domains are birefringent, pointing to order within these domains resulting in an anisotropic structure. Figure 5 presents optical images of these coatings through polarized filters. The horizontal lines through some of the pictures are owing to the coating bar.

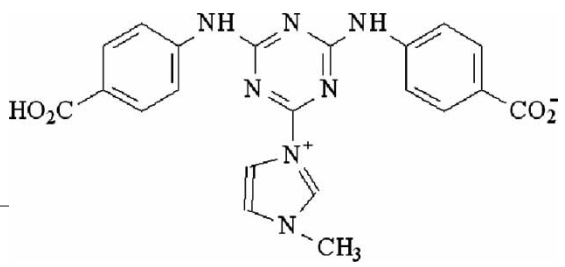

Figure 2. Molecular structures of NMI.

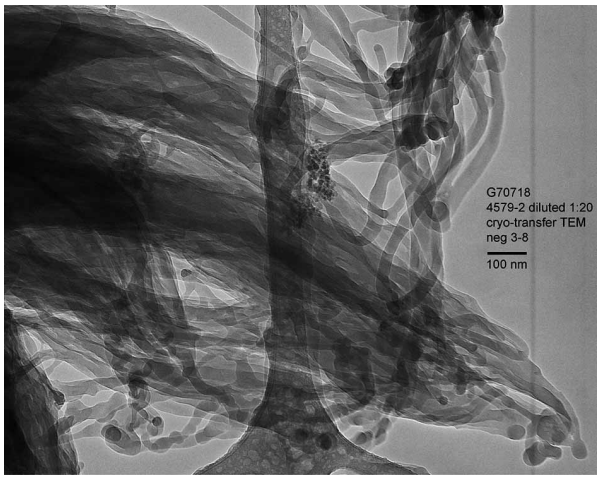

Figure 3. TEM images of 20% NMI solution.

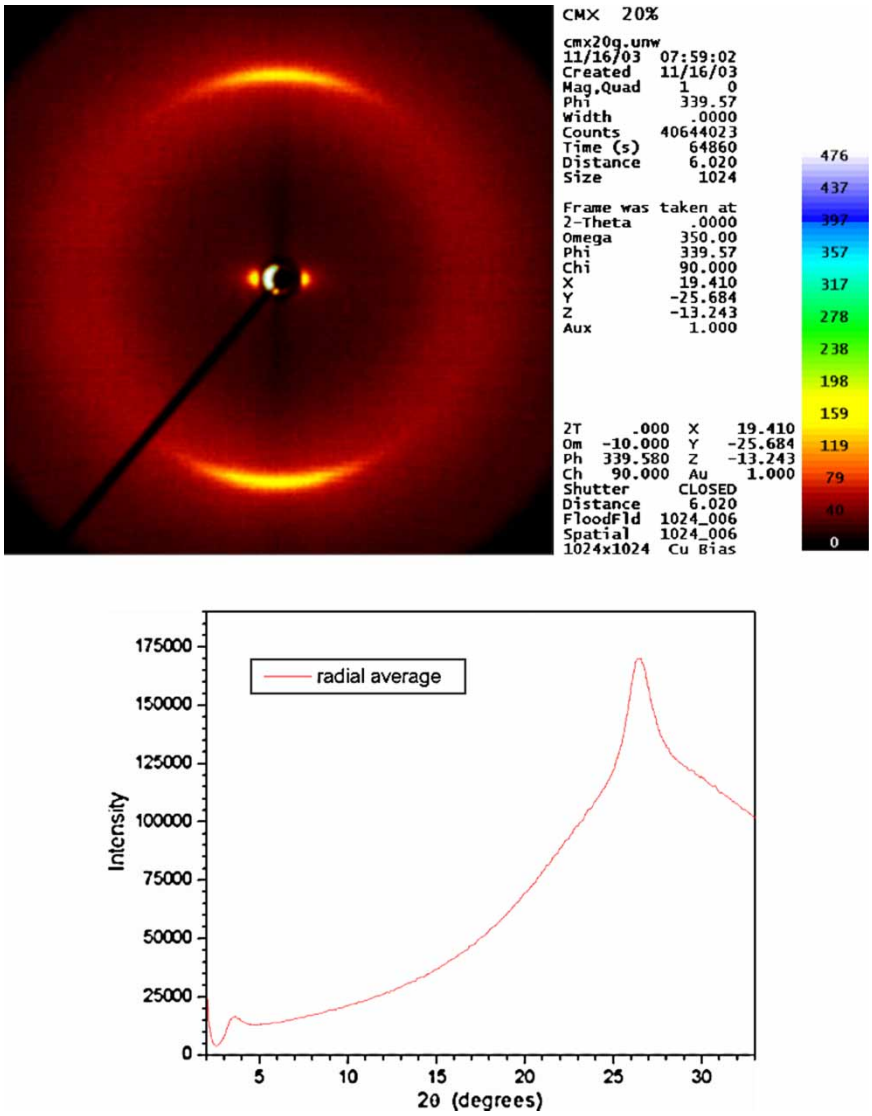

Figure 4. Transmission 2D detector image and radially averaged (= 1D) X-ray diffraction pattern of 20% solution of NMI chromonics shows short range order at about 3.3 Å corresponding to the spacing between π rings.

All these different analytical techniques point to a highly ordered self-assembly of aqueous solutions of NMI at higher than 10% concentration. The reasons for such self-assembly are poorly understood. While, studies of similar materials suggest π−π stacking as the basis for enthalpic driven self-assembly, what components molecular interactions drive such self-assembly are not clear. Thus, one cannot predict whether a given molecular structure will result in similar self-assembly. Molecular simulations are used to help resolve these questions.

3. Simulation methods

The semi-empirical quantum mechanics code MOPAC [6] with AM1[7]parameters in software CAChe‡ were used to understand the single molecule (or ionized form), its charge distribution and its conformations. Conductor-like screening model (COSMO [8]) is employed to determine the conformation and electronic structures of NMI in water. This MOPAC (AM1, COSMO) method was also used to do some preliminary studies of binding of these molecules or stacks at room temperature and in the presence of water. Dipole moments are determined using MOPAC (AM1, COSMO) to simulate water environment.

More detailed investigation of the self assembly behavior of NMI in water was performed by using molecular dynamics (MD) algorithms within CERIUS2¶ with a dreiding force field [9] that was optimized for water. Ten NMI molecules were randomly placed in a unit cell of water (approximately 1000 molecules). Periodic boundary conditions were used during the simulation. Some of the snapshots are visualized such that the unit cells are placed periodically—this allows for visually identifying the continuity of stacks as they pass across unit cell boundaries. However, this also creates artificial appearance of order and we must be careful in our

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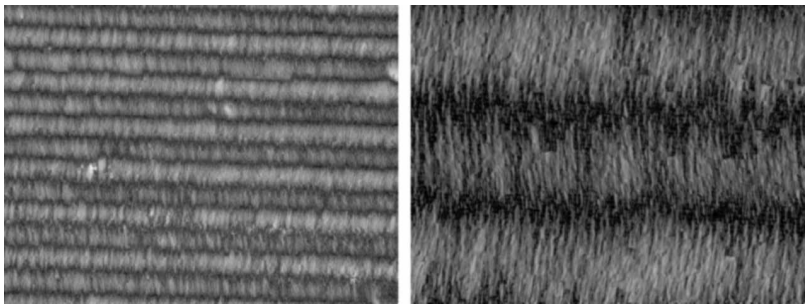

Figure 5. Domains of NMI show order when coated on a glass substrate. 20 X magnification (left column) shows long range order while 100 X (right column) shows fine structures in the ordered stacks.

analysis. In addition, the boundaries of the unit cell also break up self-assemblies of longer length scales.

MD simulations were conducted in an NPT ensemble. Following approximately 3000 steps of minimization, the system was allowed to equilibrate over 100,000 steps (equivalent to about 200 ps). The results presented are snapshots or averages after that period. Charge equilibration was performed on the system every 20,000 steps. Using two processors§, the time for computation varied between 100 and 300 h; simulation of significantly larger or more complex systems is unfeasible. The system does not reach equilibrium within the simulation time-period; however, it becomes unfeasible to carry the simulation until global minimum—corresponding to a stable equilibrium structure—is attained. While the regularity of order that might be imagined, the equilibrium structure of a liquid crystal is not obtained. Yet, the trajectories for spontaneous self-assembly do provide significant understanding of the evolving self assembly.

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4. Results

The dipole moments and the electrostatic isopotential of these molecules in different pH environments were calculated with MOPAC (AM1, COSMO). For a neutral NMI molecule with a chloride ion, figure 6 presents these calculated results in a visual format: (a) side view of molecular structure with dipole moment; (b) side view of electrostatic potential; (c) front view of molecular structure with dipole moment; (d) front view of electrostatic potential. The magnitude of the dipole moment is 13.629 Debye. For the zwitterions form of the chromonics molecule: (e) front view of molecular structure with dipole moment; (f) front view of electrostatic potential. The magnitude of the dipole moment is 37.018 Debye. For the completely ionized chromonics molecule with an ammonium counterion; (g) front view of molecular structure with dipole moment; and (h) front view of electrostatic potential. The magnitude of the dipole moment is 51.130 Debye.

The dipole moments and the electrostatic potential surfaces suggest possible ways in which these molecules may self-assemble to minimize the energy. These

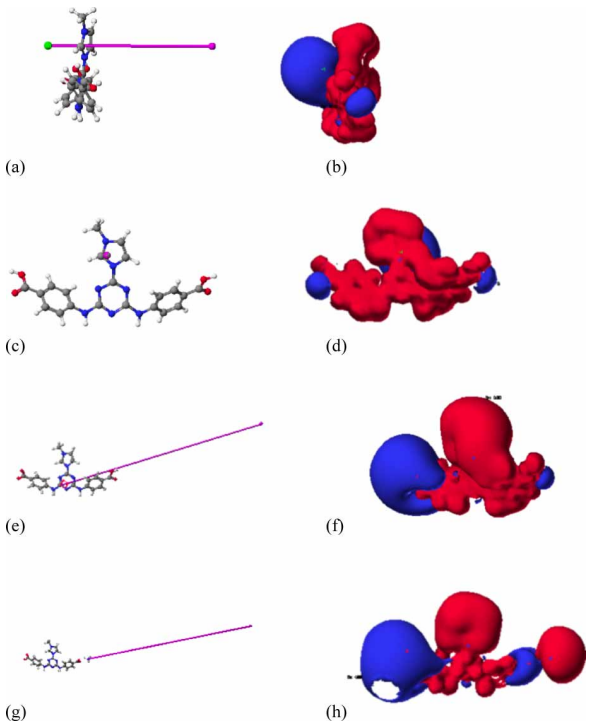

Figure 6. Dipole moments (the purple cylinder represent the direction of dipole moments) and isolectrostatic potential (red, repulsive toward proton; blue, attractive to proton) of NMI in water determined from MOPAC (AM1,COSMO) calculations. Figures (a)–(d) show the front and side views of the dipole moment and electrostatic potential of a neutral chromonics molecule with a chloride ion. Figures (e)–(f) show the zwitterions form of the chromonics molecule. Figures (g)–(h) show the completely ionized chromonics molecule with an ammonium counterion.

simulations suggest that the zwitterions may potentially form dimers in a manner that the dipole vectors of figure 6(e) cancel each other out. Similarly, the fully ionized molecules with ammonium counter-ions can pair up as well. In addition, these molecules can self assemble into a configuration of "*n*" molecules in a way that the dipole vectors of all of these "*n*" molecules cancel each other. Thus, one could envision helical or other complex structures becoming the basis for these self-assemblies. Figure 7 presents these possible configurations for fully ionized NMI with its counterions. The dipole moment for this dimmer is 2.1 Debyes.

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The fully ionized NMI molecules with their counterions have the highest dipole. MD simulations starting with randomly placed NMI molecules, as described above, lead to stacks of molecules. Figure 8 shows an example of the transition from a random spread of molecules in a unit cell to the stack on the right hand side of the cell. Figure 9 shows two different configurations of spontaneously self-assembled NMI molecules that have been observed during simulations after about 100 ps. The figure on the right is a stack of rings with four NMI ions forming each ring. The figure on the left has three molecules per ring. Simulations clearly show that the fully ionized molecules self-assemble.

X-ray diffraction patterns calculated for these simulated self-assemblies shown in figure 10 compare well with diffraction patterns from experiments shown in figure 4. The simulation spectra have more noise and show extra peaks corresponding to the periodicity of the unit cell. However, the signature peaks at 3.3 and 25 Å are prominent.

Similar simulations with the non-ionized form of NMI or with the zwitterions forms do not result in self-assembled structures, though some dimers of the zwitterions are observed during simulation. It is possible that the zwitterions self-assemble but may require a longer time for self-assembly. To test this hypothesis, self-assemblies of NMI in their zwitterion forms were constructed similar to the self-assemblies of fully ionized NMI that have been observed. All the self-assemblies fell apart into disordered structures within 100 ps. Figure 11 shows an example of such a transition. The non-ionized NMI structures also showed similar trends. Clearly, these simulations predict structure of NMI and its lyotropic behavior that is consistent with experimental observations though they do not indicate the exact structure of the NMI self-assemblies.

The energy during the simulation drops and by about 100,000 iterations has flattened out. The energies listed for the following calculations are averaged over this region for each system. The energy of a unit cell of 1000 water system was calculated following an NPT simulation as with other cases described above. This energy was used as datum. Another NPT simulation was performed on a unit cell with one fully ionized NMI molecule and an ammonium counterion along with 1000 water molecules. Comparing the energies of NMI in water with a purely water system provides for the energy of "solution" of one NMI molecule in water and these are listed in the second column of table 1.

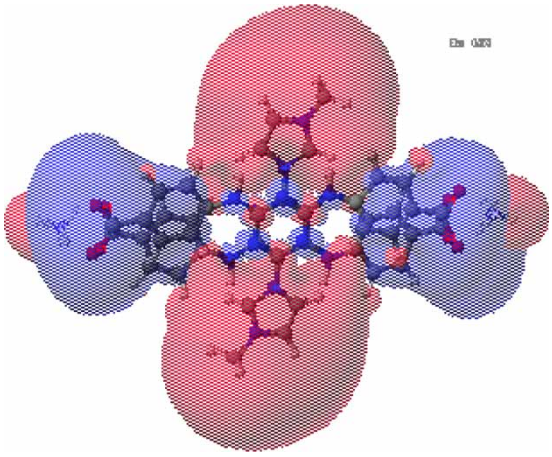

Figure 7. Possible configuration of a dimer formed by two NMI molecules such that their electropositive and electronegative regions overlap appropriately minimizing the net dipole. The dipole for this dimer is only 2.1 Debyes.

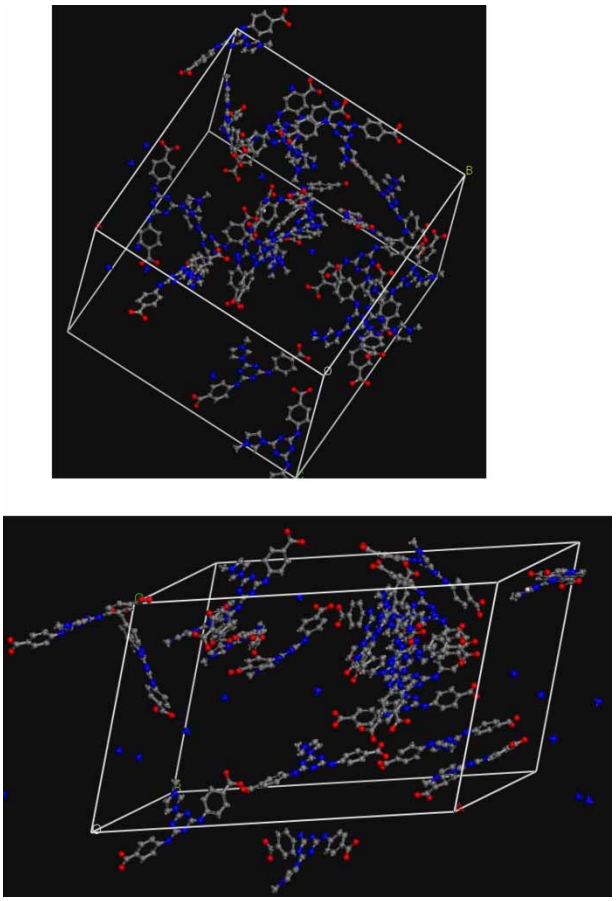

Figure 8. Spontaneous aggregation of fully ionized chromonics molecules in an aqueous environment. The snapshot at top shows the random positions early in the simulation, the one at the bottom is a snapshot after 100 ps.

The energies of 10 NMI molecules that had stacked into a column in 1000 water molecules were compared with 1000 water molecules. By dividing these energies by the number of NMI molecules in the simulation (10), the energy of one NMI molecule in a stack in water is estimated. This is listed in column three. The energies of 16 NMI molecules that had formed four-membered rings that stacked into a column in 1000 water molecules were compared with 1000 water molecules. By dividing these energies by the number of NMI molecules in the simulation (16), the energy of one NMI molecule in a ringed-stack in water is estimated. This is listed in column four. These numbers describe the energies for one NMI

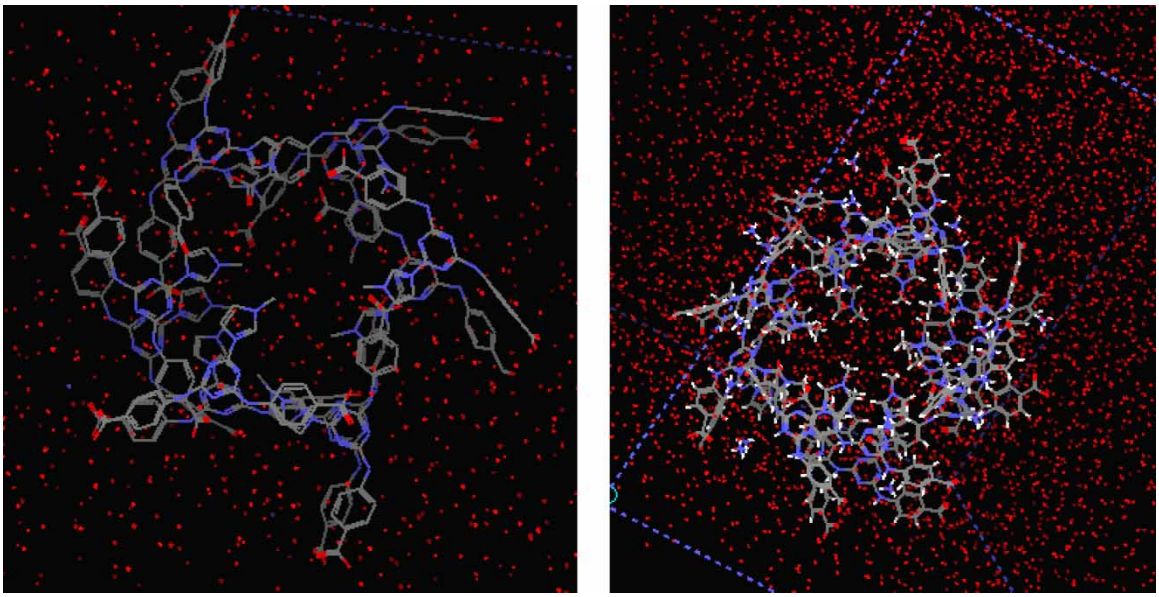

Figure 9. Spontaneously formed three- and four-membered ring stacks of NMI in water.

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molecule to be "dissolved" in water, to be in water as part of a stack and to be in water as part of a ring stack. The lower energy in a ring stack might be due to increased interactions between the carboxy groups in a ring rather that in a column. More favorable interactions between π rings may also be a factor. Clearly, from an enthalpic perspective the NMI molecules would prefer to be part of a ring stack.

The last two columns present the energy of self-assembling into a stack and into a ringed stack per molecule. This is estimated by subtracting values in column two from column three and four, respectively—i.e. by accounting for the energy of interaction of a single molecule and its interactions with the neighborhood water molecules. These stacking energies reflect the driving force for stacking owing to interactions between the NMI molecules and the interactions between the water molecules that are excluded from the stacking volume. Again, enthalpic considerations suggest that a ringed stack is preferred. The energy of self-assembly suggests that the ringed stacks are very stable.

The table also presents the various molecular components of the energy pointing out that the coulombic and the hydrogen bond interactions form a significant portion of the total interaction energies. In addition, as is possible in silico "experiments", the contribution from π−π interactions were estimated by turning off all charge contributions in the quasi-equilibrium structures and then calculating coulombic interactions without allowing any charge renormalization. This interaction—at −0.65 kcal/mol on average—represents about 40% of the original columbic interaction pointing to the importance of π−π interactions in these configurations.

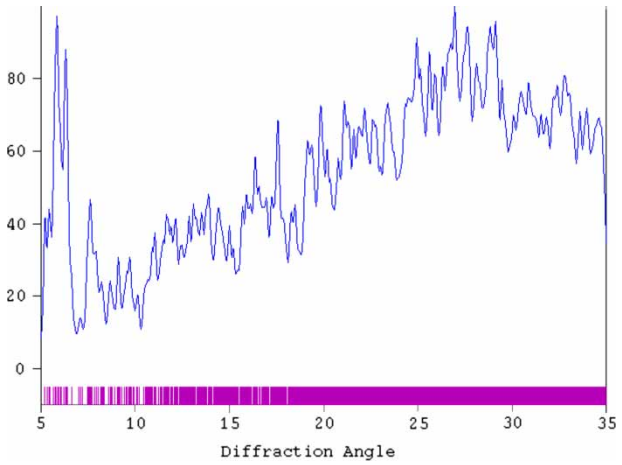

Figure 10. X-ray diffraction patterns calculated for four-membered ring stacks show a self-assembling dimension at 2Θ values of 27° compared to a 2Θ value of 26° from experimental measurements.

5. Conclusions

MOPAC (AM1, COSMO) calculations show significant dipole moments for the non-ionized and zwitterions forms. However, the electropositive and electronegative domains are not as distinct as in the fully ionized NMI with its counter ion. This perhaps disrupts the π−π interactions. In addition, the carboxy groups while they can still hydrogen bond, their interactions with other carboxy groups or with water molecules are weaker than if they were ionized. These differences become significant in the self-assembly of the fully ionized species. MD simulations show some dimers as suggested in figure 8. In addition, the configurations of stacks and ringed-stacks seen in the self-assembled structures are consistent with the suggestions from MPOAC calculations. The results from these simulations are consistent with experimental

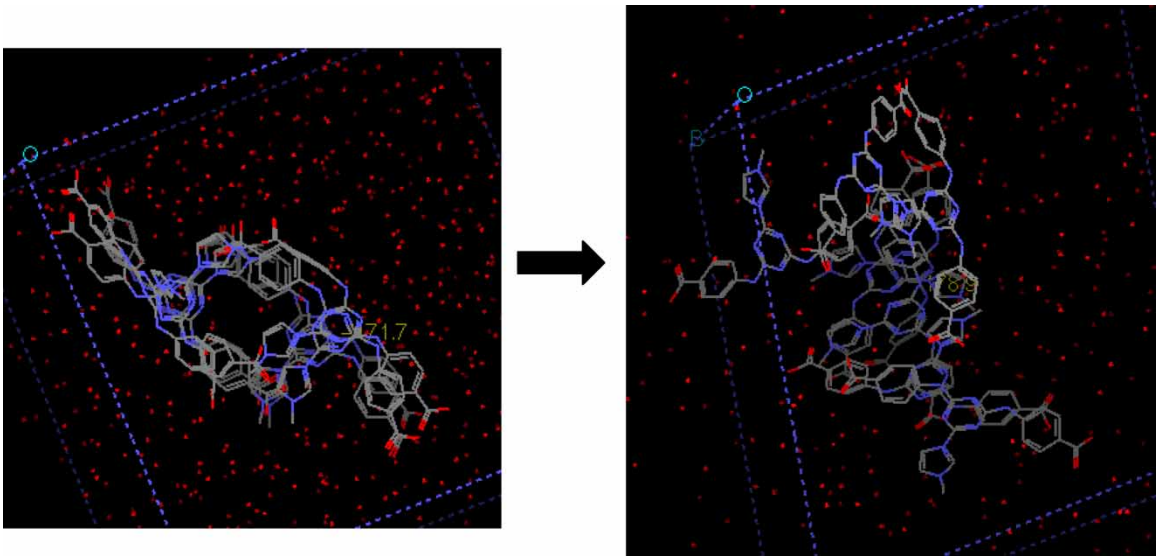

Figure 11. Zwitterion forms of NMI break into a disordered mass over 100 ps during an MD simulation.

Table 1. Energy of self assembly for chromonics in water.

kcal/mole	*Molecule*	*Stack*	*Ringed stack*	*Stacking energy*	*Ringed stacking energy*
Non bond	0.6	0.06	−1.19	−0.54	−1.79
Van der Waals	0	−0.07	−0.21	−0.07	−0.21
Coulombic	0.4	0.1	−1.15	−0.3	−1.55
H bond	0.3	0.05	0.17	−0.25	−0.13

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results—X-ray spectra, as well as formation of liquid crystalline solutions—and present mechanisms of self-assembly that are reasonable from an atomistic perspective.

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