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Arginine as a ‘Molecular Glue’ for Robust Hierarchical Supramolecular Assembly

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Arginine as a 'Molecular Glue' for Robust Hierarchical Supramolecular Assembly

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ABSTRACT:

Hierarchical supramolecular assembly—materials ordered across multiple length scales via weak non-covalent interactions—is nature's primary strategy for constructing complex functional materials; however, its implementation in synthetic systems is fundamentally limited by intrinsic structural fragility. While biological systems achieve robustness through embedding their assemblies within dynamic protein scaffolds, synthetic supramolecular architectures often degrade under real-world conditions. Here, we demonstrate that arginine acts as a 'molecular glue' to mediate the hierarchical assembly of a cyanine-based model system, resulting in unprecedented structural robustness. Through a combination of optical spectroscopy, cryogenic-electron and near-field scanning optical microscopy, and density functional theory, we show that these arginine-mediated assemblies remain robust even upon dilution in challenging biological environments (cell culture media), or after complete dehydration on solid substrates. Our bioinspired approach overcomes the longstanding stability limitations of non-covalent materials, providing a versatile, robust framework for next-generation organic device applications in nanomedicine, renewable energy, or information technology.

Achieving molecular-level robustness in advanced functional materials remains a central pursuit in across interdisciplinary science and technology. Robustness is not simply resilience to changing conditions, rather, it is the ability of a system to respond adaptively to changes in its environment—while maintaining its functionality[1-3]. In Nature, robust solutions already exist. Hierarchical supramolecular self-assembly—the construction of complex, multi-scale architectures via weak non-covalent interactions—is nature's most effective strategy for building robust functional systems, ranging from the mechanical integrity of collagen[4] and cell membranes[5] to the efficiency of photosynthetic light-harvesting complexes[6-7] photosynthetic organisms, for example, these assemblies are not static; they are embedded within non-rigid, dynamic, flexible protein scaffolds that allow the system to respond and adapt to environmental perturbations—such as temperature fluctuations and chemical impurities—while maintaining its internal order and functionality and remaining while remaining dynamic through built-in molecular interactions (*e.g.*, protein-pigment hydrogen bonding)[8-9]. However, translating this hierarchical design principle to synthetic systems remains fundamentally limited by the inherent structural fragility of non-covalent materials. Unlike their biological counterparts, synthetic supramolecular assemblies often lack adaptive scaffolds [10], rendering them susceptible to disassembly or degradation—whether in solution or on solid substrates—under the demanding conditions foundational to real-world applications.

Here, we demonstrate a bioinspired approach employing fundamental building blocks of proteins—amino acids (**Fig.1**)—to provide a proof of concept that arginine mediates hierarchical assembly: by integrating into the supramolecular process, arginine acts as a 'molecular glue' rather than a traditional structural scaffold or 'mortar', bridging the gap between the synthetic fragility of non-covalent materials and biological robustness. This provides a versatile design paradigm for next-generation organic devices in nanomedicine, renewable energy, and information technology. Crucially, the arginine-mediated process maintains the assembly's dynamic, non-covalent character [58]—a feature pivotal to the system's ability to respond adaptively to changes in its environment; this is demonstrated by triggering controlled disassembly into monomers upon methanol dilution (**Fig.2**), which provides direct evidence for the underlying non-covalent-driven mechanism. Time-resolved spectroscopy informs arginine's effects on exciton lifetimes (**Fig.2**), while density functional theory calculations (**Fig.3**) offer quantitative insights into the hydrogen-bond-driven mechanism mediating the hierarchical assembly of our cyanine-based model system [11-12]. Taken together, these results provide evidence for arginine's role as a 'molecular glue' that imparts unprecedented structural robustness without sacrificing the assembly's dynamic, non-covalent character. To validate application-ready resilience of this design approach, we examine the structural integrity of these assemblies under varied, high-stress conditions required in real-world applications: in particular, dilution within the chemically complex matrix of aqueous solution-based cell culture medium—Dulbecco's Modified Eagle Medium (DMEM)—and upon complete dehydration following immobilization onto solid substrates (**Fig.4**).

Inspired by nature, we employ a library of amino acids based on their side chain character—such as aromatic or aliphatic, basic or acid, polar or apolar, hydrophilic or hydrophobic—including lysine, histidine, aspartic acid, glutamic acid, isoleucine, asparagine, and arginine (**Fig.1A**). To elucidate the impact of amino acids[13] on hierarchical supramolecular nanostructures, one effective strategy is to employ a model system that permits *in situ* monitoring in solution throughout the self-assembly process. We employed the well-characterized supramolecular model system self-assembled in aqueous solution from a cyanine dye derivative [11,12,14-22] (**Fig.1B-L**): the amphiphilic cyanine dye molecules—3,3′-bis(2-sulphopropyl)-5,5′,6,6′-tetrachloro-1,1′-dioctylbenzimideacarbocyanine, commonly appreciated as C8S3—self-assemble via pi-pi stacking and hydrophobic forces into double-walled nanotubes (NTs) which subsequently evolve into hierarchically assembled bundles (b-NTs). Specifically, following the rapid formation of the inner cylinder[16] (6±1 nm; ~seconds) and the outer cylinder formed by the assembly of several patches with different orientations[20], (13±1 nm; ~2 minutes)[20], this metastable double-walled structure matures over weeks or months into b-NTs that consist of close-packed cylinders, each with (6±1 nm)[16], that are surrounded by an outer envelope[12]. Because NTs and b-NTs exhibit well-defined and distinct spectral signatures (**Fig.1J**), this system enables direct *in situ* monitoring of the hierarchical assembly process via steady-state optical spectroscopy.

The absorption spectrum (**Fig. 1J**) of the assemblies exhibits a pronounced red-shift and line-narrowing compared to the monomer, indicating that close-packed chromophores facilitate strong dipole-dipole coupling and molecular Frenkel excitons delocalized over at least 25 molecular units[11]. These spectral features originate from the double-walled NT structure: lower-energy bands at 599nm and 589nm correspond to the inner and outer cylinders, respectively, while the higher-energy features comprise overlapping exciton bands from both walls (**Fig. 1J**). These individual NTs further self-assemble into hierarchically structured b-NTs (**Fig.1B-I**). Although their optical properties are distinct, assembly kinetics remain non-deterministic, requiring variable incubation periods of weeks to months (**Fig. 1H–I, K–L**). The b-NTs exhibit unique spectral features—specifically, a narrow exciton band at 603nm and a broad absorption feature (multiple overlapping exciton bands) around 580nm—allowing for *in situ* spectral differentiation from individual NTs (**Fig. 1J**)[12]. Because the optical properties of supramolecular Frenkel excitonic assemblies are highly sensitive to minute changes of the details of the molecular packing within the assembly, steady-state optical spectroscopy can be utilized as an elegant tool not only to distinguish between NTs and b-NTs morphologies in solution, but also to probe minute changes within their supramolecular structure[12].

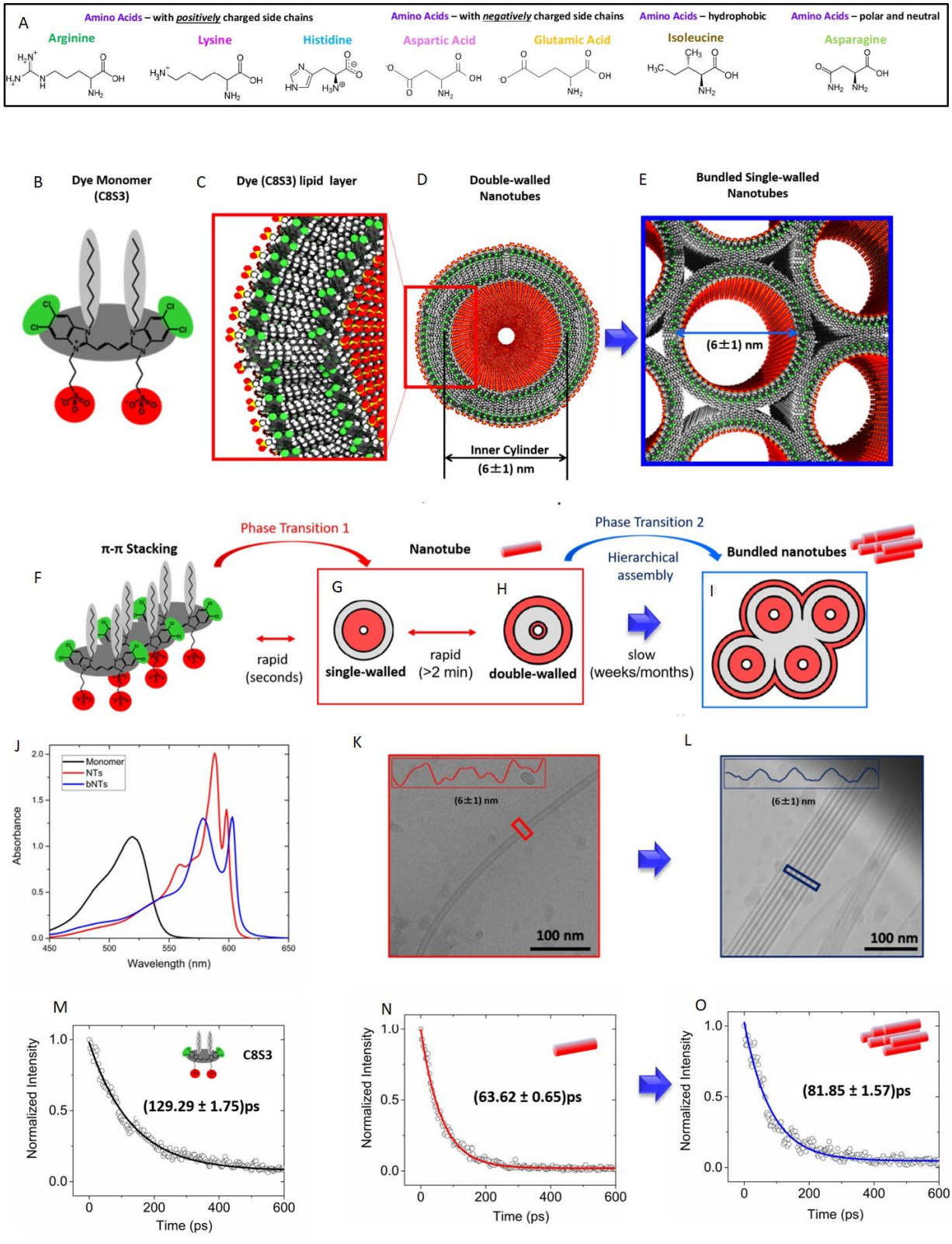


Figure 1 | Amino Acids & Artificial Model System for Hierarchical Supramolecular Assembly. **(A)** Chemical structures of the amino acids used; (**B**) Schematic of amphiphilic cyanine dye (C8S3) monomers self-

assembling in aqueous solution (see Methods) into lipid layers (**C**) that form metastable assemblies of bi-layered, (**D**) double-walled supramolecular nanotubes, individual NTs, with inner and outer cylinders, which (**E**) further self-assemble into closed-packed (bundled) single-walled nanotubes, b-NTs. **(F)** Cyanine dye monomers allow pi-pi stacking **(G)** followed by rapid—within seconds [20]—formation of single-walled nanotubes **(H)** with rapid—starting in less than 2min[ref]—outer-wall formations and **(I)** followed by slow—several weeks to months [12]—hierarchical self-assembly into bundled single-walled nanotubes, neat b-NTs. **(J)** Steady-state absorption spectrum taken from solution of free cyanine dye monomer (black), individual NTs (red), and neat b-NTs (blue). The Cryo-TEM micrographs depicts the **(K)** double-walled character of individual NTs, and **(L)** single-walled character of neat b-NTs. The fluorescence lifetime taken from solution of **(M)** free C8S3 cyanine dye monomers (129.29±1.75)ps, **(N)** individual NTs (63.62±0.65)ps, and **(O)** neat b-NTs (81.85±1.57) nm.

RESULTS & DISCUSSION

Hierarchical Assembly—*Increased Exciton Lifetime.* The organization of nanoscale systems via weak non-covalent interactions—whether in molecular aggregates, quantum dot superlattices, or plasmonic assemblies—fundamentally dictates material properties, spanning from optoelectronic characteristics, spanning from optoelectronic characteristics[23,24] to even redox activity[15,25]. To assess whether hierarchical self-assembly impacts excited-state dynamics in supramolecular systems, such as exciton lifetime, we employed time-resolved fluorescence spectroscopy. Consistent with the superradiance typical of J-aggregates[26-28], the individual nanotubes (NTs) exhibit a substantially decreased exciton lifetime compared to free C8S3 monomers. Specifically, the exciton lifetime decreases from (129.0±1.8)ps for the C8S3 monomers (**Fig.1M**) to (63.62±0.65)ps for individual NTs (**Fig.1N**). Upon hierarchical assembly, however, the fluorescence lifetime of b-NTs increases by approximately 28% to (81.85±1.57)ps (**Fig.1O**). We attribute this increased lifetime to the enhanced structural rigidity of the hierarchically assembled b-NTs; the dense packing of cylinders within this architecture restricts rotational motion and vibrational degrees of freedom, thereby likely suppressing non-emissive decay pathways[29-31].

Hierarchical Self-assembly—*Unstable upon Environmental Stress.* While hierarchical self-assembly offers no defense against photooxidation—visible light exposure (6 h) triggers irreversible oxidation [15] that abolishes excitonic bands in both NTs and b-NTs (**Fig.S1A,B**)—these b-NTs exhibit notable thermal resilience. Unlike NTs, which undergo irreversible degradation and monomer disassembly under extreme heat stress (**Fig.2A,B**), b-NTs preserve their excitonic character, re-forming directly upon cooling (**Fig.2C**). This enhanced stability may stem from more complex, intermolecular interactions due to larger number of components [32]; for instance, proteins are known to gain thermostability through higher-order structures [33]. Nonetheless, extreme thermal stress still induces notable structural and spectral modifications in b-NTs (**Fig.2D**).

Inspired by Nature—*Employing Amino Acids.* Inspired by nature's ability to embed light-harvesting assemblies within dynamic protein scaffolds, we screened a library amino acid (Fig.1A) to evaluate their potential to mediate the hierarchical self-assembly towards the formation of b-NTs. We systematically assessed the impact of various side-chain chemistries—including negatively charged (aspartic and glutamic acid), hydrophobic (isoleucine), polar (asparagine), and positively charged (lysine and histidine) amino acids—on the optical properties of individual NTs in solution (**Methods Section**). Given the precarious equilibrium of these supramolecular systems, the introduction of any solute inevitably alters their solution environment. Consistent with this sensitivity, with the exception of lysine, histidine and arginine, none of these amino acids successfully mediated the formation of b-NTs; instead, they disrupted the assembly process (**Supplementary Information, Section 2**). While the assemblies overall excitonic character was preserved, the resultant changes in spectral shape indicated that these additives perturbed the molecular packing rather than promoting the hierarchical assembly into b-NTs.

In striking contrast, we discovered that arginine mediates the hierarchical self-assembly of b-NTs: arginine accelerates the process, reducing assembly kinetics from an unpredictable timeframe (ranging from weeks to months) to less than 24 hours. After a 24-hour incubation in an arginine-supplemented aqueous solution, individual NTs exhibit the characteristic spectroscopic signatures of b-NTs (**Fig.2E**). As expected, this effect is both concentration- and time-dependent (**Supplementary Information, Section 3**). These results demonstrate that arginine mediates the hierarchical organization of individual NTs into b-NTs without altering the supramolecular structure of the final hierarchical assembly. Due to the amphiphilic character of the cyanine dye monomers, the assembly is highly sensitive to solvent polarity. Water has a high dielectric constant ($\varepsilon \sim 80$) and is an efficient hydrogen-bond donor and acceptor, whereas methanol has a significantly lower dielectric constant ($\varepsilon \sim 33$) and, while still protic, possesses distinct steric and solvation properties[34]. To test whether the arginine-mediated process maintains the assembly's dynamic, non-covalent character—which is critical for its ability to respond adaptively to environmental changes—we subsequently increased the methanol content to lower the solvent's polarity. This reduction in polarity successfully triggered the disassembly of the arginine-mediated structures back into individual monomers (**Fig.2F**), confirming the preservation of weak non-covalent interactions within the b-NT assemblies.

Arginine—*Assembly Robust Against Extreme Heat Stress.* While arginine does not enhance photooxidation resistance, hierarchically assembled bundles in presence of Arginine (Arg-b-NTs) exhibit unprecedented resilience to extreme thermal stress (**Fig.2G-H**). Unlike neat b-NTs, which degrade (**Fig.2D**), Arg-b-NTs undergo no spectral changes or loss of excitonic properties even after 10 heat cycles (**Fig.2G-H**). This robustness is unique to arginine; while simple ionic compounds (such as NaCl, NaOH, KOH, and CsOH) accelerate hierarchical self-assembly, they fail to confer thermal robustness

(**Supplementary Information, Section 5**). Upon extreme heat stress, not only were the excitonic properties of Arg-b-NTs maintained but also the system's overall long-range morphology. Cryogenic transmission electron microscopy (cryo-TEM) micrographs taken from shock-frozen solution of the arginine-mediated b-NTs before (**Fig.2K-left**) and after extreme heat stress exposure (**Fig.2K-right**) allows investigating the b-NTs morphology as it is in solution. Line scans perpendicular to the b-NTs were extracted from CryoTEM micrographs before and after exposure to heat-stress (**Fig.2K, bottom**). Both samples reveal a center-to-center distance of (9±1)nm, showing no significant deviation from the spacing observed in neat b-NTs (**Fig.2K**). This spacing is consistent with a close-packed arrangement of individual cylinders—each with 6±1nm in diameter [16]—separated by an inter-cylinder gap of approximately 4-3 nm, a distance dictated by the intrinsic spatial dimensions of the monomers' hydrophobic side chains (**Fig.1B**).

Arginine—*Assembly with 50% Reduced Exciton Lifetime.* While arginine drives the hierarchical self-assembly of b-NTs without altering their steady-state absorption spectra—indicating an identical supramolecular structure to neat b-NTs—it surprisingly alters the system's excited-state dynamics: in fact, the fluorescence lifetime of Arg-b-NTs assembled in the presence of arginine is significantly reduced to (40.58 ± 0.56)ps, which is a 50% reduction (**Fig.2L**) compared to the neat b-NTs (**Fig.1O**) indicating the presence of new non-radiative decay channels. The observed decrease in fluorescence lifetime upon the introduction of arginine necessitates an analysis of the competing radiative and non-radiative decay pathways. While system structural rigidification typically restricts vibrational motion—a process that would suppress non-radiative decay (k_nr) and extend the fluorescence lifetime—our data reveal a contrasting shortening of the lifetime. This suggests that the arginine-mediated assembly introduces a new, competitive non-radiative decay channel that dominates the system, effectively masking the expected stabilization effect of rigidification. To further isolate these contributions, we examined the radiative decay rate (k_r); because significant alterations in k_r are generally accompanied by distinct shifts in the absorption spectrum—particularly the 0-0 transition intensity—the absence of such clear spectral changes leads us to conclude that the reduction in lifetime is primarily driven by the enhancement of non-radiative decay rather than radiative coupling[35].

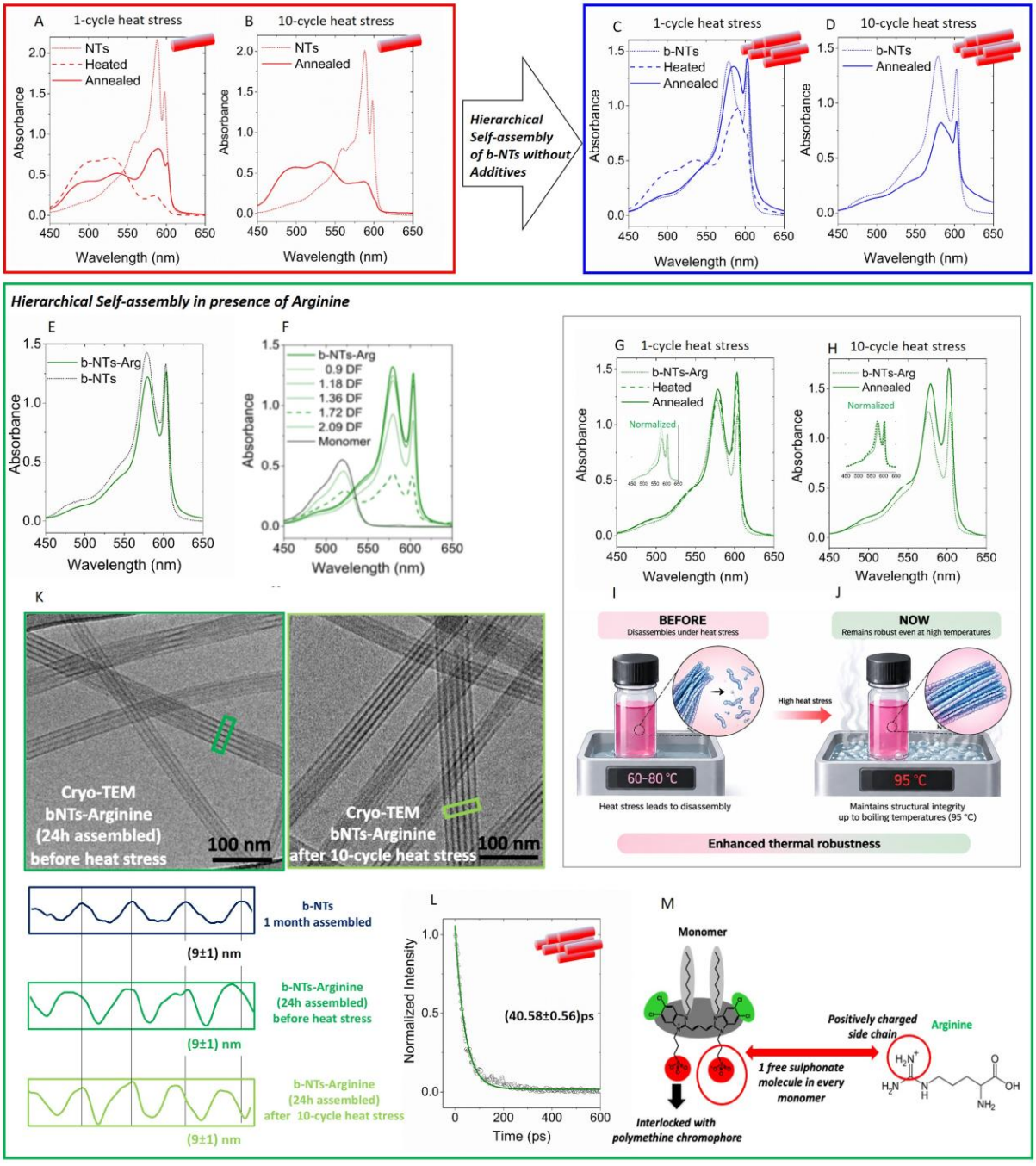


Figure 2 | Arginine—Ultra-Fast Exciton Lifetime & Robust Against Extreme Heat Stress. Steady-state absorption spectra taken from solution of **(A)** individual NTs before heat-stress (red-dotted), during heating (spectrum is taken during boiling, red-dashed) and, after cooling/annealing the NTs solution to room temperature (red-solid), **(B)** individual NTs before heat-stress (red-dotted) and after extreme heat stress of 10-cycles of heat stress (red-solid). Neat b-NTs **(C)** before heat-stress (blue-dotted), during heating (spectrum is taken during boiling, blue-dash), after cooling/annealing the NTs solution to room temperature (blue-dashed) and, **(D)** neat b-NTs before (blue-dotted) and after extreme heat stress of 10-cycles of heat stress (blue-solid). Steady-state absorption

spectra from **(E)** neat b-NTs assembled upon storing in darkness for up to 2months (black-dotted) and, b-NTs assembled in the presence of arginine within less than 24h (green-solid)—arginine concentration in aqueous solution is 9.00mM. Steady-state absorption spectra taken from solution of **(F)** b-NTs assembled in the presence of arginine diluted with methanol at dilution factors between 0.9-2.09, monomer solution (black-solid spectrum). **(G)** b-NTs assembled in presence of arginine before heat-stress (green-dotted), during heating (spectrum is taken during boiling, green-dashed) and, annealed (green-solid), INSET: the normalized spectra and **(H)** before (green-dotted) and after of extreme heat stress of 10-cycle heat stress (green-solid) and the normalized spectra (inset). **(I)** Schematic illustration of the disassembly of NTs and neat b-NTs under heat stress. **(J)** Schematic illustration of the enhanced thermal robustness of Arg-b-NTs, **(K)** The Cryo-TEM micrographs taken from shock frozen solution of b-NT assembled in the presence of arginine before heat stress (left micrograph), and after 10-cycle heat stress (right micrograph). A line scans taken from (Fig.1L) from neat b-NT (dark blue), from b-NTs assembled in the presence of arginine (dark green) and from b-NTs assembled in the presence of arginine after extreme heat stress (light green) reveal center-to-center distance of (9 ± 1)nm. Time-resolved fluorescence spectroscopy **(L)** revealed exciton lifetime of b-NTs assembled in presence of arginine of only (40.58±0.56)nm which is 50% reduced compared to exciton lifetime from neat b-NTs. (**M**) Schematic illustrates interaction of C8S3 cyanine dye monomer with positively charged side chain (-NH2) of arginine: the molecule of cyanine dye includes contains two negatively charged sulphonate groups where one sulfonate groups are interlocked with polymethine chromophore [17] and the other sulfonate groups is free for potential interaction with positively charged side chain (-NH2).

Arginine—*Participates in Hydrogen Bonding.* Because the assembly's excited-state dynamics are strongly influenced by changes in its surrounding chemical environment, elucidating the stoichiometry between arginine and the NTs is a prerequisite for understanding their interaction. For the NTs, the hydrophilic sulfonate groups of the cyanine monomer not only impart hydrophilicity but also play a crucial role in structural organization: the sulfonate chains in both the inner- and outer-wall cylinders exhibit a highly conserved, interlocked arrangement with the polymethine chromophore [17]. Therefore, for each cyanine monomer, one sulfonate group is interlocked with the polymethine chromophore, while the other remains free (**Fig.2M**). Given this structural arrangement, only one sulfonate group per monomer is available for electrostatic interaction with arginine. Specifically, each arginine molecule contains a single positively charged guanidinium group on its side chain, which can bind to the NT's free sulfonate groups. Consequently, the expected stoichiometry between arginine and the cyanine dye monomer is [1:1]. Ultimately, the fact that the stoichiometry between arginine and the cyanine dye monomer is higher than the expected stoichiometry based on arginine's side-chain interaction with negatively charged sulfonate groups (**Supporting-Information, Section 6.1**) suggests that arginine not only interacts electrostatically with the negatively charged sulfonate groups but may also participate in hydrogen bonding interactions with both NTs and the aqueous solution[36].

Arginine—*Proposed Mechanism.* Amino acids profoundly influence supramolecular structures in nature—such as light-harvesting complexes, where pigment-protein hydrogen bonding maintains robustness—with arginine uniquely inhibiting aggregation via its guanidinium side chain[37-39]. Hydrogen-bond networks can provide structural anchoring that promotes molecular packing while suppressing intermolecular disorder[40]. To elucidate arginine's stabilizing role in b-NT assembly, we examined its multi-dentate hydrogen bonding[41]. Cooperative strengthening of hydrogen-bonding interactions has been demonstrated computationally in extended hydrogen-bonded molecular assemblies[42]. Furthermore, mechanistic studies in coordination and organometallic chemistry demonstrate how cooperative molecular interactions can control stability while preserving dynamic behavior [57]. Because guanidinium forms exceptionally strong bonds with sulfonate and carboxylate anions compared to ammonium groups[43], we hypothesized that arginine acts as a 'molecular glue' (**Fig.3A**). Previous experimental and molecular dynamics investigations demonstrate that sulfonate exhibits a stronger affinity for the guanidinium side chain of arginine than for the ammonium group of lysine[44].

To probe the intermolecular interactions between the functional groups of the amino acid and the cyanine molecule, we constructed a variety of small molecule models comparing arginine with lysine, a structurally related amino acid that shows no effect on the heat-stress robustness of the b-NT assemblies (**Fig.3B-E** and **Supporting Information**). DFT calculations—binding enthalpies computed with B3LYP-D3BJ/SMD using GD3BJ dispersion correction and a universal continuum solvation model with SMD: water)—comparing arginine with lysine show that guanidinium's geometry forms optimal dual hydrogen bonds with sulfonate oxygens, yielding binding energies ~1–2 kcal/mol more stable than ammonium interactions[45,46] (**Fig.3B–D**). Furthermore, arginine bridges individual cyanine molecules by simultaneously docking to multiple sulfonate groups, increasing binding strength by 7.6 kcal/mol (**Fig.3E**).

Next, we sought to validate these results experimentally. Time-resolved fluorescence spectroscopy is a powerful technique to elucidate hydrogen bonding dynamics by monitoring changes in fluorescence decay upon photoexcitation. Because hydrogen bonds significantly influence excited-state relaxation, variations in fluorescence lifetime provide critical insights into the interaction between arginine and the NTs' sulfonate groups[47]. While rigidification of the assembly typically suppresses non-radiative decay, thereby increasing the fluorescence lifetime, we observe a dramatic 50% reduction in lifetime for b-NTs in the presence of arginine compared to neat b-NTs **(Fig.2F and Fig.2O).** This indicates that the arginine-induced hydrogen bonding environment introduces a new, dominant non-radiative decay pathway (k_nr) that outweighs any stabilizing effects of rigidification **(Supporting Information, Section 6.2).** This quenching effect serves as a kinetic signature of the interaction between the arginine and the NTs sulfonate groups. Control experiments using guanidine instead of arginine successfully replicated both rapid

hierarchical assembly and thermal robustness, confirming the guanidinium moiety as the primary active driver (**Supporting Information, Section 7**).

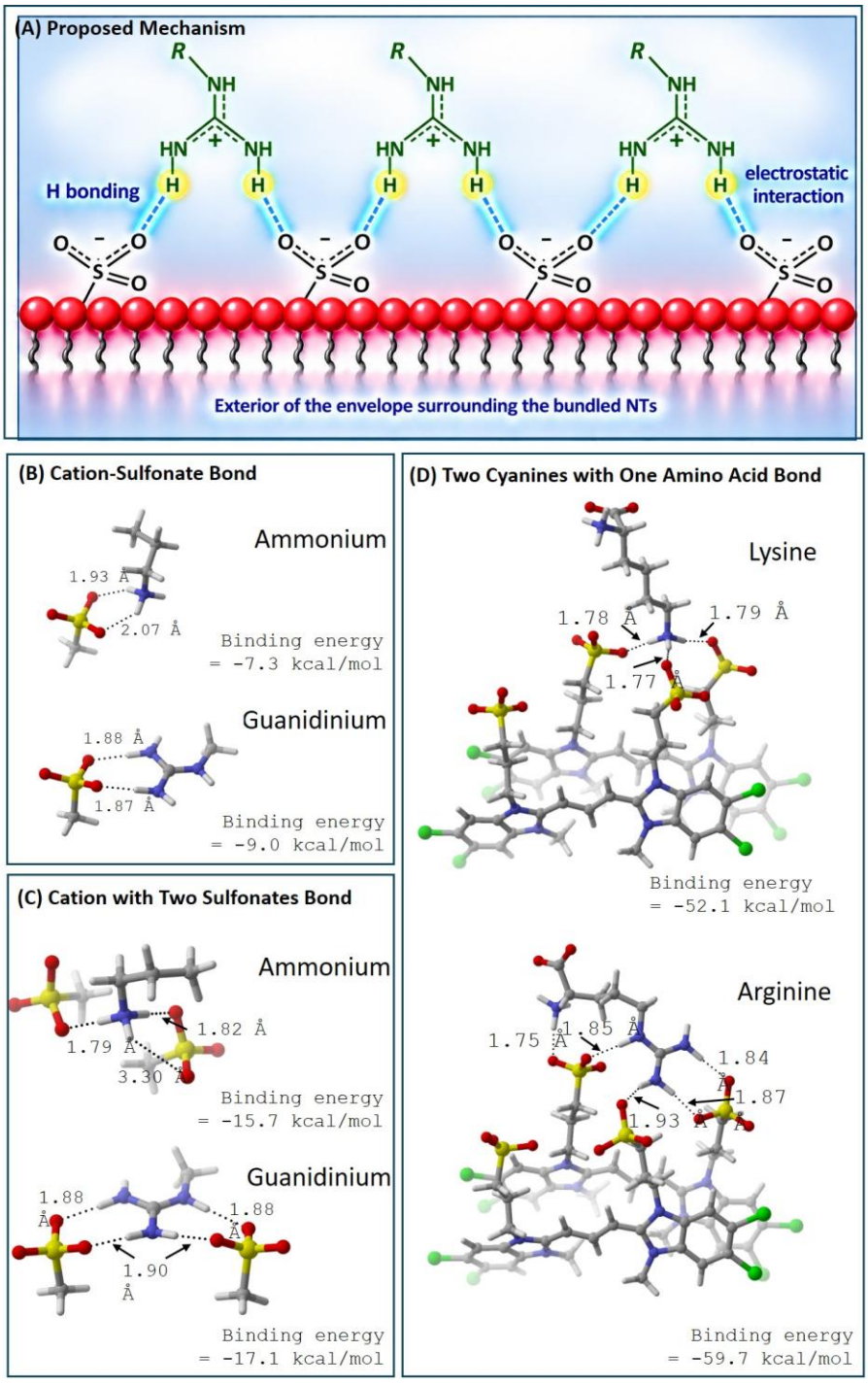


Figure 3 | Arginine—Proposed Mechanism and Density Functional Theory Calculations. **(A)** Reduced florescence lifetime due to arginine could indicate hydrogen bond formation, in addition to electrostatic interaction, between the sulfonate groups of NTs and the arginine molecules. **(B - D)** Density functional theory

calculations (B3LYP/6-31G+(d), GD3BJ, SMD=water) of various amino acid-cyanine model systems and obtained binding energies.

Arginine—*Robust Under Physiological Conditions & Complete Dehydration.*

Solution-based applications of non-covalent assemblies are often hindered by their high sensitivity to both solution impurities and strong concentration dependence[48]. To validate the application-ready resilience of this design approach, we examined the structural integrity of these assemblies under high-stress, real-world conditions: specifically, for example, upon dilution within the chemically complex matrix of cell culture medium (Dulbecco's Modified Eagle Medium, DMEM) as illustrated in **Fig4A**. Remarkably, Arg-b-NTs remained unaltered for over 24 hours, maintaining their characteristic red-shifted spectrum and narrow ~603 nm exciton band (**Fig4B**). These findings demonstrate the biological viability of Arg-b-NTs, successfully overcoming the traditional structural limitations of non-covalently bonded assemblies for applications requiring dilution with impurities such as under physiological conditions.

Integrating hierarchical supramolecular assemblies into solid-state organic devices requires immobilizing them from solution onto solid substrates while preserving their structural and optoelectronic properties[14]. However, because solution-based supramolecular organization relies heavily on non-covalent interactions with solvent molecules, solvent evaporation typically disrupts ordering and causes a loss of excitonic character. Indeed, when NTs and neat b-NTs were successfully deposited via a drop-flow technique[14], their excitonic features collapsed upon complete drying—dehydration—and revealed spectroscopic characteristics of cyanine monomers (**Fig.4C-D**). In stark contrast, Arg-b-NTs exhibited nearly identical fluorescence spectra in solution and after complete dehydration on a solid substrate (**Fig.4E**). These results indicate that arginine effectively acts as a 'molecular glue'—replacing the stabilizing role of the solvent—to preserve the close-packed supramolecular arrangement in the dry state. Atomic force microscopy (AFM) topography confirmed that Arg-b-NTs retain their long-range nanotubular morphology after complete drying (**Fig.4F**). Furthermore, spatially resolved near-field scanning optical microscopy (NSOM) confocal fluorescence spectra validated that individual dried Arg-b-NTs maintain their characteristic excitonic emission (**Fig.4G**). The robustness upon dehydration in combination with significantly decreased exciton lifetime makes arginine-driven hierarchical supramolecular assemblies a highly promising J-aggregate or Fenkel excitonic molecular material for applications requiring ultra-short radiative lifetimes, for example, high-speed data transmission (**Fig.4I**), where information transmission speed is fundamentally limited by the radiative lifetime inherent to conventional light-emitting materials[49]. Together, these findings demonstrate that arginine endows non-covalent assemblies with unprecedented dry-state robustness, unlocking their potential for solid-state device integration.

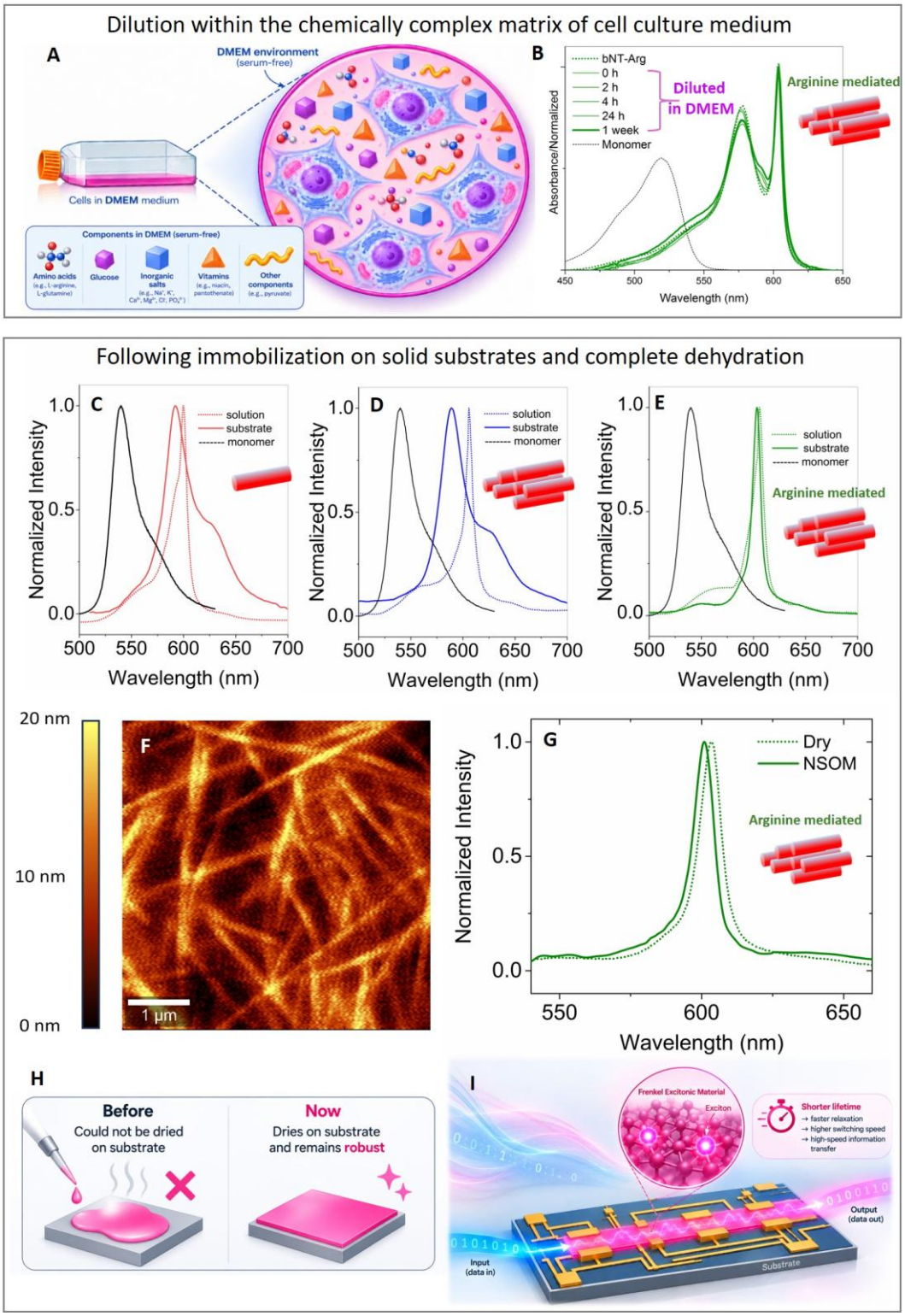


Figure 4 | Arginine—Robust Under Demanding Conditions Foundational to Real-world Applications. **(A)** Schematic illustration of the complex matrix of cell culture medium—Dulbecco's Modified Eagle Medium (DMEM). **(B)** Time-evolution 5x diluted Arg-b-NTs in biological cell culture medium. Energetic position & characteristic shape of excitonic bands unaltered even 7 days after dilution with 5x dilution with DMEM. Steady-state

fluorescence spectra of **(C)** individual NTs in solution (red-dotted) and after immobilization onto solid substrate followed by dehydration (red-solid), monomer (black-solid) **(D)** neat b-NTs in solution (blue-dotted) and after immobilization onto solid substrate followed by dehydration (blue-solid), monomer (black-solid) and **(E)** b-NTs assembled in presence of arginine in solution (green-dotted) and after immobilization onto solid substrate followed by dehydration (green-solid), monomer (black-solid). **(F**) AFM topography scan of b-NTs assembled in presence of arginine, immobilized onto a glass slide shows long-range morphology maintained upon solid-substrate deposition. (**G)** Steady-state fluorescence spectrum of taken from b-NTs assembled in presence of arginine after immobilization onto solid substrate followed by dehydration (green-dotted) and far-field total emission spectrum of taken by via NSOM confocal fluorescence mode (green-solid, emission spectra taken from the scanned area in Fig. 4F). (**H)** Schematic illustration highlighting the enhanced robustness of arginine-mediated NT assemblies upon immobilization and complete drying on a solid substrate, in contrast to the previously observed loss of structural integrity upon dehydration. **(I)** Schematic illustration of the potential integration of robust excitonic assemblies into solid-state optoelectronic architectures, highlighting their shortened excited-state lifetime and potential for faster exciton dynamics and high-speed information transfer.

CONCLUSION

In conclusion, this proof-of-concept study demonstrates how to overcome the longstanding structural fragility of synthetic hierarchical supramolecular assemblies. By employing fundamental protein building blocks—specifically small-molecule arginine—as a 'molecular glue' rather than a static external scaffold, we mediate hierarchical self-assembly from the ground up. This design approach yields materials that are inherently stable, adaptive, and robust under demanding real-world conditions—such as solution dilution, impurity exposure, and substrate dehydration—without relying on protective coatings. Through multimodal experimental characterization—combining time-resolved and steady-state optical spectroscopy, CryoEM, and NSOM—alongside DFT calculations on a model cyanine system, we propose a hydrogen-bond-driven mechanism governing this arginine-mediated assembly. Multi-dentate hydrogen bonding between the guanidinium moiety and surface sulfonate groups drastically accelerates assembly kinetics from months to hours while preserving non-covalent, adaptive character. Crucially, this bio-inspired design confers unprecedented resistance against extreme environmental perturbations, preserving nanoscale morphology and Frenkel exciton states in both complex biological media (**Fig. 4A–B**) and the dry state (**Fig. 4C–H**). By showcasing that robustness does not require rigid covalent frameworks, this work bridges the gap between fragile synthetic assemblies and robust biological architectures. Ultimately, the ability of guanidinium-based additives to preserve delicate exciton states establishes a generalizable, non-neutron/non-destructive design paradigm for non-covalent functional materials, offering a blueprint for stable, application-ready systems. This opens transformative avenues for integrating delicate

supramolecular architectures into solid-state organic optoelectronics for in situ bio-sensing applications in aqueous environments (*e.g.*, liquid biopsy cancer diagnostics), renewable energy devices (*e.g.*, solar cells), and information technology applications (*e.g.*, optical data processing, **Fig. 4I**). Furthermore, this strategy holds potential for broader applications across diverse engineered systems, including other solution-based supramolecular assemblies, polymer architectures, and colloidal nanoparticles. Beyond solution-phase uses, these assemblies could be coupled to arginine-functionalized surfaces—analogous to poly-lysine patterning strategies[50]—to enable advanced 2D organization. Finally, building on recent breakthroughs in computational protein design[51–56]—such as engineering dynamic, multivalent interfaces—our results suggest exciting opportunities for integrating light-harvesting systems with tailored, arginine-rich binding interfaces for robust functionality in both solution and the solid state.

METHODS

Preparation of C8S3 Monomer Stock Solution. The C8S3 monomer stock solution was prepared by dissolving solid cyanine dye C8S3 (MW= 902.8 g mol^{-1}, FEW Chemicals, Dye.S0440) in pure methanol (≥99.9%, Fisher Chemical). Final concentration of stock solution used in all experiments is between 3.1 - 3.4 mM [ref].

Preparation of NTs. To prepare NTs, that is, individual double-walled NTs, 130 µL of C8S3 monomeric stock solution was added into 500 µL ultrapure water (>18.2 M cm, Barnstead). The solution was stored in the dark for 24 h before adding additional 500 µL ultrapure water. Final dye concentration was between 0.35-0.40 mM, stored in plastic vials [ref].

Preparation of Neat b-NTs. Neat b-NTs. that is, closed-backed/bundled single-walled NTs with surrounding outer layer [refPNAS2014] hierarchically self-assembled from individual NTs without external forces during incubation time of least one month at room temperature under dark conditions. For preparing neat b-NTs, NTs were stored in the dark for up to 1-2 months in glass vials.

Preparation of b-NTs in Presence of Arginine. The stock solution of arginine was prepared by dissolving L-Arginine monohydrochloride (≥98%, Sigma-Aldrich) in ultrapure water. Arginine solution was added into aqueous solution of double-walled NTs and stored in the dark for 24h. The final concentration of arginine in the solution of double-walled NTs was determined to be 9 mM.

Absorption Spectroscopy Characterization. Steady-state ultraviolet–visible (UV-vis) absorption spectroscopy (Agilent; Cary) and fluorescence spectroscopy (Horiba Jobin Yvon) are used to monitor changes to the supramolecular structure of NTs, b-NTs, and b-NTs in presence of arginine.

Emission Data on Solid Substrate. Steady-state fluorescence spectroscopy has been performed with a 400-nm CW diode laser as the pump source, while the fluorescence is registered with an Ocean Optics (QE65 Pro) spectrophotometer.

Heat Stress Experiments. NTs, b-NTs, and b-NTs prepared with arginine exposed to heat stress using a thermal cycler (Techne; Prime). The samples were heated to 95°C at a ramp rate of 0.1°C/s and incubated at that temperature for 5 minutes, then cooled down to room temperature at 23°C at the same rate. Changes

to the supramolecular structure were monitored using ultraviolet-visible absorption spectroscopy at boiling temperature and after cooled down to room temperature. Increased heat stress applied to b-NTs and b-NTs prepared with arginine. The samples incubated under repeated heating cycles. The samples were heated to 95°C at a ramp rate of 0.1°C/s and incubated at that temperature for 5 minutes, then cooled down to room temperature at 23°C at the same rate and incubated at that temperature for 5 minutes. To apply extreme heat stress, this procedure was repeated for a total of 10 cycles.

Methanol Dilution. Double-walled NTs, b-NTs, and b-NTs in presence of arginine were diluted with methanol at dilution factors of 0.9, 1.18, 1.36, and 1.72; b-NTs in presence of arginine were also diluted at dilution factor 2.09.

Light Exposure. The photostability experiment of NTs, b-NTs and b-NTs in presence of arginine was carried out by measuring the absorbance change under exposure of visible light for 5 min., 30 min. and 60 min.

Immobilization and Dehydration on a Solid Substrate. The NTs, b-NTs, and b-NTs in presence of arginine were deposited on a glass slide via a drop-flow technique as described elsewhere (Eisele et al. Nature Nanotechnology 2009) and were aggressively dried using an airblower in the dark under ambient conditions for 24h.

Cryogenic Transmission Electron Microscopy (Cryo-TEM). High-resolution characterization of samples was performed with Cryo-TEM. 4.5 µl of b-NTs prepared with arginine was deposited on glow-discharged lacey carbon grids with ultrathin carbon film (Ted Pella; 01895-F) and vitrified in liquid ethane using a freeze-plunging device (Vitrobot; FEI), then imaged at liquid nitrogen temperatures using Halo TEM (FEI) or Tecnai Spirit TEM (FEI) operating at 300 kV with a 2 k×2 k Gatan wide-angle charge-coupled device (CCD) detector or at 120 kV with a 4 k×4 k Eagle CCD detector (pixel size=2.4Å) with ~2–3 µm defocus to optimize phase contrast.

Confocal Microscopy and Atomic Force Microscopy. Collection of far-field emission upon near-field excition was performed with a multifunctional Near-field Scanning Optical Microscope (NSOM) equipped with a piezo-driven scan stage (WITec; alpha300 RS). A continuous-wave laser (Coherent; Compass Sapphire; excitation=488nm; output=72mW) was coupled to a single-mode optical fibre (WITec; 187643) and passed through an excitation objective (Zeiss; EC Epiplan 20×/0.4; free working distance (FWD)=3.2mm) to focus through an aperture of NSOM cantilevers (WITec; drive amplitude=0.100 Vpp;

resonance frequency=84.76679 kHz). The sample was raster scanned in the x and y directions by a piezo-driven scan stage and the emission was collected through a detection objective (Nikon CFI Achro; 60×/0.8; FWD=3.0mm), filtered through 532nm long-pass filter (Semrock; BLP01-532R-25), then fibre-coupled to an ultra-high-throughput spectrometer (WITec; UHTS 300; G1=600gmm−1; centre wavelength=600nm) equipped with an electron-multiplying CCD camera (Andor; Newton 970; 1,600×200 array; 16μm×16μm pixel size). The force threshold between the tip and sample was stabilized at 1V, with 5% proportional and 5% integral gains.

Time-Resolved Optical Spectroscopy. Time-resolved fluorescence spectra and fluorescence lifetime with varying pump intensities are measured with a femtosecond Ti: sapphire laser (Spectra-Physics Tsunami) coupled with a regenerative amplifier (Spectra-Physics Spitfire). The Ti: sapphire resonator generates 130-fs, 800-nm pulses at an 80 MHz repetition-rate. The regenerative amplifier lowers the repetition rate to ~1 KHz, resulting into high energy pulses at the order of a few nJ per pulse. The second harmonic (400 nm) of the 800-nm pulses is the pump source for the one-photon time-resolved spectroscopy. Streak images are obtained with a streak camera (Hamamatsu Streak Scope C4334) coupled with a Spectrograph (Chromex 250is). Image analyzer (HPD-TA 6.4.0) is used to extract the fluorescence spectra and fluorescence lifetime from the streak images. The fluorescence decay data sets are fitted to single exponentials to obtain the corresponding lifetimes. Note that the samples are held in standard quartz cuvettes, while pumping the samples.

Density Functional Theory (DFT) Simulations. Density functional theory (DFT) calculations were performed using Gaussian 16 (ref: Gaussian 16, Revision C.01 Gaussian, Inc., Wallingford CT, 2016.) using B3LYP/6-31+G(d), GD3BJ, SMD=water. The sole exception was for the cyanine dimer and amino acid ensembles: to minimize computational cost, these were calculated by first performing an optimization using B3LYP/6-31+G(d), GD3BJ, CPCM solvation (water), then performing a single point energy calculation upon this geometry with SMD solvation. Binding energies were calculated as the ensemble's electronic energy minus the sum of the electronic energies of the individual molecules [45-46].

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AUTHOR CONTRIBUTIONS

D.M.E. directed the project. **Kelestemur S.** designed the experiments, synthesized the samples, performed steady-state absorbance and fluorescence measurements, conducted temperature-dependent studies, dilution experiments, performed time- and concentration-dependent experiments on the interactions of amino acids, counter-ions, and guanidine with NTs, analyzed the experimental data, prepared the samples for time-resolved fluorescence lifetime, atomic force microscopy (AFM), confocal optical microscopy, and cryo-TEM measurements, initiated collaborations with Hackney H.E. and Perepichka D.F. Jubair A. under the supervision of **D.M.E.**; **A.J.** and **V.K.** performed time-resolved fluorescence lifetime measurements and steady-state fluorescence measurements on solid substrates under the supervision of **S.K.G. and D.M.E.**; **H.E.H.** performed density functional theory (DFT) calculations under the supervision of **D.F.P.**; **J.D.P.** performed atomic force microscopy and confocal optical microscopy measurements under the supervision of **D.M.E.**; **G.F.**, **N.M.**, **B.H.**, **A.M.**, **L.E.**, **R.V.**, J.Z, H.L., **I.G.**, M.R.R. and **D.C.** contributed to data collection, sample preparation, and data interpretation through fruitful discussions under supervision of **D.M.E**.; **N.Y.** contributed to biophysical and biochemical data analysis under supervision of **D.M.E**.; **O.G.** and **S.O'B.** proposed experiments and contributed to data interpretation.; **I.K.** contributed to data interpretation and structural characterization.; **S.J.** contributed to the interpretation of spectroscopic data of heat-stressed samples and DFT modeling.; **M.D.** contributed to biomedical structural integrity analyses under the supervision of **S.W.**; **T.Q.N.** and **E.C.** proposed experiments and contributed to the design of experiments and data interpretation. **D.F.P.** and **S.K.G.** supervised theoretical and spectroscopic components, respectively. **All authors** provided fruitful discussions and beneficial interpretation of the data and analyses. **S.K.** and **D.M.E.** co-wrote the manuscript with input from all authors.

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