Hierarchical self-assembly, a ubiquitous process in biological systems, is the guiding principle of bottom-up nanotechnology, harnessed to generate highly ordered functional superstructures from simple building units. Of these, self-assembled bioinspired peptide-based nanostructures have been intensely studied due to their biocompatible and biodegradable nature. One widely applied building block is the aromatic dipeptide diphenylalanine (FF), the core recognition motif of the Alzheimer’s β-amyloid polypeptide. FF-based molecular assemblies, in particular nanotubes, possess extreme physical and chemical stability along with interesting mechanical, optical, and piezoelectric properties. Diphenylalanine (FF) represents the simplest peptide building block that self-assembles into ordered nanostructures with interesting physical properties. Among self-assembled peptide structures, FF nanotubes display notable stiffness and piezoelectric parameters (Young’s modulus = 19–27 GPa, strain coefficient $d_{33} = 18$ pC/N). Yet, inorganic alternatives remain the major materials of choice for many applications due to higher stiffness and piezoelectricity. Here, aiming to broaden the applications of the FF motif in materials chemistry, we designed three phenyl-rich dipeptides based on the $\beta\beta$-diphenyl-Ala-OH (Dip) unit: Dip-Dip, cyclo-Dip-Dip, and tert-butyloxycarbonyl (Boc)-Dip-Dip. The doubled number of aromatic groups per unit, compared to FF, produced a dense aromatic zipper network with a dramatically improved Young’s modulus of $\sim 70$ GPa, which is comparable to aluminum. The piezoelectric strain coefficient $d_{33}$ of $\sim 73$ pC/N of such assembly exceeds that of poled polyvinylidene-fluoride (PVDF) polymers and compares well to that of lead zirconium titanate (PZT) thin films and ribbons. The rationally designed π−π assemblies show a voltage coefficient of 2–3 Vm/N, an order of magnitude higher than PVDF, improved thermal stability up to 360 °C (~60 °C higher than FF), and useful photoluminescence with wide-range excitation-dependent emission in the visible region. Our data demonstrate that aromatic groups improve the rigidity and piezoelectricity of organic self-assembled materials for numerous applications. The assemblies coupled with the extensive hydrogen bond network leads to strong piezoelectricity ($d_{33} = 17.9$ pC/N and $d_{15} = 60$ pC/N). Thus, dipeptides with a higher content of aromatic groups may self-assemble into highly rigid, strongly piezoelectric structures that may provide high-performance materials for piezoMEMS.
tides was achieved through the solvent-switch method, followed by determination of their crystal packing and characterization of their thermal, mechanical, electrical, and optical properties. The phenyl-enriched structures showed material performance superior to that of FF nanotubes, with improved mechanical rigidity, thermal stability, and piezoelectricity, along with photoluminescence in the visible region of the electromagnetic spectrum. Our results demonstrate that chemical densification of phenyl groups strengthens the supramolecular packing in the aromatic zipper structure, resulting in the fabrication of organic materials with highly improved electromechanical performance with potential application in the development of eco-friendly miniaturized devices.

RESULTS AND DISCUSSION

Synthesis and Self-Assembly of the Aromatic-Rich Peptides. The ultrashort aromatic-rich dipeptides were designed by substituting each phenylalanine amino acid in the FF, cyclo-FF, and Boc-FF motifs with the Dip residue, thus resulting in two additional phenyl rings (Figure 1). The morphological features of the self-assembled peptide structures were examined after preparing the samples by standard protocols (Supporting Information). In MeOH Dip-Dip exhibited a 2-fold topology comprised of nanospheres inside voids (Figure S1a), whereas in 70% MeOH (or HFIP) in water it formed nanorods (Figure S1b,c). Diffraction-quality crystals were grown in two different solvents, 50% MeOH (1/1, v/v in water) and pure MeOH. Microscopic analysis of the Dip-Dip crystal grown from 50% MeOH revealed an interesting laminated organization (Figure 1b), as previously observed for Boc-FF. Crystals grown in MeOH resembled nanorods (Figure S1d). On the other hand, cyclo-Dip-Dip formed elongated nanofibers in MeOH (Figure S1e), from which nanorod-like crystals were obtained (Figure 1e), and shorter fibers in MeOH–H2O mixture (Figure S1f). The PXRD profiles of freeze-dried powder from different solutions and simulated pattern obtained from single crystals. The simulated and experimental profiles correspond to PXRD patterns predicted from the crystal structure and measured from powdered crystals, respectively.
showed similar atomic packing (Figure 1f). The third designed variant, Boc-Dip-Dip (Figure 1g), formed assemblies in MeOH–H2O ranging from spheres and fibers to tubes (similar to Boc-FF, Figure S1g,h),30 and showed nanorod-like crystals (Figure 1h). The nanospheres were amorphous in nature while the tubes were crystalline (Figure 1i). In-depth understanding of fundamental mechanisms underlying the oriented organ-

Figure 2. Single crystal structure of the aromatic-rich dipeptides. (a–c) Dip-Dip grown from 50% MeOH. (d–f) Dip-Dip grown from pure MeOH. (g–i) cyclo-Dip-Dip. (j–l) Boc-Dip-Dip. (a, d, g, j) Asymmetric unit. (b, e, h) β-sheet structure. (k) Pair of H-bonded sheets. (c, f, h, l) Molecular packing and interpeptide contacts in the zipper-region. Oxygen and nitrogen atoms are represented in red and blue (where present, F atoms are colored yellow, in cocrystallized trifluoroacetic acid remaining from the last deprotection step). In (b) and (h), peptides are superimposed over an ideal β-sheet secondary structure to aid visualization. Axes orientations are presented. Insets showing the corresponding magnified images to clearly indicate the molecular distances in the zipper regions for different peptides on a comparable length scale.

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ization process of peptides and other small organic molecules still remains unclear.32–34 It has been generally observed that concerted creation of large numbers of intermolecular interactions such as H-bonds and π–π contacts are involved in formation of ordered supramolecular structures. Different kinds of nanostructures and morphologies are stabilized according to the balance between these noncovalent
interactions and entropic and kinetic effects. Moreover, solvent plays a crucial role in shaping the energy landscape of peptide self-assembly process through direct solvent–solute interactions of hydrogen-bond donor (HBD) and hydrogen-bond
acceptor (HBA) ability, polarity, surface tension, and dielectric constant. Although a recent review proposed architecture growth mechanisms, more detailed structural and theoretical studies are required to understand the underlying molecular mechanisms of hierarchically oriented organization of the studied peptides and gain deeper insights into the energy landscape.

Single Crystal Analysis of the Aromatic-Rich Peptides. To provide insight into the molecular organization of the aromatic-rich dipeptides and involvement of different noncovalent interactions, single crystal X-ray analysis was performed and compared to the molecular arrangement of FF (Figure 2 and Figure S2). In the structure of FF (Figure S2), the molecules form a parallel \( \beta \)-sheet structure by lateral stacking and create rings of hexagonal symmetry 13.6 Å in diameter via head-to-tail H-bonding. Dip-Dip, on the other hand, crystallized with two ordered peptide molecules and several interlayer water molecules in the asymmetric unit (Figure 2a). The simulated powder X-ray pattern of the crystal exactly matched the PXRD pattern of the nanoassemblies obtained from the MeOH–H\(_2\)O mixture, indicating similar packing (Figure 1c). The symmetry of Dip-Dip is orthorhombic \( P2_12_12_1 \), lower than the hexagonal \( P6 \) symmetry of FF. In the crystallographic \( \bar{a} \) direction, the individual subunits packed into an antiparallel \( \beta \)-sheet structure through the stacking of partly aligned strands (Figure 2b). Edge-to-face and edge-to-edge \( \pi-\pi \) interactions further stabilized the crystal packing. The increased number of nonpolar interactions may promote the formation of nanoplates as previously observed for FFF, but not for FF. A water-mediated cyclic arrangement was formed by three peptide molecules and two water molecules (Figure S3). However, the diameter of the ring was much smaller (∼5 Å) than the large hydrophilic channel of FF (13.6 Å) (Figure S4). Adjacent sheets of Dip-Dip were stabilized through hydrophobic and dry zipper-like interactions between tightly packed aromatic rings, which stacked into continuous rows of combined sheets (Figure 2c). However, the rows of adjacent sheets were fully separated by wet interfaces lined with water molecules, thereby forming an alternating dry and wet interface. This structural pattern is similar to that of amyloid cross-\( \beta \) and the recently identified cross-\( \alpha \) structure. When grown from pure MeOH, the molecule crystallized in the \( P2_1 \) space group (Figure 2d). Instead of forming parallel or anti parallel \( \beta \)-sheet structure, the peptide molecules produced a zigzag orientation through intermolecular H-bonding in the \( \bar{b} \) direction (Figure 2e). Neighboring sheets were stabilized through a similar zipper-like interaction of aromatic rings (Figure 2f) with larger packing distances compared to the crystal obtained from MeOH–H\(_2\)O.

Cyclo-Dip-Dip crystallized in the orthorhombic \( P2_12_12_1 \) space group without any solvent molecules (Figure 2g). Parallel stacking of the aligned stands along the crystallographic \( \bar{a} \) direction produced a parallel \( \beta \)-sheet structure that was stabilized by two H-bonds and two face-to-face \( \pi-\pi \) interactions between aromatic rings (Figure 2h). In the \( \bar{b} \) plane, nearby stands organized into a single layer via hydrophobic interactions. In the higher order packing, cyclo-Dip-Dip formed a layer-by-layer arrangement in which two nearby layers were stabilized through zipper-like interactions of less tightly packed aromatic rings (Figure 2i).

On the other hand, Boc-Dip-Dip crystallized in the monoclinic \( C_2 \) space group (Figure 2j). As the N-terminus was protected by the Boc group, individual molecules were connected only through H-bonds between C-terminal acid groups. The zigzag H-bonding produced pairs of interconnected sheets (Figure 2k). In the \( \bar{a} \) direction, adjacent dimeric sheets interacted via aromatic zipper-like interactions (Figure 2l). Due to reduced H-bonding and the pair structures of interconnected sheets, there might be slippages between the adjacent sheets, thus forming a slip plane as reported in other organic crystals.

First-principles calculations of the binding energies between molecules in the crystals was carried to understand the energy landscape of self-assembly (Supplementary Figure S5 and Table S1). The data indicate that strong stabilizing interactions occur due to partially or fully overlapping aromatic rings, together with hydrogen bonds formed by the peptide backbone. Only ring contacts showed interactions >1 eV in magnitude. As Dip-Dip has a less bulky backbone and so the molecules packed closer together facilitating closer ring contacts along the \( \bar{a} \) axis (Figure 2e) with a corresponding binding energy of −1.75 eV. Dip-Dip H-bonds along \( \bar{b} \) show a binding energy of −0.98 eV. For Boc-Dip-Dip and cyclo-Dip-Dip strong aromatic interactions were computed along the \( \bar{b} \) axis (Figure 2h and l) with binding energies of −1.54 and −1.12 eV, respectively. These calculated structures support our hypothesis that the aromaticity could contributes most to the rigidity of the materials, and the computed binding energies quantify the driving force for the underlying molecular mechanism that is crucial to the understanding of the role of aromatic interactions.

Optical Properties of the Aromatic-Rich Peptides. Given the tight yet diverse crystal packing of the aromatic-rich dipeptide assemblies, their optical absorption and photoluminescence were next examined. Figure 3a depicts the normalized absorption spectra, showing two main peaks in the UV region at 220–230 and 260 nm and two satellite subpeaks at 253 and 270 nm, corresponding to \( \pi-\pi^* \) transition. The peptides displayed an emission peak in the UV region, with Dip-Dip showing emission at 285 nm, similar to FF nanotubes, and a red shift observed for both cyclo-Dip-Dip and Boc-Dip-Dip (Figure 3b). Surprisingly, a second emission peak in the visible region, around 400–450 nm, was also observed, similar to FF and cyclo-FF nanofibers formed by thermally induced phase transition (Figure 3b). Fluorescent characterization of the Dip-Dip and cyclo-Dip-Dip crystals showed wide-spectrum emission in the visible light region between 415 and 475 nm, when excited at 280–410 nm (Figure 3c and Figure S6a). Boc-Dip-Dip showed a slightly different fluorescence pattern with peaks at 411, 436, and 462 nm when excited at 370 nm (Figure S6b). In contrast, both linear-FF and cyclo-FF, either in the native or thermally disrupted state, exhibit a constant emission irrespective of the excitation wavelength. Interestingly, the plot of consecutive emission maxima versus excitation wavelengths showed an excellent linear correlation between the excitation and emission peak, demonstrating a consistent shift for various excitation wavelengths (Figure 3d and Figure S6c). Fluorescent microscopy imaging confirmed that Dip-Dip and its derivatives showed fluorescent emission at four different channels upon a wide range of excitation wavelengths in the visible region (Figure 3e and Figure S7). Fluorescence lifetime microscopy (FLIM) analysis revealed a lifetime of 1.8 ns, 2.0 and 1.9 ns for Dip-Dip (Figure 3f), cyclo-Dip-Dip (Figure S8a) and Boc-Dip-Dip crystals (Figure S8b), respectively. The red edge excitation shift (REES) shown by
the aromatic-rich peptides is common in highly ordered ionic liquid assemblies, graphene oxides, peptide nucleic acid (PNA) based supramolecular assemblies, and nanostructures formed by oligosaccharides.49,50

Thermal and Mechanical Stability of the Aromatic-Rich Peptides. To examine the thermal stability of the tightly packed self-assembled aromatic-rich peptide crystals, thermogravimetric analysis (TGA) was performed. Dip-Dip crystals showed ~14% weight loss (between 50 and 185 °C, Figure 4a), presumably due to the evaporation of encapsulated water molecules and conversion into cyclo-Dip-Dip (Figure 4a, Figure S9), similar to the conversion of linear-FF to cyclo-FF.51 A major decrease in weight occurred only above 360 °C and a plateau was reached around 440 °C, unlike FF which degrades completely around 360 °C51 (Figure 4a). These results indicate that the Dip-Dip crystals are more resistant to thermal degradation than FF.

The high thermal stability of the crystals at the macroscopic level indicated a higher mechanical stiffness. To test this at the microscopic level, we used AFM-nanoindentation (Figure S10, S11, S12, and S13).23,52,53 Dip-Dip exhibited a Young’s modulus of 70.3 ± 20.6 GPa (Figure 4b), point stiffness of 449.1 ± 88.3 N m⁻¹ (Figure 4c) and shear modulus of 9.3 ± 0.5 GPa (Figure 4d), 4-fold, 2-fold, and 8-fold higher than FF, respectively (Figure 4e).23,24 The Dip-Dip Young’s modulus is comparable to that of metals such as aluminum and gold, and is much higher than softer metals such as magnesium, tin and several rigid organic materials (Figure 4f, Table S2).27,54−59 Cyclo-Dip-Dip and Boc-Dip-Dip also showed a similar improvement in the elastic properties with Young’s moduli...
of 41.5 ± 26.0 GPa and 43.9 ± 9.4 GPa, point stiffness of 268.4 ± 129.7 N m⁻¹ and 227.9 ± 44.2 N m⁻¹ and shear modulus of 4.1 ± 0.4 GPa and 3.9 ± 0.1 GPa, respectively (Figure S14). While the magnitude of elastic constants of these crystals is somewhat lower than Dip-Dip, it is still much higher than cyclo-FF (13.3 ± 1.1) and Boc-FF (7.9 ± 5.5) crystals (Figure S14). The dramatic increase in the mechanical strength of Dip-Dip derivatives compared to FF is probably due to the higher supramolecular packing density and number of zipper-like interlocks in the structural arrangement stemming from the doubled number of aromatic groups in the molecular structure (Figure 2c), which has been quantitatively linked to stiffness of FF crystals. Examination of the DFT-optimized crystal structures indicates that the Dip-Dip crystal is stabilized by hydrogen bonds between the peptide backbone and the waters of crystallization along the $b$ axis, while the molecular sheets run parallel to the $c$ axis. This tightly packed networks contribute to the high measured mechanical stability of Dip-Dip. By contrast, cyclo-Dip-Dip assembles with the molecular chains orientated at a large angle to the crystallographic axes. This reduces the elastic anisotropy in the crystal but also decreases the overall Young’s Modulus due to the reduced longitudinal strength. The third variant Boc-Dip-Dip illustrates the balance between single-molecule and supramolecular packing effects in crystal engineering. Boc-Dip-Dip exhibits a Young’s modulus similar in magnitude to that of cyclo-Dip-Dip because its simple peptide backbone is more compressible than cyclo-Dip-Dip but the Boc-Dip-Dip chains run parallel to a crystallographic axis.

**Piezoelectric Properties of the Aromatic-Rich Peptides.** All three aromatic-rich dipeptides crystallize in non-centrosymmetric structures suggesting a measurable piezoelectric response. The magnitude of the piezoelectric response is governed by both the molecular and supramolecular crystal dipoles, as summarized in Table S3. Among the studied aromatic-rich dipeptides, the supramolecular packing of Boc-Dip-Dip displayed many features of highly piezoelectric organic crystals, with a relatively small number of molecules per unit cell, high monoclinic angle, and a significant molecular dipole.

Electronic structures calculated using density functional theory (DFT) predicted a dipole moment of 2.1 D in the Boc-Dip-Dip molecule along the direction normal to the central amide linker (Figure 2j–l, Table S3), which facilitates a measurable effective $d_{31}$ response in the crystal (Figure 4g). To test this, piezoresponse force microscopy (PFM) experiments were carried out for the Boc-Dip-Dip crystal (Figure S15 and S16). Boc-Dip-Dip showed a large effective piezoelectric response with $d_{31}^{eff} = 73.1 ± 13.1$ pC/N (Figure 4g and Figure S16a), 8-fold and 4-fold higher than Boc-FF (8.4 ± 17.7 pC/N, Figure S16b,c) and FF₂ crystal (18 pC/N, Figure 4h), respectively. The large Boc-Dip-Dip piezo response was much higher than reported in biological materials (silk, ~50 pC/N) and polded PVDF (~30 pC/N), and at the lower limit of unpoled PZT thin films and ribbons (80–100 pC/N) (Figure 4b, Table S4). The effective piezoelectric response is also consistent with the large calculated supramolecular dipole in the Boc-Dip-Dip crystal, 1.8 D (Figure 4i). The high monoclinic angle of 113.8° suggests relatively low shear stiffness and measurable shear piezoelectric response. Both Boc-Dip-Dip and Dip-Dip crystalize in a monoclinic space group (Table S5, S6), which allows the possibility of a finite longitudinal response. However, twice as many molecules are present in the unit cell of Dip-Dip compared to Boc-Dip-Dip, indicating a larger number of interacting dipoles that reduce the net crystal dipole in the unit cell (Table S3).

Hence, even though Dip-Dip has a larger calculated single-molecule (gas phase) dipole of 3.4 D compared to the 2.1 D molecular dipole in Boc-Dip-Dip, the net crystal cell dipole is only 0.5 D (Table S3, Figure S17). PFM measurements indicate that any piezoelectric response is below the noise level of the technique, approximately 1 pC/N (Figure S16d). The third variant, cyclo-Dip-Dip crystallizes in space group number 19, which only allows for three shear piezoelectric constants ($d_{14}$, $d_{25}$, and $d_{36}$), similar to some amino acid crystals such as l-Alanine (Figure S16e).

The $d_{33}^{eff}$ coefficient of 73.1 pC/N measured for Boc-Dip-Dip is among the highest measured for organic molecular crystals (Figure 4g, Table S4), suggesting its potential application in mechanical energy harvesting devices under tensile/compressive loading. The corresponding predicted voltage coefficient is 2–3 Vm/N (assuming a dielectric constant of 3–4, see Methods) which is almost an order of magnitude higher than polar PVDF based polymers. Fabrication of a very simple proof-of-concept power generator from Boc-Dip-Dip crystals sandwiched between two Ag-coated silicon electrodes showed high output open-circuit voltage ($V_{oc}$) of 1 V and short-circuit current ($I_{sc}$) ~ 60 nA under applied force of 40 N (Figure S18).

**CONCLUSION**

In conclusion, the designed aromatic-rich dipeptides self-assemble into distinct supramolecular architectures, including layered, needle-like, and tubular structures. The well-ordered supramolecular packing in their crystalline state shows an ultradense aromatic network coupled with extensive H-bonding. The very strong piezoelectric response of the aromatic-rich dipeptides, combined with their very high mechanical and thermal stability and visible photoluminescence, suggests their use as organic eco-friendly materials for the design of highly integrated microdevices for energy harvesting, piezoelectric sensing, and touch screens in electronic devices.

**METHODS**

**Synthesis, Purification, and Characterization of Cyclo-Dip-Dip.** Synthesis of cyclo-Dip-Dip was carried out using the reported cyclization procedures starting from a linear dipeptide. First, a Boc-Dip-Dip-OMe peptide was synthesized using conventional solution-phase procedures. HATU (1.0 mmol) was added to a solution of Boc-Dip-OH (1.0 mmol) in CH₂Cl₂ (20 mL) at 0 °C. Et₃N and methyl ester of Dip amino acid (1.0 mmol) were then added and the solution was stirred until the reaction was complete. Next, the organic layer was washed with 5% Na₂CO₃ (2 × 10 mL) and the solution was kept under stirring at room temperature for 2 h. After removal of the excess formic acid from the solution was boiled for 24 h and the solvent level maintained by the addition of fresh isopropyl alcohol. After completion of the reaction as monitored by liquid chromatography–mass spectrometry (LC-MS), the solvent was evaporated in vacuo and the residue was crystallized from a 70% MeOH–H₂O mixture (7–3, v/v).
Scanning Electron Microscopy. Dipeptide samples were dissolved in a 70% MeOH–H₂O (7–3, v/v) mixture at a concentration of 0.5 mg/mL. A 5 μL aliquot of the solution was allowed to dry on a microscope glass coverslip at ambient conditions and was coated with Au. Scanning electron microscopy image were recorded using a JCM-6000PLUS NeoScope Benchtop SEM (JEOL, Tokyo, Japan).

Crytsallization. Single crystals of the peptides, suitable for X-ray diffraction, were grown by slow evaporation of Dip-Dip (10 mg/mL, 1–1 MeOH–H₂O, v/v), Dip-Dip (10 mg/mL, MeOH), cyclo-Dip-Dip (2 mg/mL, 7–3 MeOH–H₂O, v/v), Boc-Dip-Dip (2 mg/mL, 7–3 MeOH–H₂O, v/v) at room temperature. Crystals of driffraction quality were obtained 2–3 days after sample preparation.

Single Crystals X-ray Diffraction. For data collection, crystals were coated in paratone oil (Hampton Research), mounted on a MiTiGencryo-loop and flash frozen in liquid nitrogen. Diffraction data were collected at 100 K. For Dip-Dip in MeOH–H₂O and Dip-Dip in MeOH were collected on a Rigaku XtaLabPro with a Copper X-ray tube and a linear detector LYNXEYE-3 from 3 to 60° respectively.

Data Processing. All structures were solved by direct methods in SHELXT-2014/564 (Sheldrick, G. SHELXL-2013. University of Göttingen, Göttingen, Germany, 2013). The refinements were performed with SHELXL-2016/4 and weighted full-matrix least-squares against F² using all data. Aoms were refined independently and anisotropically, with the exception of hydrogen atoms, which were placed in calculated positions and refined in a riding mode. Crystal data collection and refinement parameters are shown in Table S1 and the complete data have been deposited in the CIF (JPK, Nanowizard II, Berlin, Germany). The force curves were obtained using the commercial software from JPK and analyzed by a custom written procedure based on Igor pro 6.12 (WaveMetrics Inc.). Silica cantilevers (PPP-NCHR Nanosensor Company with the half-open angle of the pyramidal face θ < 10°, tip radius: 8 nm, frequency in air: 204–497 kHz) were used in all experiments. The spring constant of the cantilevers was in the range of 10–130 N m⁻¹. The maximum loading force was set at 800 nN for both the Dip-Dip and cyclo-Dip-Dip crystals. All AFM experiments were carried out at room temperature. It is worth mentioning that the tips used in the AFM experiments do not have Coo symmetry, which may account for the large variations of modulus in the measurements.

In a typical experiment, the peptide crystals were spread over the surface of the quartz substrates (Supplementary Figure S10) and the cantilever was moved above the crystal with the help of an optical microscope. The cantilever was brought to the crystal samples at a constant speed of 15 μm s⁻¹ and held on the crystal surface at a constant force of 800 nN. The cantilever was then retracted and moved to another spot for the next cycle. The indentation fit was performed using a custom-written program in Igor and manually checked after the fitting. The curves were then fitted manually. Each approaching force–deformation curve was fitted in the range of 15 nm from the contact point or the maximum indentation depth to the contact point if the maximum indentation depth was less than 15 nm. By fitting the approaching curve to the Hertz model (eq 1), we could obtain the Young’s modulus of the crystals.

The measured point stiffness (Kcan) is comprised of the stiffness constants of the cantilever (Kcan) and the crystals (Kcr). Assuming that the peptide crystal and the cantilever act as two springs oriented in a series, the point stiffness of the crystals can be calculated using the following relation: Using the eq 2 below and an averaged measured value (Kcan) of 33.2 N m⁻¹ and 25.6 N m⁻¹ for the Dip-Dip and cyclo-Dip-Dip crystals, the average stiffness of the crystals was calculated to be 63.4 and 40.5 N m⁻¹, respectively. To estimate the material property of the crystals, we assumed that the mechanical behavior of the peptide crystal can be described as linear elastic, which is a good approximation for solids under small strains.

Fluorescence Lifetime Microscopy. The fluorescence lifetime images were acquired using LSM 7 MP 2-photon microscope (Carl Zeiss, Weimar, Germany) coupled to a Becker and Hickl (B&H) simple-Tau-152 system. Chameleon Ti:sapphire laser system with an 80 MHz repetition rate was used to excite the sample at a wavelength of 800 nm. Images were acquired through a Zeiss 20 × 1 NA water-immersion objective. A Zeiss dichroic mirror (LP 760) was used to separate the excitation and the emission light. Emission light was collected using a hybrid GaAsP detector (HPM-100-40, BH, Berlin, Germany). The image acquisition time was set to 150 s to collect a sufficient number of photons.

Young’s Modulus Calculations. Atomic force microscopy (AFM) experiments were carried out using a commercial AFM (JPK, Nanowizard II, Berlin, Germany). The force curves were obtained using the commercial software from JPK and analyzed by a custom written procedure based on Igor pro 6.12 (WaveMetrics Inc.). Silica cantilevers (PPP-NCHR Nanosensor Company with the half-open angle of the pyramidal face θ < 10°, tip radius: 8 nm, frequency in air: 204–497 kHz) were used in all experiments. The spring constant of the cantilevers was in the range of 10–130 N m⁻¹. The maximum loading force was set at 800 nN for both the Dip-Dip and cyclo-Dip-Dip crystals. All AFM experiments were carried out at room temperature. It is worth mentioning that the tips used in the AFM experiments do not have Coo symmetry, which may account for the large variations of modulus in the measurements.

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Shear Modulus. The crystals were spread across the stainless-steel micro mask with one end of the crystal spreading above the mask and the other end. The cantilever was moved above the free end of the crystals and the AFM experiments were performed as described above. The shear modulus was calculated using the Euler beam model (2). The shear modulus corresponds to the crystal deflection of the impending end, P corresponds to the applied force, l corresponds to the distance from the fixed end to the point where the force is applied, and E corresponds to the shear modulus. I corresponds to second moment and can be calculated using eq 4, in which is the breadth and h is the thickness.
Density Functional Theory (DFT) Calculations. Single-molecule dipoles were calculated from gas phase molecular electronic structures solved using the Gaussian16 software package, with the hybrid DFT B3LYP functional and 6-311+g** basis set. Electronic structures of the crystalline assemblies were obtained using periodic DFT with the VASP code, using the PBE functional, projector augmented wave (PAW) pseudopotentials and plane-wave basis sets. Due to the large size of the crystals, structures were optimized using a single I-point conjugate gradient minimization, with a plane wave cutoff of 400 eV. Convergence tests indicated that this modest cutoff is sufficient to obtain reliable electronic structures. Crystal dipole moments were calculated from the optimized structures using the CP2K code. The Berry phase approach using the Gaussian and Plane Waves (GPW) method was applied for energy calculation. The same PBE exchange-correlation functional was used as for the VASP calculations. The Orbital Transformation SCF algorithm was used with Goedecker, Teter and Hutter (GTH) type pseudopotentials and a molecular optimized double-$\zeta$ Gaussian basis set (akin to 6-31G**, similar to the basis set used for the single-molecule calculations). The cutoff for the plane waves and gaussians was 750 and 60 Ry, respectively and energy converged to $10^{-8}$ hartree.

Grimme D3 dispersion corrected DFT was used to calculate binding energies between pairs of molecules extracted from their parent crystal structures. The dimer models were built using Avogadro, VESTA, and OpenBabel. The operation of piezoresponse force microscopy (PFM) is detailed in Supplementary Figure S15a. PFM studies were carried out using an NT-MDT Ntegra Spectra operating in contact PFM mode. In this mode, an AC voltage is applied to the AFM probe while it is in contact with the sample, thus generating a piezoelectric response within the sample which is then measured. The same PBE exchange-correlation functional was used as for the VASP calculations. The Orbital Transformation SCF algorithm was used with Goedecker, Teter and Hutter (GTH) type pseudopotentials and a molecular optimized double-$\zeta$ Gaussian basis set (akin to 6-31G**, similar to the basis set used for the single-molecule calculations). The cutoff for the plane waves and gaussians was 750 and 60 Ry, respectively and energy converged to $10^{-8}$ hartree.

Nonpiezoelectric samples were used (Supplementary Figure S15). Supplementary Figure S15b shows a representative plot for poled PVDF (positive control), which has a piezoelectric response. On the other hand, Dip-Dip and cyclo-Dip-Dip upon applied voltage. While Boc-FF (Supplementary Figure S16a) and Boc-Dip-Dip (Supplementary Figure S16b,c) showed a linear relationship of the piezoresponse versus applied voltage, the results for Dip-Dip (Supplementary Figure S16d) and cyclo-Dip-Dip (Supplementary Figure S16e) were similar to the nonpiezoelectric negative controls (Supplementary Figure S15).

The presence of 5 shear components, 2 transverse components and 1 longitudinal component all guarantees a nonzero effective piezoelectricity. On the other hand, Dip-Dip and cyclo-Dip-Dip crystals belong to point group 222. This is a much higher symmetry point group which only allows the following piezoelectric components:

$$\begin{pmatrix}
0 & 0 & 0 & d_{14} & 0 & d_{16} \\
0 & 0 & d_{21} & d_{22} & 0 & d_{25} \\
0 & 0 & 0 & 0 & d_{34} & 0 & d_{36}
\end{pmatrix}$$

Only 3 shear components are allowed and the shear strain that would develop as a result of these components is respectively centered on the 3 crystallographic axes. These strains would not contribute to an effective piezoelectric response.

Piezoelectric Voltage Coefficient Calculations. A theoretical value for the piezoelectric voltage coefficient, which is the figure of merit for energy harvesters, etc., can be derived from the following equation if the piezoelectric strain constant $d$ is known, as well as the relative permittivity of the material:

$$g = \frac{d}{\varepsilon_{0}S}$$

Assuming the relative permittivity is close to 3 (which is typical of similar materials), the calculation will take the form:

$$g = \frac{73 \times 10^{-12} \text{C/N}}{8.85 \times 10^{-12} \text{C/N} \times 3} = 2.75 \text{ V/m/N}$$
Characterization of the Power Generator Based on Boc-Dip-Dip Powder. Boc-Dip-Dip powder was fabricated into nanogenerator devices with sandwich structure.23,57 The nanogenerator was vertically fixed to a steel platform, and mechanical forces were periodically applied by a linear motor (E1100-1S-1C type with Force Control, LinMot). An aluminum foil was closely coated on the nanogenerator device to avoid interference from the linear motor. A low-noise voltage preamplifier (Stanford SR560) and a low-noise current preamplifier (Stanford SR570) were used to collect the output open-circuit voltage and short-circuit current, respectively. To avoid interference from the outside environment, all output performance was collected in a Faraday cage.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsnano.0c01654.

Morphology of aromatic-rich dipeptide supramolecular structures; Single crystal structure of FF; Water mediated cyclic ring formed by Dip-Dip molecules; Comparison of the diameter of the cyclic arrangement formed by (a) Dip-Dip and (b) FF molecules; Illustration of how pairs of molecules were extracted from optimized crystal structures; Fluorescent characterization of cyclo-Dip-Dip and Boc-Dip-Dip crystals; One bright-field and four fluorescence images of the cyclo-Dip-Dip crystal; FLIM characterization; Mass spectra showing the conversion of linear Dip-Dip into cyclo-Dip-Dip with increase in temperature; Schematic illustration of the AFM experiments; Schematic illustration of shear modulus measurement; Typical force curves and fit of AFM nanoindentation for aromatic-rich dipeptides; Optical images of the AFM indentation experiments of aromatic-rich peptides before and after indentation; Mechanical properties of the aromatic-rich dipeptides; Illustration of the piezoelectric measurements and control experiments; Piezoelectric measurements of the aromatic-rich dipeptides; Calculated supramolecular crystal dipole moment; Output of a Boc-Dip-Dip-based nanogenerator (PDF)

Crystal data for cyclo-Dip-Dip (CIF)
Crystal data for Dip-Dip in MeOH−H2O (CIF)
Crystal data for Boc-Dip-Dip (CIF)
Crystal data for Dip-Dip in MeOH (CIF)

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6V.B., S.B., and B.X. contributed equally to this work. S.B. analyzed the crystallographic data. B.X. and Y.C. performed the AFM nanoindentation experiment. J.O.D., EUH., C.S., and S.A.M.T designed and performed PFM experiments. S.G., S.A.M.T., P.A.C., and D.T. designed and carried out electronic structure calculations to understand dipole moment contributing to piezoelectricity. H.Y. and R.Y. carried out power generation experiment. L.J.W.S. collected single crystal XRD data. K.T. helped in discussion. V.B., S.B., and E.G. wrote the paper. All authors discussed the results and commented on the manuscript.

Notes
The authors declare no competing financial interest.

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