Structural Insights into the Mechanism of Chiral Recognition and Chirality Transfer in Host-Guest Assemblies at the Liquid-Solid Interface

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ABSTRACT: Understanding structure-efficiency relationships in chiral recognition and chirality transfer constitutes an important step towards the rational design of improved chiral probes and chirality auxiliaries or inducers. Recently discovered enantioselective host-guest adsorption opened a new pathway towards the enantioselective reconstruction of on-surface monolayers. In

this study, we explored the importance of size matching between host cavity and chiral guest for the efficiency of chiral recognition and subsequent chirality induction in the initially racemic host.

Introduction

The importance of molecular and supramolecular chirality can hardly be overestimated.¹⁻³ Numerous studies deal with the impact of chirality on the properties of (bio)materials.⁴⁻⁷ While the majority of these studies relate to bulk materials or isolated objects often in solution,⁸⁻⁹ significant progress is made recently in the study of monolayer films on solid surfaces, thanks to advanced spectroscopy techniques, and in particular local probe techniques such as scanning probe microscopy, including scanning tunneling microscopy (STM).¹⁰⁻¹⁹ The latter technique allows for the characterization and visualization of molecular adsorbates with submolecular resolution on atomically flat conductive surfaces.

An intriguing aspect is the concept of induction of chirality. A small amount of a chiral modifier or inducer may lead to the homochiral organization of a prochiral compound, so promoting the formation of one supramolecular enantiomorph (and not its mirror image).^{4, 20-22}

Upon substituting a fraction of achiral molecules in a supramolecular matrix by chiral molecules, the supramolecular matrix can be forced to adopt one handedness. Such chiral modifiers are often called “sergeants”, who dictate the self-assembly of the prochiral component. This phenomenon is well-documented for monolayer formation, also at the solid/liquid interface.^{14, 23-25}

Another less well-documented mechanism that may induce chirality is based on host-guest chemistry, where the chiral guest biases or templates the chiral organization of the prochiral host. This is, in particular, relevant for molecular nanoporous networks, where the chiral guest occupies supramolecular nanowells formed by the achiral host.²⁶⁻²⁷

Recently, we have shown how both processes can act simultaneously, by investigating the self-assembly on graphite of a 1:9 mixture of a chiral alkoxyated dehydrobenzo[12]annulene (DBA) derivative and its achiral analogue (Figure 1a).²⁸ The molecules organize into a 2D honeycomb lattice, leading to a regular array of nanowells (Figure 1b,c). We found that for a fixed ratio of both components in solution, changing the overall DBA concentration led to extreme differences in the handedness of the monolayer formed at the interface between 1-phenyloctane and highly oriented pyrolytic graphite (HOPG) upon annealing.²⁸ The extensive data set could be interpreted by taking into account two self-assembly pathways, that are actually also two different chiral induction mechanisms. The sergeant-soldiers mechanism is always at work during the nucleation phase, and the co-adsorption of chiral sergeant molecules in the honeycomb pattern of the achiral molecules biases the system's handedness. Depending on the chemical potential of the solution, the host-guest mechanism might take over at the ripening stage. In this mechanism, the chiral molecules occupy the supramolecular nanowells formed by the achiral DBAs. The chiral guest molecules adopt a windmill conformation in which all stereogenic methyl groups orient up with respect to the graphite surface, adopting a preferred molecularly chiral, swirl-like shape. In this particular system, the chiral molecules prefer to occupy and stabilize nanowells that have a different handedness than the ones that are formed via the sergeant-soldiers mechanism, rendering both mechanisms competitive with a different outcome.

Figure 1. (a) Chemical structures of achiral and chiral DBAs used in this study. (b,c) Molecular models depicting clockwise (CW) and counterclockwise (CCW) nanowells, in which the chiral molecule cDBA-OC12(S) is co-adsorbed (b) as a sergeant in the CW DBA network; while (c) as guests in the CCW nanowells of the host network. For the chiral molecules, C, H and O atoms are colored green, white and red, respectively, while for the achiral molecules C, H and O atoms are blue, white and red, respectively. In (b), the stereogenic centers, together with the surrounding methylene groups, are represented in black, mimicking the “black contour” features in the STM images of cDBA-OC12(S).

Here, we present our investigation of the efficiency of chiral recognition and chirality induction of porous DBA networks by interactions with chiral cDBA-OC12(S). We screen the effect of the size of the achiral DBA molecules for a fixed sergeant or guest, i.e. cDBA-OC12(S), aiming at favoring the “host-guest” mechanism over the “sergeant-soldiers” approach. In particular, this study shines light on the relation between the size of the guest and diameter of the host network, with respect to enantioselective adsorption and chiral induction. This approach is unique: to the best of our knowledge, there are no other examples reporting the effect of the diameter of

supramolecular nanowells on the enantioselective adsorption of a chiral guest and its impact on chiral induction processes.

Methods

STM experiments: All STM images were captured using an Agilent PicoLE system (now Keysight 5100) operating in a constant-current mode with the tip immersed in an open liquid cell. A liquid cell (limiting the exposed HOPG surface to a circle with diameter = 3.1 mm) constructed of polytetrafluoroethylene (PTFE) was used to hold ~40 μ L of the desired solution on the HOPG substrate. STM tips were prepared by mechanical cutting of Pt/Ir wire (80/20, diameter 0.2 mm). Images are acquired using the imaging parameters I_{set} (tunneling current) = 0.2 nA and V_{bias} (substrate bias) = -0.2 V. These are optimal settings for the visualization of DBA cores (to determine the chirality of nanowells and the incorporation (if any) of cDBA-OC12(*S*) which is imaged with black contours¹²). The negative substrate bias indicates a tunneling current from the substrate to the STM tip.

Immediately prior to imaging, the HOPG substrate (grade ZYB, Advanced Ceramics) was freshly cleaved using an adhesive tape. The HOPG substrate was then placed onto an *in situ* temperature-control stage, which consists of a copper base plate with an in-built resistive heating element and a thermocouple. The temperature of the heating stage was controlled via a feedback loop using a Lakeshore model 331 temperature controller. This arrangement gave an accessible temperature range from room temperature up to ~80 °C (353 K).

All DBA derivatives used here were synthesized according to previously published methods.^{24, 27, 29-30} 1-Phenyloctane (Sigma, 98%) was used without further purification to dissolve the DBA derivatives. The solutions were prepared by serial dilution from stock solutions ($C = 1 \times 10^{-3}$ M) by weighing appropriate amount of solid compounds.

The direct deposition of premixed host and chiral guest DBAs in solution can become problematic, when an excess of chiral DBA and/or very diluted solutions of achiral host DBAs are used. Deposition of such mixture can result in a significant adsorption and self-assembly of the chiral DBA itself (Figure S2). As a deposition protocol, we used, therefore, the sequential deposition method. First, an achiral DBA molecule is deposited on HOPG from a dilute solution (20 μ L). Formation of a globally racemic host network, so with both CW and CCW domains, is quasi-instantaneously. 5 to 10 minutes later, 20 μ L of the cDBA-OC12(*S*) solution is added, initiating host-guest interactions. This method was previously validated for the DBA-OC12/cDBA-OC12(*S*) system.²⁸ Concentrations of different compound combinations are optimized to minimize the surface coverage of non-porous polymorphs and to assure a reasonable surface coverage of the achiral DBAs (see Table 1 and respective figure captions).

For annealing experiments, all solutions were deposited at room temperature (20–22 °C, humidity 30–45%). After the initial room temperature study (~1-2 h), the sample is slowly (2 °C/min) heated, annealed to 80 °C, and then slowly cooled down (2 °C/min) to room temperature. The loss of solvent and thus the changes in the concentration upon annealing were insignificant since a control experiment revealed that the sample showed only a weight loss of 9% on annealing at 80 °C for 2 h. STM imaging was resumed once the sample reached room temperature. For analysis purposes, the percentage distribution of handedness (CW and CCW honeycomb nanowells) on the surface was determined as an average based on three experimental sessions. Each value and experimental error (standard deviations) of surface coverage were determined by using more than ten high-resolution images ($\geq 50 \times 50$ nm²) per session. To collect sufficient amount of data (10-20 images per sample) and to minimize the tip-assisted desorption, the imaging was done with frequent changes of the scanning area (1-2 images per location). Multiple locations

far away from each other were probed to get reliable statistics. This procedure was satisfactory for confirming the equal probability of the CW and CCW honeycomb structures formed by achiral DBA-OC12.²⁸

Details of molecular mechanics calculations: Molecular mechanics calculations were performed with MM+ force field as implemented in HyperChem® Prof. 7.52.³¹ Geometries were optimized to rms deviation of the energy gradient smaller than 0.01 kcal/(mol·Å). A single layer of properly cut graphene nanoflake was used. During the optimizations, the atom positions in the graphene sheet were fixed (C-C bond distance was kept 1.40 Å). To calculate host-guest interactions, a six-membered nanowell was built for each host network size and optimized first. To cut down computational costs and to eliminate edge effects in cluster calculations all alkyl chains that were not involved into dimeric interdigitation were truncated and modified to dihydrofuran rings (Figure S3a). After optimization of the host network, the atomic positions were fixed along with those of the graphene nanoflake. Only then cDBA-OC12(S) guest was introduced and its adsorption geometry was optimized. The validity of such force field calculations was previously demonstrated.^{27, 32}

The enthalpy of guest adsorption $\Delta H_{\text{ads}}(\text{guest})$, and its decomposition into host-guest interactions ($\Delta E_{\text{HG_inter}}$), guest binding to the underlying substrate ($\Delta E_{\text{SG_bind}}$) and the conformational energy of the guest ($\Delta E_{\text{G_conf}}$) were estimated as:

$$\Delta H_{\text{ads}}(\text{guest}) = E_{\text{SHG}} - E_{\text{SH}} - E_{\text{G}}^0, \Delta E_{\text{HG_inter}} = E_{\text{HG}} - E_{\text{H}} - E_{\text{G}}, \Delta E_{\text{SG_bind}} = E_{\text{SG}} - E_{\text{S}} - E_{\text{G}}, \text{ and}$$

$$\Delta E_{\text{G_conf}} = E_{\text{G}} - E_{\text{G}}^0, \text{ where}$$

E_{G}^0 – is the enthalpy of formation of the most stable conformation of the guest, obtained *via* geometry optimization of single cDBA-OC12(S) molecule *in vacuo*;

E_{SH} – is the enthalpy of formation of substrate-host aggregate, obtained by geometry optimization of truncated DBA host hexamer on a frozen flake of graphene of appropriate size;

E_{SHG} – is the enthalpy of formation of substrate(graphene)-host-guest aggregate, obtained by geometry optimization of cDBA-OC12(*S*) guest on a fixed geometry of substrate-host aggregate (see E_{SH} above);

E_{SG} , E_{HG} , E_S , E_H and E_G are the enthalpies of formation obtained by single point energy calculations of substrate-guest, host-guest, substrate, host and guest parts of the optimized substrate-host-guest aggregate (see E_{SHG} above). All these quantities are given in Table S1 and S2.

$\Delta\Delta H_{ads(guest)}^{CCWvsCW}$, $\Delta\Delta E_{HG_inter}^{CCWvsCW}$, $\Delta\Delta E_{SG_bind}^{CCWvsCW}$ and $\Delta\Delta E_{G_conf}^{CCWvsCW}$ differentials were calculated by subtracting corresponding energy of CW aggregate from the energy of CCW aggregate (e.g. $\Delta\Delta E_{HG_inter}^{CCWvsCW} = \Delta E_{HG_inter}^{CCW} - \Delta E_{HG_inter}^{CW}$). They were used in the construction of graph in Figure 6 and in the discussion of the nature of enantioselectivity of cDBA-OC12(*S*) adsorption (discussed below). All these quantities are given in Table S3.

Results and discussion

Model systems and methodology. We investigated host-guest co-assemblies of different host DBAs (Figure 1a) with the same chiral guest cDBA-OC12(*S*). This allowed varying the size of the hexagonal nanowells of the DBA networks (~1 - 6.5 nm side-to-side distance). DBAs with n-alkoxy chains containing an odd number of carbons ('odd DBAs') were not used since they are more prone to form distorted nanowells compared to 'even DBAs'.³²

1-Phenyl octane (PO) is the optimal solvent for this study since it facilitates both the formation of porous host networks as well as host-guest co-assembly.²⁸⁻²⁹ As deposition protocol, we used the sequential deposition method in which first an adlayer of an achiral DBA molecule was formed at the PO/HOPG interface, followed by the addition of cDBA-OC12(*S*) (see Methods section).

This assures that cDBA-OC12(*S*) is primarily adsorbed in the nanowells, rather than forming self-assembled domains and phase separate.

With the sequential deposition method at room temperature, the incorporation of chiral molecules (i.e. the formation of chiral sergeants) is impossible for DBA-OC6, DBA-OC8 and DBA-OC10 networks due to distortions that each cDBA-OC12(*S*) sergeant would cause replacing much smaller DBA molecules. In addition, incorporation of the chiral molecules is also unlikely for DBA-OC14, DBA-OC16 and DBA-DA25 networks due to unfavorably small cDBA-OC12(*S*) adsorption energy compared to the energy of larger DBA molecules. In the case of DBA-OC12 network, the incorporation of cDBA-OC12(*S*) is greatly diminished by the use of sequential deposition protocol.³³ Thus, chirality induction *via* the *sergeant-soldiers* mechanism is essentially suppressed, allowing us to focus exclusively on the efficiency of the host-guest chirality induction pathway.

Host-guest interactions in DBA assemblies are concentration dependent²⁸ and are different for different DBAs. Concentrations of the achiral host DBAs were optimized to lead to a maximum surface coverage of hexagonal nanowells (Table 1). This was particularly important in the case of larger DBAs: DBA-OC14, DBA-OC16, and DBA-DA25, since their alkyl chains are so long that the concentration window for the formation of porous networks is limited. It was found that even under very dilute solution concentration (5.0×10^{-7} M), the surface coverage of linear polymorphs before annealing was as large as $61 \pm 21\%$, $68 \pm 19\%$, $52 \pm 25\%$ for DBA-OC14, DBA-OC16 and DBA-DA25, respectively (Figure 2a-c), in phenyloctane. Nevertheless, the concentration of 5.0×10^{-7} M was determined to be optimal for these larger DBAs, since further dilution can significantly reduce the surface coverage (area of the substrate not covered by DBA networks increase) of these DBAs. Once the host network is formed, the sequential addition of chiral molecules does not affect

it: within one hour after addition of cDBA-OC12(*S*) solutions, no noticeable change in linear/porous ratio was observed.

Table 1. Guest occupancy (in %) and chirality induction in selected DBA-OC_{*n*}/cDBA-OC12(*S*) mixtures (sequential addition of equal volumes (20 μ L) of the respective solutions)

system	concentration ^a	% guest occupancy			homochiral induction after annealing?
		achiral DBA ^b	with cDBA CW	with cDBA CCW	
DBA-OC6	5.0×10^{-6} M	< 1	< 1	< 1	no
cDBA-OC12(<i>S</i>)	5.0×10^{-5} M				
DBA-OC8	5.0×10^{-6} M	< 1	< 1	< 1	no
cDBA-OC12(<i>S</i>)	5.0×10^{-5} M				
DBA-OC10	5.0×10^{-6} M	< 1	3 $\pm$ 1	18 $\pm$ 6	yes
cDBA-OC12(<i>S</i>)	8.0×10^{-6} M				
DBA-OC12	5.0×10^{-6} M	1 $\pm$ 1	1 $\pm$ 1	33 $\pm$ 1	yes
cDBA-OC12(<i>S</i>)	5.0×10^{-7} M				
DBA-OC14	5.0×10^{-7} M	65 $\pm$ 3	80 $\pm$ 3	90 $\pm$ 3	yes
cDBA-OC12(<i>S</i>)	5.0×10^{-7} M				
DBA-OC16	5.0×10^{-7} M	90 $\pm$ 4	90 $\pm$ 4	96 $\pm$ 4	yes
cDBA-OC12(<i>S</i>)	5.0×10^{-7} M				
DBA-DA25	5.0×10^{-7} M	95 $\pm$ 4	96 $\pm$ 4	96 $\pm$ 4	no
cDBA-OC12(<i>S</i>)	5.0×10^{-6} M				

^aThe concentrations of the solutions used to deposit on graphite. ^bAchiral DBA guest occupancy was measured for both CW and CCW nanowells, since achiral DBAs do not show enantioselective guest adsorption, as has been verified for DBA-OC12.^[15]

To probe the efficiency of the host-guest chiral induction process, after the initial room temperature study (~1-2 h), the sample is slowly (2 $^{\circ}$ C/min) heated, annealed to 80 $^{\circ}$ C, and then slowly cooled down (2 $^{\circ}$ C/min) to room temperature, followed by STM imaging.

For consistency, the efficiency of chirality induction is calculated taking into account homochiral hexagonal nanowells only, ignoring distorted nanowells and linear assemblies. In the optimization experiments, the concentration of cDBA-OC12(*S*) was increased ($C_{\text{chiral dopant}} \leq 10 \times C_{\text{achiral host}}$) until either reaching successful chiral induction of the host or observing major part of the surface (>60%) being covered by pure cDBA-OC12(*S*) assemblies after annealing (*vide infra*).

Figure 2. Self-assembled monolayers formed from a mixture of (a) DBA-OC14, (b) DBA-OC16, and (c) DBA-DA25 with cDBA-OC12(*S*) at the 1-phenyloctane/HOPG interface obtained at room temperature (deposition of 20 μL of an achiral DBA (5×10^{-7} M) followed by addition of 20 μL of the chiral cDBA-OC12(*S*) (5×10^{-7} M)). The linear polymorph is highlighted in red. Tunneling parameters: $I_{\text{set}} = 0.2$ nA and $V_{\text{bias}} = -0.2$ V.

Preferential adsorption and chiral induction experiments. cDBA-OC12(*S*)/DBA-OC12 was the first system for which enantioselective guest adsorption and guest-host chirality induction were demonstrated.²⁷⁻²⁸

Smaller DBA-OC10 nanowells are less apt to accommodate cDBA-OC12(*S*) guests.²⁷⁻²⁸ At 5.0×10^{-7} M concentration of cDBA-OC12(*S*), there are <1% guests in both CW and CCW nanowells of DBA-OC10 (Figure 3a). As a consequence, no homochiral induction was observed after annealing. Increasing the cDBA-OC12(*S*) concentration from 5.0×10^{-7} M to 8×10^{-6} M yielded clear enantioselectivity in guest adsorption (Figure 3b). Annealing such system resulted in homochiral CCW DBA-OC10 networks (Figure 3c). At room temperature, the occupancy of CCW nanowells before ($18 \pm 6\%$) and after annealing ($14 \pm 5\%$) are similar within error.

Figure 3. Representative STM image of the DBA-OC10/cDBA-OC12(*S*) system at the 1-phenyloctane/HOPG interface. (a) Sequential deposition of DBA-OC10 (20 μL , 5.0×10^{-6} M, 1-phenyloctane) followed by cDBA-OC12(*S*) (20 μL , 5.0×10^{-7} M, 1-phenyloctane). (b) Sequential deposition of DBA-OC10 (20 μL , 5.0×10^{-6} M, 1-phenyloctane) followed by cDBA-OC12(*S*) (20 μL , 8.0×10^{-6} M, 1-phenyloctane). White dashed lines indicate domain borders. Yellow and green circles highlight the guests in CW and CCW nanowells, respectively. The corresponding image

without coloured markers is provided in Supplementary Figure S4. (c) CW homochiral surface obtained after slow annealing of (b). $I_{\text{set}} = 0.2 \text{ nA}$ and $V_{\text{bias}} = -0.2 \text{ V}$.

Further decrease in the size of the nanowells (DBA-OC8 and DBA-OC6 hosts) results in the suppression of stable host-guest interactions with the chiral guest (Figure 4a,b): there is no enantioselective adsorption, and the guest occupancy of both CW and CCW nanowells is as low as that of auto-host-guest in pure DBA-OC6 and DBA-OC8 assemblies ($<1\%$, Table 1). The annealing resulted in domain ripening with no noticeable chirality induction (Figure 4c,d). Actually, after annealing the surface is only covered by the achiral molecules, even when a 10 fold excess of cDBA-OC12(*S*) is used. Thus, DBA-OC10 self-assembly is the smallest DBA host tested for which preferential adsorption and chirality induction by cDBA-OC12(*S*) guest are experimentally observed.

Figure 4. (a) 1:1 sequential addition of DBA-OC6 ($5.0 \times 10^{-6} \text{ M}$) followed by cDBA-OC12(*S*) ($5.0 \times 10^{-5} \text{ M}$) imaged at room temperature at the 1-phenyloctane/HOPG interface. (b) 1:1 sequential addition of DBA-OC8 ($5.0 \times 10^{-6} \text{ M}$) followed by cDBA-OC12(*S*) ($5.0 \times 10^{-5} \text{ M}$)

imaged at room temperature at the 1-phenyloctane/HOPG interface. (c, d) Homochiral surfaces were not obtained after annealing of sample (a) and (b), respectively. cDBA-OC12(S) molecules are not adsorbed. $I_{\text{set}} = 0.2$ nA and $V_{\text{bias}} = -0.2$ V.

Contrary to DBA-OC6 and DBA-OC8, a large majority of the nanowells formed from DBA-OC14 or DBA-OC16, prior to addition of cDBA-OC12(S), are occupied by the achiral molecules themselves (without any preference for CW or CCW nanowells). The monolayers of pure DBA-OC14 and DBA-OC16 assemblies show large guest adsorption of 65% and 90%, respectively (Figure S5a-d; 2.5×10^{-7} M). Under similar conditions, the introduction of cDBA-OC12(S) changes the guest occupancy in favor of CCW nanowells (Table 1). The appearance of guest molecules is not uniform. We arbitrarily divide them into ‘fixed’ (with the bright aromatic core of the guest visible) and ‘fuzzy’ (when STM contrast confirms the presence of an adsorbate in the nanowells, however, no individual feature of the guest can be identified) (Figure S6).²⁷ Interestingly, increase in the guest occupancy of CCW nanowells upon the addition of cDBA-OC12(S) is primarily associated with the increase of ‘fixed’ guests (by $\sim 4\%$ and 5% for DBA-OC14 and DBA-OC16, respectively). The annealing of these samples leads to the enantioselective ripening where only CCW nanowells are present on the surface (i.e. 100% chiral induction, Figure S7). In addition, after annealing, the surface coverage of linear polymorphs was decreased to $24 \pm 14\%$ and $52 \pm 25\%$ for DBA-OC14 and DBA-OC16, respectively.

As the largest DBA host in this study, we investigated the possibility of enantioselective adsorption and chirality induction in DBA-DA25 self-assembly. Similar to DBA-OC14 and DBA-OC16, DBA-DA25 also adsorbs in its own nanowells (Figure S5 e,f). Here, up to 95% of CW and CCW nanowells are filled. The addition of cDBA-OC12(S) (5×10^{-7} M) does not result in any noticeable change in guest occupancy (Figure 5a). Interestingly, some nanowells appear to have

more than one ‘fixed’ guest (Figure 5b-d). After annealing, both CW and CCW nanowells of DBA-DA25 remain on the surface, while the coverage of linear polymorph decreases to $21 \pm 16\%$. Increasing the concentration of the chiral guest ($\times 10$ times molar ratio, Table 1) does not lead to homochiral DBA-DA25 self-assembly but instead yields a surface covered by cDBA-OC12(S) with random inclusions of small CW and CCW domains of DBA-DA25 (Figure 5e).

Figure 5. a) Representative STM image of a monolayer obtained after addition of a tenfold excess of cDBA-OC12(S) (20 μ L, 5.0×10^{-6} M, 1-phenyloctane) onto a preformed monolayer of DBA-DA25 (20 μ L, 5.0×10^{-7} M, 1-phenyloctane). (b-d) Enlarged STM images focused on a single hexagonal nanowell of DBA-DA25, in which up to 3 guest molecules can be observed. (e) A surface covered by cDBA-OC12(S) self-assembly with random inclusions of small CW and CCW domains of DBA-DA25 after annealing (a) to 80 $^{\circ}$ C. White dotted lines indicate domain boundaries. $I_{\text{set}} = 0.2$ nA and $V_{\text{bias}} = -0.2$ V.

Insights into the mechanism of chiral recognition and chirality transfer. All experimental observations mentioned in the previous section should be analyzed in the view of *chiral recognition - chirality transfer* concepts (or their equivalents: *preferential adsorption - chirality induction*). With sergeant-soldiers mechanism being suppressed for these systems, the chirality

induction *via* host-guest mechanism becomes the main pathway for the chirality transfer from the chiral cDBA-OC12(*S*) guests (molecular chirality) to the host DBA network (supramolecular chirality). Such chirality transfer involves two steps: 1) chiral recognition of supramolecular nanowells by the chiral guest (i.e. the preferential adsorption of the guest in CW or CCW domains, depending on the molecular chirality of the guest) that lifts off the thermodynamic degeneracy between supramolecular enantiomers CW and CCW domains of the host network, and 2) 2D crystal ripening in which thermodynamically more stable domains grow at the expense of the thermodynamically less stable ones. Thus, for chirality induction to occur, the chiral guest should be able to adsorb in the nanowells of the host network, and do this preferentially in only one of two chiral nanowells.

Both requirements are met for DBA-OC10, DBA-OC12, DBA-OC14 and DBA-OC16 host systems. Indeed, in all four assemblies, the addition of cDBA-OC12(*S*) increased the occupancy of the nanowells, with particular preference for those with CCW supramolecular chirality. On the other hand, the chirality induction should not occur if the chiral guest does not adsorb in the nanowells *or* if it adsorbs equally well in CW and CCW nanowells of the host. Very low guest occupancy in DBA-OC8/cDBA-OC12(*S*) and DBA-OC6/cDBA-OC12(*S*) corroborates the failure of chirality transfer due to the very low (if any) adsorption of the chirality inducer (cDBA-OC12(*S*) guests). Defining the exact origin of a similar failure for DBA-DA25/cDBA-OC12(*S*) system is problematic, since, it was not possible to determine the occupancy of cDBA-OC12(*S*) guests in CW and CCW nanowells. Two regimes can be envisioned: a) at low concentrations of cDBA-OC12(*S*), the adsorption of cDBA guests is negligible, and instead, the auto-host-guest binding prevails; and b) at high concentrations of cDBA-OC12(*S*) the occupancy of the chiral guests should increase, however, considering that both CW and CCW domains were found after annealing such

samples, the adsorption of the chiral guests in DBA-DA25 nanowells must be lacking enantioselectivity.

To gain structural insights into the origins of the observed enantioselectivity (or its absence) we performed molecular mechanics calculations of model host-guest complexes using MM+ force field³¹. Due to complexity of the systems, neither entropy / Gibbs free energy nor solvation effects were considered in this modeling. While molecular mechanics calculations usually do not have sufficient precision to operate with absolute values of energies they, nevertheless, can provide reasonably accurate trends/relationships for the thermodynamic stability of chemically similar systems.³² Thus, the above mentioned size-dependence of host-guest interactions is also reflected in guest adsorption enthalpy- $\Delta H_{\text{ads}}(\text{guest})$, corroborating the increase of cDBA-OC12(*S*) adsorption in the order: DBA-OC6 < DBA-OC8 << DBA-OC10 < < DBA-OC14 $\cong$ DBA-OC16 $\cong$ DBA-DA25 < DBA-OC12 (Figure 6 and Table S2).

Figure 6. MM+ optimized molecular models and estimated enthalpies $\Delta H_{\text{ads}}(\text{guest})$ of cDBA-OC12(S) guest adsorption in selected DBA nanowells. Different orientations of the guest molecules were probed to ensure that global minimum is reached. The graph (bottom right corner) illustrates the relative importance and specific contributions of the host-guest interactions, substrate-guest binding and guest conformational distortions to the enthalpy of adsorption of cDBA-OC12(S) guest in CCW and CW nanowells. Here, energy differentials were calculated for each host-guest diastereomeric pair by subtracting values for CW co-assemblies from corresponding energy values for CCW co-assemblies, e.g. red data points represent the differences $\Delta\Delta H_{\text{ads}}(\text{cDBAOC12(S)})^{\text{CCWvsCW}} = \Delta H_{\text{ads}}(\text{cDBAOC12(S)})^{\text{CCW}} - \Delta H_{\text{ads}}(\text{cDBAOC12(S)})^{\text{CW}}$.

Direct comparison ($\Delta\Delta H_{\text{ads}}(\text{cDBAOC12}(S))^{\text{CCWvsCW}}$, Figure 6, Figure S3) of the enthalpies of guest adsorption in CCW and CW enantiomeric networks shows a preference of cDBA-OC12(*S*) to adsorb in CCW nanowells for all tested DBA hosts. Notably, the hosts that failed at chiral recognition and induction in experiments also had the smallest magnitude of $\Delta\Delta H_{\text{ads}}(\text{cDBAOC12}(S))$: -1.6 kcal/mol, -3.3 kcal/mol and -2.8 kcal/mol for DBA-OC6, DBA-OC8 and DBA-DA25, respectively. Even in one of its most compact conformations²⁷, the dimensions of cDBA-OC12(*S*) guest are too large to get inside of the DBA-OC8 and DBA-OC6 nanowells, DBA-OC10 can fit cDBA guest only partially, DBA-DA25, DBA-OC16 and DBA-OC14 have sub-optimal (compared to DBA-OC12 host) interactions with the guest due to the host being larger than cDBA guest (Figure 6).

Supramolecular chirality of the hosts (CW or CCW) and intrinsic chirality of cDBA-OC12(*S*) guest yield pairs of diastereomeric host-guest networks in which not only host-guest interactions, but also guest conformation and binding to the underlying graphite differ. Only CCW DBA-OC12 host had all three components better than its CW enantiomer, thus reflecting close-to-optimal fit between cDBA-OC12(*S*) guests and CCW- DBA-OC12 nanowells. For all other tested hosts simultaneous enantioselective improvement of host-guest, substrate-guest and guest conformation contributions is not possible (graph in Figure 6 and Table S3): e.g. the improvement of guest binding to the substrate in the case of CCW DBA-OC10 host was accompanied by inferior (compared to the corresponding host-guest assembly of CW DBA-OC10 host) guest conformation and host-guest interactions.

Finally, we would like to mention that the chirality induction is influenced not only by the difference in the thermodynamic stability of diastereomeric host-guest adlayers (defining the direction of ripening), but also by their desorption-adsorption kinetics (defining the rate of

ripening). As pointed out by one of the reviewers, it is possible that cDBA-OC12(*S*) molecules hinder the desorption of their hosts, thus improving the kinetic stability of the latter compared to the adsorption-desorption dynamics in the guest-free enantiomeric networks. Initial work on the adsorption-desorption measurements in such host-guest systems is done and will be presented elsewhere.

Conclusions

We have investigated the efficiency of chiral recognition and chirality induction processes in several host-guest systems formed at the liquid/solid interface. Host-guest systems and experimental conditions were carefully chosen in such a way as to maximally suppress the chirality induction *via* the *sergeant-soldiers* mechanism while allowing for the host-guest chiral induction pathway. We found that the induction takes place only when guest occupancy is sufficiently high and enantioselective. Thus, cDBA-OC12(*S*) failed to induce chirality not only in DBA-OC6 and DBA-OC8 hosts for which it is too large to fit as a guest, but also in DBA-DA25. In the latter case, cDBA-OC12(*S*) guest is too small to compete with non-enantioselective auto-host-guest adsorption of achiral DBA-DA25. Furthermore, DBA-DA25 nanowells are so large that they can easily accommodate cDBA-OC12(*S*) in fully stretched conformation - the least suitable for the recognition and transfer of chiral information between DBA hosts and guests.

We anticipate that the methodology and findings presented in this work will aid in future studies of chirality at interfaces and, in particular, in the improved rational design of more efficient enantioselective host-guest systems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the [ACS Publications website](#) at DOI:

Additional STM images and molecular models.

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Notes

The authors declare no competing financial interest.

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