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COMMUNICATION

The simplest supramolecular helix†

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Diethylamine is the smallest and simplest molecule that features a supramolecular helix as its lowest energy aggregate. Structural studies and large scale sampling simulations show that the helical arrangement is more stable than cyclic structures, which are the dominant species for other small hydrogen bonding molecules.

Helices are ubiquitous in the natural world.¹ The discovery of the helical nature of proteins² and DNA³ inspired the syntheses of a plethora of artificial systems. Helicity gives rise to desirable material properties for applications in optoelectronics, chiral separation and asymmetric synthesis.⁴⁻⁶ Developing synthetic strategies for helical structures has been a focal point in the search for new materials and supramolecular assembly has played a key role giving access to more complex and dynamic structures.⁷⁻¹⁸ Supramolecular interactions are only modestly directional and therefore difficult to control, thus elaborate molecular designs are often required to direct aggregates into a given shape. This raises the question: What minimal level of molecular complexity is needed for an intrinsically stable supramolecular helix, and what would be the smallest and simplest achiral molecule that could maintain such an arrangement?

The problem of minimal helical complexity has previously been approached by investigating interactions between basic shapes. Wales et al. explored how simple models with dipoles self-assemble, demonstrating for example that dumbbells consisting of two spheres with a central dipole form a helical chain in the presence of an applied electric field.^{19,20} Pickett, Mughal, and others have studied sphere packings confined inside cylinders which generate helical arrangements at certain sphere-to-cylinder ratios.²¹⁻²³ While reflecting on similarly basic archetypes, we found that simple dumbbells consisting of two equal spheres connected by a rod form stable helical

stacks (Fig. 1, see SI for more details). This model illustrates the conventional wisdom that, for a helix to form, components must interact at two competing length-scales. Here they arise from the stacking of the central rods and the packing of the peripheral spheres, while a strong directional field, gravity, keeps the assembly together.



Fig. 1 A helical stack of ten 3D-printed dumbbells with $D_{\infty h}$ symmetry. The dumbbell second from the bottom is supported by two stacks of coins to keep the helical stack upright.

With these simple models in mind, we investigated the minimum requirements for an intrinsically stable supramolecular helix consisting of achiral components. There must be an internal directional field that is sufficiently strong to bind molecules into a chain, while molecules must also interact at two competing length-scales to induce a helical twist. Our interest was spurred by our initial discovery, described in here, that diethylamine consists of helical strands in the solid state. The molecule has two steric groups that flank the central H-bonding site. Similar to the peripheral spheres of dumbbells in Fig. 1 they lock the supramolecular chain into a helix, while hydrogen bonding provides the directional field that binds it. We have investigated a series of dialkylamines with X-ray crystallography and DFT calculations to assess the inherent stability of their helices. Large scale sampling simulations using quenched molecular dynamics were performed to locate the helix within the hierarchy of lowest energy conformers for dialkylamines and other small H-bonding molecules.

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Crystal structures of small dialkylamines (MeEtNH, MePrNH, Et₂NH, Pr₂NH, EtBuNH, Bu₂NH, Hx₂NH, Et*i*PrNH, *i*Pr₂NH and *i*Bu₂NH) were analysed to explore the extent of helical aggregates amongst these substances. Single crystals of the low-melting compounds were obtained by zone-melting.[‡] With the exception of Et₂NH, which undergoes a phase transition at 148 K, all compounds showed uniform solid phase behaviour above 100 K. Crystals of Et₂NH, Pr₂NH, EtBuNH and Et*i*PrNH comprise helical assemblies that are held together by hydrogen bonding. The helix of Et₂NH is retained across the phase transition. Fig. 2(a) depicts a strand of the high temperature phase. The helices of Et₂NH, Pr₂NH and EtBuNH contain three molecules per pitch. The CH₂CH₂NHCH₂CH₂-units slot into each other at an angle facilitating additional van der Waals contacts to second nearest neighbours along the chain and thereby inducing a helical twist. Fig. 2(b) illustrates this by depicting the neighbouring molecules of Et₂NH with their Hirshfeld surfaces, which indicate the space the molecules occupy in the crystal.²⁴ The helix in crystals of Et*i*PrNH shows similarly competing interactions, but coils more tightly with four molecules per pitch. The crystal structures feature glide reflections and thus contain enantiomers. Since the helices consist of achiral molecules there is no chiral bias that controls their handedness.

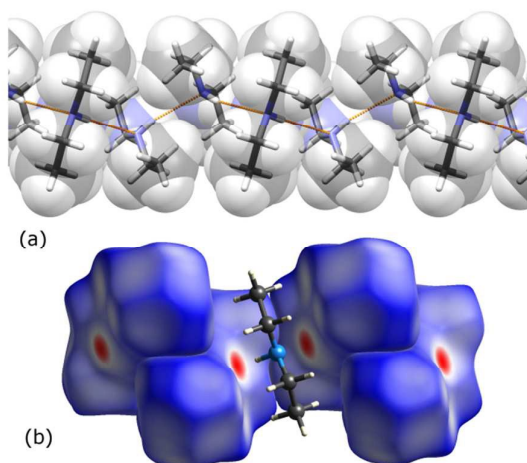


Fig. 2 (a) Helical strand of the crystal structure of Et₂NH. (b) Illustration of the interactions of an Et₂NH molecule within the helix. Its neighbours are depicted with their Hirshfeld surfaces; the red patches indicate H-bonding interactions.²⁴

All other compounds exhibit non-helical crystal structures. Methyl derivatives generate hydrogen-bonded aggregates with interacting molecules aligned in parallel, which shows that the methyl group is too small to cause a helical twist. MeEtNH forms a crinkled chain and MePrNH a tetrameric ring system. Two longer side chains, as in Bu₂NH and Hx₂NH, prevent hydrogen bonding in favour of the parallel packing mode that is characteristic of linear alkanes,^{25,26} while amines carrying two branched groups, *i*Pr₂NH and *i*Bu₂NH, only form short H-bonded chains.

Table 1 Binding energies per molecule for infinite helices and crystals (in kJ/mol)

	E_{inf}	$E_{crystal}$	k^a
Et ₂ NH	-47.3	-78.0	0.25
Et <i>i</i> PrNH	-48.8	-83.6	0.27
EtBuNH	-55.2	-95.3	0.29
Pr ₂ NH	-56.4	-96.1	0.30

^a fractional contribution of interactions between second nearest neighbours in the helix as calculated from Equation (1).

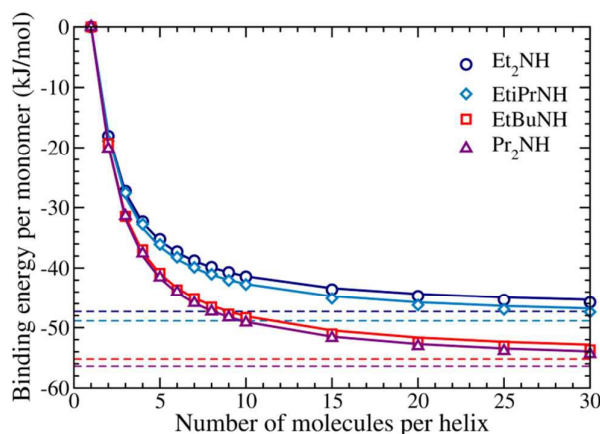


Fig. 3 Density functional theory results for isolated helices showing binding energies as a function of helix length. The solid lines correspond to the fit of Equation 1, the dashed horizontal lines denote the infinite helices.

To examine whether the helices are intrinsically stable or are merely a consequence of the crystal packing, we carried out extensive density functional theory calculations for the helices of Et₂NH, Pr₂NH, EtBuNH and Et*i*PrNH.[§] For each crystal, we optimized the unit cell, a single repeat unit of the periodic helix, and finite supramolecular chains of up to 30 monomers. Table 1 compares the binding energies per molecule of the isolated infinite helices (E_{inf}) to those of the bulk crystal. Isolated helices constitute local minima for all four compounds. In the crystal they contribute to more than half of the crystal binding energy. The structural features of the calculated helices are very similar to the X-ray structures; the optimized structures of Et₂NH, Pr₂NH and EtBuNH also contain three molecules per helical pitch. Fig. 3 illustrates how the binding energy per molecule $E_m(n)$ increases with helix length. If there were only nearest neighbour interactions (of which there are $n-1$ per chain), the binding energy per molecule in the dimer would be $E_{inf}/2$. However, the data show that $E_m(2)$ is only about one third of E_{inf} . The added cooperative effect in longer chains can be attributed to the interactions between second nearest neighbours of which there are $n-2$ per chain. The contribution of these can be expressed as follows:

$$E_m(n) = (1-k) E_{inf} (n-1)/n + k E_{inf} (n-2)/n \quad (1)$$

where $1-k$ and k represent the fractional contributions of the interactions between nearest and second nearest neighbours, respectively. This function fits very well to the calculated binding energies for all four helical dialkylamines with k

ranging from 0.25 for Et₂NH to 0.30 for Pr₂NH as demonstrated in Fig. 3. The positive values of *k* correspond to attractive second-neighbour interactions such as van der Waals (vdW) or electrostatic forces. To distinguish these, we subtracted the vdW components from the DFT total energies. Without vdW contributions, the second-neighbour contributions to the binding energy disappear almost completely, suggesting that the cooperative effect is based on vdW forces.

To establish a low-temperature hierarchy of lowest energy conformers for low molecular aggregates of dialkylamines and other small H-bonding molecules, we performed sampling simulations using quenched molecular dynamics.⁵⁵ These simulations generate optimized structures which we compare separately rather than treating a Boltzmann-averaged ensemble. Weak restraints representing the hydrogen bond were used to keep the monomers close together during the simulation to free them of any structural bias beyond focusing on dimers, trimers, tetramers etc. In our sampling we consistently identified the helical conformation among the lowest energy aggregates for Et₂NH, EtPrNH, EtBuNH, and Pr₂NH. In the case of Et₂NH, the helix is found to be the most stable conformer for supramolecular chains of up to six monomers. For the other three molecules, there are numerous coiled conformers in addition to the helix where the side chains interact via vdW forces and which are incompatible with a crystal. However, the ordered helix is still among the most stable arrangements for these molecules, supporting our case that there is an intrinsic stabilizing mechanism arising from the interplay between steric interactions of side groups and hydrogen bonding for suitably sized alkyl groups.

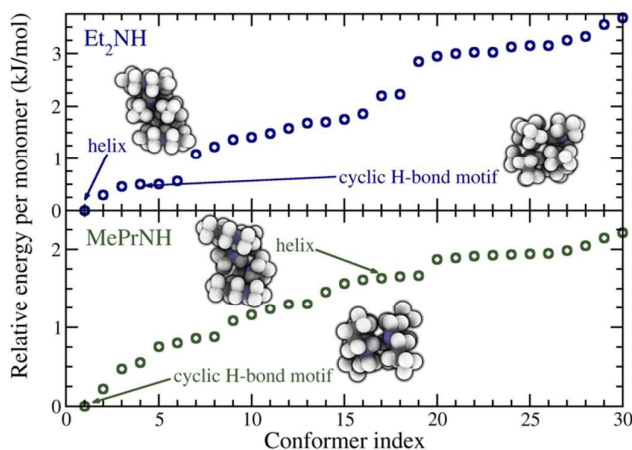


Fig. 4 Energetic hierarchy for four-molecule conformations of Et₂NH (top) and MePrNH (bottom). Each simulation uncovered a helical tetramer chain, which is the most stable for Et₂NH but relatively unstable for MePrNH. Both simulations also found the cyclic H-bond motif seen in the crystal structure of MePrNH, which also turned out to be the most stable conformation for that molecule while being less favoured for Et₂NH.

When performing molecular dynamics-based sampling for four units of MePrNH, we find that the most stable conformer is a cyclic tetramer – similar to the crystal structure. In this simulation the helical conformation is found at much higher energy. As illustrated in Fig. 4, the cyclic tetramer is also a motif found in Et₂NH, but there the energetic ordering is

reversed with the helix being more stable. The stability of the helical conformers of the dialkylamines discussed here is extraordinary, considering they have one fewer hydrogen bond than the corresponding cyclic structures. This feature is not seen in other simple molecules that form hydrogen bonds, such as alcohols and monoalkylamines, even though some of them exhibit helical structures in the crystal for certain polymorphs.^{27–30} Molecular sampling of tetramers of these molecules show that they all favour cyclic over helical aggregates (see SI). This indicates that the hydrogen bonding site of a simple monofunctional molecule must be flanked by at least two alkyl groups that are larger than methyl to direct the assembly into a helical chain.

Returning to simpler models, the diethylamine molecule can be described as a dumbbell, similar to that pictured in Fig. 1. Inspired by the helicity study of Wales et al.¹⁹ we replicated the helix of diethylamine with a simple dumbbell model but in the absence of an external field using a model consisting of three connected Lennard-Jones (LJ) spheres as shown in Fig. 5. The outer spheres are identical representing the two steric alkyl groups, while a strong dipole moment perpendicular to the mean plane of the dumbbell is placed on the smaller central sphere, mimicking the hydrogen bond. We used linear and angular dumbbells with internal angles varying from 120° to 180° to reflect the C_s-symmetry of the diethylamine molecule.

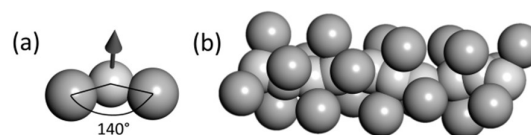


Fig. 5 Helices from simple dumbbell models consisting of three connected Lennard-Jones spheres. (a) Single particle with an internal angle of 140° and a dipole moment perpendicular to the plane of the particle. (b) The global energy minimum for ten of these particles is a well-defined helix.

We then obtained the global potential energy minima for clusters of these particles using the basin hopping method.³¹ The observed structures depend substantially on the relation between the LJ interactions, the dipole moment strength, and the internal angle (see SI). For weak dipoles, particles cluster in cyclic ring structures which are held by non-directed LJ interactions. Stronger dipoles on the other hand lead to linear chains where the individual particles are aligned along the dipole axis. For angular dumbbells with internal angles centring around 150° the global minimum structure is a helix over a wide parameter range of competing dipole and LJ interactions. Similar to the diethylamine molecules the angular dumbbells incline with respect to the helical axis and thereby enabling second-neighbour contacts. One such helix is shown in Fig 5 for a system of 10 dumbbells.

In summary, we have shown that simple dialkylamines with side groups only larger than methyl are the least complex molecules that can assemble into stable supramolecular helices. The helical twist is a consequence of competing length scales of interactions to nearest and second nearest

neighbours in the chain, represented by directional hydrogen bonding along the backbone and by weaker non-directional van der Waals interactions among the side groups. DFT calculations on isolated strands confirmed that the helix is intrinsically stable and that the cooperative effect of additional interactions between second nearest neighbours is a contributing factor. Large scale sampling of low molecular aggregates using quenched molecular dynamics simulations found that the helix is among the most stable arrangements for these molecules. Comparison with other small molecules indicates that diethylamine is the smallest and simplest molecule that features a supramolecular helix as its lowest energy aggregate.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Samples were crystallized using the zone-melting technique described by Boese and Nussbaumer.³² Single crystal X-ray structures³³ were obtained at 100 K; the high temperature phase of Et₂NH at 160 K. See SI for further details. Crystallographic data are available at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 1826573-1826583.

§ Density functional calculations were carried out with the Materials Studio 2017 R2 package.³⁴ First, the unit cells were optimized using the CASTEP code³⁵ with PBE exchange correlation,³⁶ and the dispersion correction by Tkatchenko and Scheffler.³⁷ To allow comparison with free molecules and short helices, all cells were further optimized using the DMol³ code with the same exchange correlation settings.^{38,39} Periodic helices were cut out from the crystal unit cells and placed in a box with transverse dimensions 30Å×30Å before being optimized again. The finite chains of length up to 30 monomers were then cut out from repeated images of the final periodic helix and optimized again. The Materials Studio fine settings were used throughout, but for DMol³, we additionally used an *xfine* integration grid as well as an auxiliary density expansion with multipoles up to order 5.

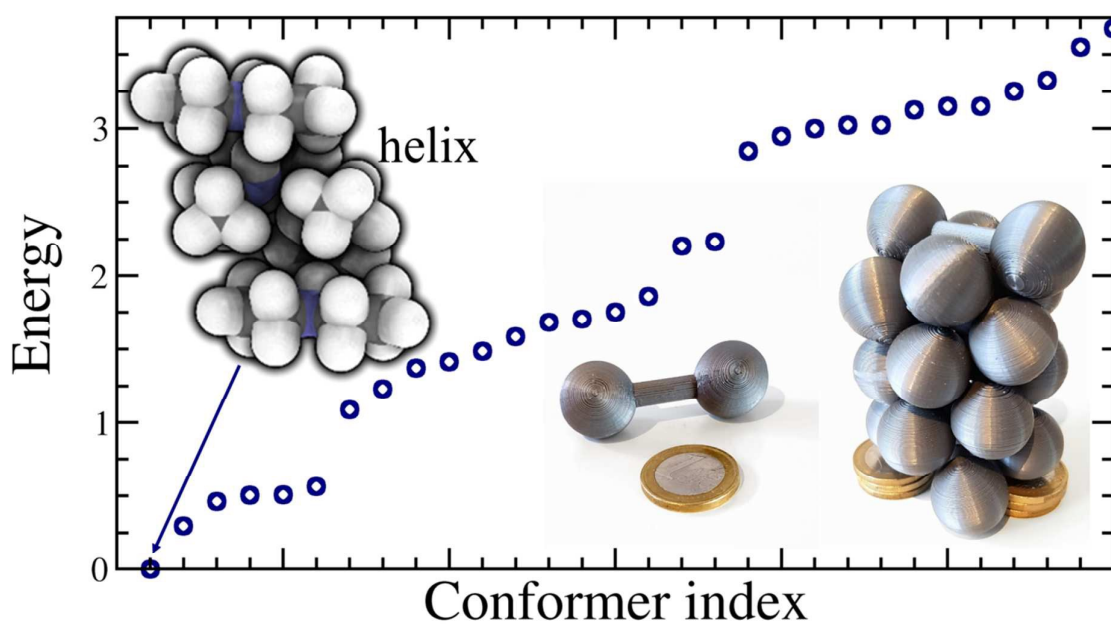
§§ Sampling simulations were performed using quenched molecular dynamics. For short chains of dialkylamines, a search for the optimal conformers were performed using extensive sampling based on quenched molecular dynamics with the Materials Studio Forcite module and the COMPASS II force field.⁴⁰ A simple protocol was used to generate and rank different conformations. The initial set of conformations was sampled using the Forcite Quench Dynamics task. A weak harmonic restraint with a force constant of 1 kcal/mol/Å² was applied between the amine groups to keep the chains together. One thousand configurations were generated from a 30 ns constant temperature molecular dynamics simulation run at 298 K. Each configuration was further optimized using DFTB+⁴¹ and the 3ob Slater-Koster library.⁴² Following optimization, a clustering algorithm based on maximal dissimilarity partitioning was applied to identify 50 representative conformations. The clustering used a distance measure based on the combination of DFTB+ total energy, DFTB+ HOMO and LUMO energies, surface area, and a structure similarity measure calculated using BIOVIA Pipeline Pilot 2017R2.⁴³ Up to 50 configurations were further optimized using DMol³ with the same settings as described above. Finally, the resulting set of conformers was ranked by total energy to identify the most stable short chain conformation for each chain length.

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*Table of contents entry***The simplest supramolecular helix**

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