Organization of the Enantiomeric and Racemic Forms of an Amphiphilic Resorcinol Derivative at the Air-Water and Graphite-1-Phenvloctane Interfaces

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This article describes a study of the outcome of racemate condensation in dif-ABSTRACT ferent types of monolayers. The study was performed on a resorcinol surfactant bearing an octadecyl chain and a lactate group which formed a monolayer at the interface of graphite and 1phenyloctane as well as a Langmuir film at the air-water interface. Control experiments with the enantiopure materials provided the characteristics of the chiral organizations. The results obtained on the racemate show that on graphite the molecule forms chiral domains, indicating that spontaneous resolution takes place at the surface, a phenomenon that has been rationalized using molecular modeling. The X-ray crystal structure of the DMSO solvate of one of the enantiomers shows a similar type of packing to this monolayer. On the other hand, in the Langmuir layer it appears that the formation of a racemic compound is favoured, as it is in the solid state in three dimensions. The work shows how the symmetry restrictions in different environments can have a critical influence on the outcome of racemate organization, and underline the tendency of graphite to favour symmetry breaking in monolayers formed at its surface. Chirality 24:155–166, 2012. © 2011 Wiley Periodicals, Inc.

KEY WORDS: spontaneous resolution; conglomerate; STM; lactate; langmuir; SAM; SFG; molecular modeling

INTRODUCTION

The factors that determine whether racemic mixtures of amphiphiles self-assemble into either homo- or heterochiral monolayer domains on a surface in the form of two-dimensional crystals are mainly based on symmetry arguments.^{1,2} The most common symmetry elements in 3D crystals are the centre of inversion, glide plane, 2-fold screw axis and translation operators.^{3,4} The first two of these-which are the most common-are associated with racemic crystals. In a 2D system a surface cannot possess a centre of inversion and can only maintain translation, rotation and reflection mirror symmetry planes normal to the surface.

In addition to the reduced symmetry possibilities in the presence of a substrate, the balance between adsorbate-substrate interactions and adsorbate-adsorbate interactions plays a role.5 Should the adsorbates have any specific interaction with the surface then symmetry of the surface plays a fundamental role in the possible packing modes of a molecule upon it. So the ability to form a racemic conglomerate will depend on the nature of the substrate because of symmetry, molecular orientation, and the strength of the molecule-surface and molecule-molecule interactions.

The symmetry elements open to molecules which pack coplanar with a surface are quite different to that of amphiphiles at a surface. The basal plane of graphite, comprised of the familiar hexagonal net of carbon-carbon bonds, does

impose restrictions on the symmetry operations open to certain molecules which pack on top of it. The most frequently encountered structural feature of adsorbents to graphite is a long alkyl chain.⁶ The reason for this trait is that saturated *n*alkyl chains form a series of $[C-H\cdots\pi]$ interactions between the methylene groups of the hydrocarbon and the aromatic rings of the graphite, which encourages these chains to lie parallel to the carbon surface.⁷ However, the moieties which are attached to the alkyl chains in physisorbed systems play a definite role in the packing of the monolayers: the symmetry and number of alkyl chains can lead to different packing

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forms and, if the cores interact strongly, their orientation relative to the substrate can be influenced.⁸ So when the whole molecule does not follow the graphite axes, but orients with a certain angle with respect to them, the glide plane symmetry is eliminated.

We chose molecule **1** as an example to probe spontaneous resolution because the 1,3 substitution pattern at the benzene ring should break strict linearity and therefore pack in a nontrivial way. The long alkyl chain ensures absorption to graphite while also helping in the formation of Langmuir layers. The source of chirality is the lactate group. At the graphite–1-phenyloctane interface, we will show that the system displays spontaneous resolution, while in Langmuir layers it appears that a racemic compound is formed. These data are put into the context of the X-ray crystal structure of the compound.



MATERIALS AND METHODS General Methods

Reagents and starting materials were used as obtained from SDS, Fluka, Aldrich Chemical and Merck. Acetonitrile (MeCN) was distilled over phosphorous pentoxide under a nitrogen atmosphere. Tetrahydrofuran was distilled over metallic sodium under an inert atmosphere. Silica gel 60 (35–70 mesh, SDS) was used for column chromatography. NMR measurements were performed using a Bruker Avance 250-MHz spectrometer. The reference used in the spectra was either tetramethylsilane or solvent residue. IR measurements were done using a Perkin Elmer Spectrum One Fourier transform spectrometer.

3-(Octadecyloxy)phenyl benzoate (2). Predried and ground K₂CO₃ (8.30 g, 25 mmol) was suspended in MeCN (170 mL) in a two neck round bottom flask and the mixture was degassed with a flow of nitrogen for 30 minutes. Resorcinol monobenzoate (5.00 g, 23 mmol) was added as a solid and the resulting mixture was heated to reflux temperature all under nitrogen. After thirty minutes, the reaction mixture was cooled, and 1-bromooctadecane (93 mmol) was introduced as a liquid. The temperature of the mixture was then raised to gentle reflux, and these conditions were maintained for 48 hrs. The reaction mixture was filtered at the pump while it was still warm, and the residual solid was washed with MeCN. After twenty minutes at the pump crystals had started to form in the liquid. After a further thirty minutes at the pump the solution was filtered and the crystals were collected under gravity filtration and then dried on a vacuum pump after being washed with cold MeCN. A further crop of crystals was obtained by evaporating some of the acetonitrile in a rotary evaporator and then allowing the resulting solution to stand for a while in air. The total amount of crystal of (2) obtained was 6.50 g (56% yield).

m.p.: 68°C; MALDI-TOF/MS m/z (%) (α CN matrix): 466.54 (100) [M]⁺ Calc. for C₃₁H₄₆O₃; 466.70; ¹H NMR (250 MHz, CDCl₃): 8.22-8.18 (m, 2H, ArH), 7.64-7.61 (m, 1H, ArH), 7.54-7.48 (m, 2H, ArH), 7.31-7.26 (m, 1H, ArH), 6.84-6.76 (m, 3H, ArH), 3.96 (t, J = 6.5, 2H, $-OCH_2(CH_2)_{16}CH_3$), 1.82-1.74 (m, 2H, $-OCH_2CH_2(CH_2)_{15}CH_3$, 1.44-1.40 (m, 2H, $-O(CH_2)_2CH_2$ (CH₂)₁₄CH₃), 1.29 (m, 28H, $-O(CH_2)_3(CH_2)_{14}CH_3$), 0.88 (t, J = 13.2, 3H, $-O(CH_2)_{17}CH_3$ ppm. FTIR (KBr): 2917 (s, CH₂), 2849 (s, CH₂), 1735 (s, CO), 1600 (m, phenyl), 1491 (m, Phenyl), 1470 (m), 1268 (m), 1242 (s), 1143 (s), 1171 (m),1063 (m), 889 (w), 775 (w), 709 (m), 681 (w) cm⁻¹. **3-(Octadecyloxy)phenol (3).** To a solution of 3-(octadecyloxy)phenyl benzoate (2) (4.00 g, 8.57 mmol) in methanol (50 mL) sodium hydroxide (2N, 1.2 mL, 25.71 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was concentrated, diluted with 30 mL of water and was acidified to pH 2 with hydrochloric acid (2N). The mixture was extracted with dichloromethane and the organic layers were combined and dried over sodium sulfate. The organic solution was filtered and concentrated to give a white solid. The residue was purified by flash chromatography (SiO₂, EtOAc/n-Hexane 1:3) to give **3** as white solid (2.50 g, 80% yield).

m.p.: 69°C; MALDI-TOF/MS (α CN) m/z (%): 362.45 (100) [M]⁺. Calc for C₂₄H₄₂O₂; M_{w} : 362.59; ¹H NMR (250 MHz, CDCl₃): 7.19-7.08 (m, 1H, ArH), 6.51-6.40 (m, 3H, ArH), 5.02 (s, 1H, ArOH), 3.92 (t, J = 6.5, 2H,O<u>CH₂(CH₂)₁₆CH₃), 1.79-1.71 (m, 2H, $-OCH_2CH_2(CH_2)_{15}CH_3$), 1.81-1.71 (m, 2H, $-OCH_2CH_2(CH_2)_{15}CH_3$), 1.37-1.42 (m, 2H, $-O(CH_2)_2CH_2$ (CH₂)₁₄CH₃), 1.27 (m, 28H, $-O(CH_2)_3(CH_2)_{14}CH_3$), 0.89 (t, J = 13.1, 3H, $-O(CH_2)_{17}CH_3$) ppm. FTIR (KBr): 3346 (m, OH), 2917 (s, CH₂), 2849 (s, CH₂), 1599 (m, phenyl), 1504 (m, phenyl), 1463 (m), 1382 (w), 1285 (m), 1226 (w), 1186 (m), 1154 (m), 683 (w) cm⁻¹.</u>

(*R*)-Methyl 2-(3-(octadecyloxy)phenoxy)propanoate ((R)-4). 3-(Octadecyloxy)phenol (3) (3.11 g, 8.58 mmol), (S)-methyl lactate (983 μ L, 10.29 mmol) and triphenyl phosphine (2.70 g, 10.29 mmol) were dissolved in dry THF (70 mL) with stirring under an atmosphere of nitrogen and the mixture was cooled in an ice–salt bath. A solution of diisopropylazodicarboxylate (DIAD, 2.03 mL,10.29 mmol) in THF (5 mL) was added drop wise over a period of 30 minutes and the mixture was stirred overnight. After addition of water 20 ml, THF was removed in vacuum and the residue was partitioned between CH₂Cl₂ and water. The aqueous phase was extracted once more with CH₂Cl₂. The combined organic phases were dried over sodium sulfate, filtered and stripped of solvent. The residue was purified by column chromatography (SiO₂, CH₂Cl₂/*n*-Hexane 1:1) to give (*R*)-4 as a white solid (2.44 g, 62% yield).

m.p.: 49°C; MALDI-TOF/MS m/z (%) (α CN): 448.67 (100) [M]⁺, Calc. for C₂₈H₄₈O₄; M_w : 448.36; [α]₅₄₆ = +5.9 deg cm² g⁻¹ (c = 50 mM, CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃): 7.14 (t, J = 8.2, 1H, ArH), 6.54-640 (m, 3H, ArH), 4.76 (q, J = 6.8, 1H, $-OCHCH_3COOMe$), 3.91 (t, J = 6.7, $-OCH_2(CH_2)_{16}CH_3$) 3.76 (s, 3H, $-OCHCH_3COOMe$), 1.79-1.73 (m, 2H, $-OCH_2CH_2(CH_2)_{15}CH_3$), 1.61 (d, J = 6.6, 3H, $-OCHCH_3COOMe$), 1.49-1.39 (m, 2H, $-O(CH_2)_2CH_2$ (CH₂)₁₄CH₃), 1.26 (m, 28H, $-O(CH_2)_3(CH_2)_{14}CH_3$), 0.88 (t, \overline{J} = 0.03, 3H, $-O(CH_2)_{17}CH_3$ ppm. FTIR (KBr): 2917 (s, CH₂), 2849 (s, CH₂), 1731 (m, CO), 1606 (m, phenyl), 1588 (m, phenyl), 1492 (m), 1471 m), 1334 (w), 1284 (m), 1263 (m), 1181 (m), 1155 (m), 1052 (m), 835 (w), 718 (w), 685 (w), 770 (w), 718 (w), 685 (w) cm⁻¹.

(*S*)-Methyl 2-(3-(octadecyloxy)phenoxy)propanoate ((*S*)-4). This compound was prepared in an identical manner to its enantiomer, but employing (*R*)-methyl lactate as the starting material. All analytical data was identical to that of the enantiomer except $[\alpha]_{546} = -5.7 \text{ deg cm}^2 \text{ g}^{-1}$ (c = 0.075 M, CH₂Cl₂).

(*R*)-2-(3-(Octadecyloxy)phenoxy)propanoic acid ((*R*)-1). To a solution of (*R*)-methyl 2-(3-(octadecyloxy)phenoxy)propanoate (*R*)-4 (1.20 g, 2.68 mmol) in methanol (30 mL) was added sodium hydroxide (aq, 2N, 4 mL) and the mixture stirred overnight at room temperature. The reaction mixture was concentrated, diluted with water and acidified to pH2 with 2N hydrochloric acid. The precipitate was filtered and washed with water. (*R*)-1 was obtained as a white solid (1.13 g, 95% yield).

m.p.: 80°C; MALDI-TOF/MS m/z (%) (α CN): 434.73 (100) [M]⁺. Calc. for C₂₇H₄₆O₄; 434.65; [α]₅₄₆ = +6.5 deg cm² g⁻¹ (c = 0.046M, MeOH); ¹H NMR (250 MHz, d_6 DMSO): 7.16 (t, J = 8.0, 1H, ArH), 6.53–6.41 (m, 3H, ArH), 4.80 (q, J = 6.7, 1H, -OCHCH₃COOMe), 3.92 (t, J = 6.1, 2H, -OCH₂(CH₂)₁₆CH₃), 1.70-1.66 (m, 2H, -OCH₂CH₂(CH₂)₁₅CH₃), 1.49 (d, \overline{J} = 6.7, 3H, -OCHCH₃COOMe), 1.48–1.39 (m, 2H, -O(CH₂)₂CH₂ (CH₂)₁₄CH₃), 1.25 (m, 28H, -O(CH₂)₃(CH₂)₁₄CH₃), 0.87-0.84 (m, 3H, -O(CH₂)₁₇CH₃); FTIR (*KBr*): 3137 (w, OH), 2918 (s, CH₂), 2849 (s,

TABLE 1. Crystallographic data of (S)-1 crystals

Empirical formula	C ₂₉ H ₅₂ O ₅ S	β (°)	91.970(3)
Formula weight	512.77	γ (\circ)	90.704(3)
Color	Colorless	Volume (Å ³)	1532.74(14)
Crystal size (mm ³)	0.4 imes 0.3 imes 0.02	Z	2
Temperature (K)	233(2)	Calculated density (g/cm ³)	1.111
Radiation wavelength (Å)	ΜοΚα 0.71073	F (000)	564
Crystal system	Triclinic	Theta range for data collection (°)	2.55-22.99
Space group	P 1 (no. 1)	Reflections collected	4870
a (Å)	5.4669(3)	Reflections observed, $I > 2\sigma$	4216
b (Å)	7.9950(4)	Parameters	644
c (Å)	35.095(2)	Restriction	0
α (°)	90.813(3)	R1 for $I > 2\sigma$ (I)	0.0439

CH₂), 1708 (m, CO), 1666 (w, CO), 1613 (m, phenyl), 1582 (m, phenyl), 1494 (m), 1470 (m), 1332 (m), 1287 (m), 1233 (m), 1186 (m), 1173 (m), 1039 (m), 853 (w), 756 (w), 720 (w), 683 (w) cm⁻¹; UV–vis (CHCl₃) λ_{max} /nm (ϵ /mol L⁻¹ cm⁻¹): 201 (18,040), 274 (1240); Calculated for C₂₇H₄₆O₄: C 74.61%, H 10.67%, found: C 74.60%, H 10.74%.

(S)-2-(3-(Octadecyloxy)phenoxy)propanoic acid ((S)-1). This compound was prepared in an identical manner to its enantiomer, but employing (S)-4 as the starting material. All analytical data was identical to that of the enantiomer except $[\alpha]_{546} = -6.9 \text{ deg cm}^2 \text{ g}^{-1}$ (c = 75 mM, CH₂Cl₂). The compound was crystallized by slow evaporation from DMSO obtaining nice needle-like crystals. Crystallographic data are given in Table 1.

Scanning Tunnelling Microscopy

STM images presented here were obtained at the liquid-solid interface using a PicoSPM (Agilent). STM tips were mechanically cut from Pt/Ir wire (80%/20%, diameter 0.25 mm). Highly oriented pyrolytic graphite (HOPG, grade ZYB, Advanced Ceramics, Cleveland, OH) was used as a substrate. A 7.6×10^{-3} M solution of the pure enantiomers was prepared in 1-phenyloctane (Aldrich, 99%) and heated for about 10 minutes at 70°C before applying a drop of one of these enantiomer solutions to the basal plane of freshly cleaved HOPG. In case of the 1:1 mixture, the concentration of each of the enantiomers is 3.8×10^{-3} M. After about half an hour, the STM tip was immersed into the solution and scanned in the variable height mode. The setpoint current (I_{set}) is typically smaller than 0.3 nA. The bias voltage was (V_{bias}) applied to the sample in such a way that at negative bias voltage electrons tunnel from the sample to the tip. For analysis purposes, the imaging of a molecular layer was immediately followed by recording at a lower bias voltage and higher setpoint current the graphite lattice, under otherwise identical experimental conditions. Drift effects were corrected for using scanning probe image processor (SPIP) software (Image Metrology ApS). Note that only images containing a small drift were used for analysis.

Langmuir Layer Preparation

Langmuir films were obtained spreading an aliquot of the materials (30 μ l, 2.3 mM) dissolved in CHCl₃ (Chemolab) on the surface of ultrapure water held in a Teflon trough (NIMA Technology, 611D). The water used for the subphase was obtained from a Millipore system (18.2 M Ω cm resistivity). The subphase temperature was controlled within $\pm 0.5^{\circ}$ C by a thermostat. After complete evaporation of the organic solvent (10 min) the compression was initiated at a speed of 50 cm² min⁻¹. Molecular area isotherms were obtained under continuous compression in the trough. Surface pressures were measured with a Wilhelmy plate balance. The isotherms reported are the average of at least three experiments. Measurements on water-subphase were performed at different pH values in the range 2–10. A Brewster Angle Microscope (NIMA, MiniBAM) with a video mounted on the Langmuir film balance was used for the visualization of monolayer.

Langmuir-Blodgett Films

By the correct choice of the subphase pH value (pH at 5.6) and surface pressure (18 mN m⁻¹) Langmuir films were deposited by vertical lifting at a speed of 10 mm min⁻¹. The glass substrates (10 mm by 14 mm) were cleaned in chromic acid, and soaked in piranha solution (H_2O_2/c oncentarted H_2SO_4 1:2) before monolayer preparation. They were washed several times with copious amounts of deionized water and finally sonicated in ethanol for 15 minutes.

Sum-Frequency Spectroscopy

Sum-frequency vibrational spectra were collected by an EKSPLA (Vilnius, Lithuania) sum-frequency spectrometer, described in detail in our earlier publications.⁹⁻¹¹ The visible beam (532 nm) is generated by doubling the fundamental output of a Nd:YAG laser (1064 nm wavelength, 20 ps pulse width, 20 Hz repetition rate). The tuneable IR beam is obtained from an optical parametric generation/difference frequency generation system, pumped by the third harmonic and the fundamental of the Nd:YAG laser. The IR and visible beams are temporally and spatially overlapped on the sample surface with incident angles of 55° and 60°, respectively. Beam energies were kept below 200 µJ. Sum frequency light is collected in the reflected direction through a holographic notch filter and monochromator, and detected by a photomultiplier tube. Spectral resolution is determined by the $<6 \text{ cm}^{-1}$ line width of the IR pulse. Spectra presented were measured using the ssp (s-polarized sum frequency, s-polarized visible, and p-polarized IR radiation), polarization combination. Spectra were collected in the 2800-3000 cm⁻¹ spectral region using 3 cm⁻¹ increments and 50 laser pulses at each step. Five spectra were collected and averaged.

Modeling

The modeling of the physisorbed layers was carried out using a molecular mechanics/molecular dynamics (MM/MD) approach. The DREID-ING¹² force field, as implemented in the FORCITE tool pack of Materials Studio, was used, since it is particularly adapted for an accurate description of the hydrogen bonding that promotes the self-assembly of the molecules. This joint MM/MD approach has been used to model the structure and energetics of self-assembled monolayers of (*S*)-resorcinol molecules on graphite. The initial geometries come from assembly models proposed on the basis of STM images; the calculations consisted in two steps of energy minimization, to relax possible geometrical constraints, followed by two subsequent MD simulation steps, first in the NVE ensemble (constant number of particles, volume and energy) for 500 ps, then in the NVT ensemble at 298K for 3 ns. The long-range nonbonded interactions were turned off with a cubic spline cutoff set at 18 Å.

RESULTS AND DISCUSSION Synthesis and X-Ray Structure

The synthetic route used for the preparation of the chiral amphiphilic derivative (S)-1 is shown in Scheme 1 (the synthesis of the *S* isomer only is shown), and its enantiomer was obtained using the same route but employing (S)-methyl



Scheme 1. Synthesis of compound 1.

lactate as the source of chirality. Reaction of commercially available resorcinol monobenzoate with 1-bromooctadecane in the presence of K_2CO_3 afforded the corresponding ether **2**. Deprotection of the phenol group with NaOH in MeOH gave **3** which was then reacted with both (*S*)-methyl lactate and (*R*)-methyl lactate giving (*R*)-**4** and (*S*)-**4** respectively. The last step was a hydrolysis conducted by using NaOH in MeOH which gave (*R*)-**1** and (*S*)-**1** which were characterized by polarimetry, NMR, FTIR, UV–vis, X-ray single crystal diffraction (vide infra) and MALDI TOF/MS. The racemic mixture was prepared by mixing equal amounts of the two enantiomers. The IR of the racemic mixture shows the single car-

bonyl adsorption at 1714 cm⁻¹ together with the O-H out of plane at 928 cm⁻¹. For a carbonyl group to appear at such low wavenumber is clearly consistent with a strong hydrogen bond. The relative broadness of the 928 cm⁻¹ band is characteristic of the centrosymmetric carboxyl dimer. The IR spectra of the enantiopure sample shows two differences with the racemate; first the carbonyl band is split into two bands at lower wavenumber (1706 and 1666 cm⁻¹), and second the OH wag is shifted to the lower wavenumber of 897 cm⁻¹. The less rigid OH group in the catemeric structure of the enantiopure derivative could explain the latter. The hydroxyl OH stretch gives a broad band at 3069 cm⁻¹.

The differential scanning calorimetry gave an exothermic peak at 80°C for both enantiomers and a peak at 120°C for the racemic mixture. The higher melting point for the equimolar mixture of the enantiomers is indicative of the formation of racemic compound in the solid.

Colorless needle-like crystals of (*S*)-1 were obtained by slow evaporation of a dimethyl sulfoxide (DMSO) solution. (*S*)-1/DMSO crystallizes in the trigonal *P*1 space group with two molecules of (*S*)-1 and two molecules of DMSO in the unit cell. An ORTEP representation of the head to tail arrangement of the molecules in the tapes formed by the alkyl chain van der Waals intersections is presented in Figure 1.

The two molecules of **1** in the unit cell adopt different conformations from one another. The alkyl chain is slightly twisted as it joins the phenyl ether group in one molecule while in the other the mean planes are virtually coplanar, as shown by the torsion angles C12-C11-C8-O4 and C39-C38-C35-O8 which are -70.4° and 178.8° . The β -methyl group in the lactate moiety lies approximately in the plane of the phenoxy group with the plane of the carboxylic acid residue anticlinically related. The angle between the phenyl group and the chiral substituent of each molecule in the unit cell is slightly different from each other: the C4-O3-C2-C1 torsion angle is 73.8° whereas C31-O7-C29-C28 measures 71.1° . The conformation of the lactate groups in this crystal structure is comparable to those of other phenyl derivatives.¹³⁻¹⁶

The acid OH group of each molecule is associated with the SO group of the nearest solvent molecule by strong hydrogen-bond (O2...O9 2.567 and O6...O10 2.549). The polar layer is reinforced by weak hydrogen-bonds (CH₃...O) between the $-CH_3$ and both the SO of DMSO molecules and the CO of the acid group of (S)-1.

The molecular packing (Fig. 2), can be described as an alternation of polar and apolar layers along the b direction of



Fig. 1. ORTEP representation of the asymmetric unit of (S)-1/DMSO crystals.



Fig. 2. Molecular packing of (S)-1/DMSO in its crystals. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the crystal. The apolar layer is composed of the alkyl chains interacting with each other by van der Waals forces and which are interdigitated. One noncovalent bond more is found in this layer: the last methyl group of each alkyl chain interacts with the nearest phenyl ring via a $C-H\cdots\pi$ interaction. The polar part is comprised of the acid groups of the chiral substituents and the DMSO molecules interacting with each other by hydrogen-bonds.

Monolayers of 1 at the Graphite-1-Phenyloctane Interface

The self-assembly of solutions of (*R*)-1, (*S*)-1 and the equimolar (R)-1/(S)-1 mixture on graphite were investigated by

scanning tunnelling microscopy (STM) at the liquid-graphite interface, which is a particularly sensitive way to study chiral structure at submolecular resolution.^{17–19} The molecules were dissolved in 1-phenyloctane (7.6×10^{-3} M) and a drop of this solution was cast onto highly oriented pyrolytic graphite (HOPG). The monolayer formation and structure was followed using STM in the constant current mode at the liquid–solid interface. After a while, the spontaneous formation of highly ordered adlayers was observed.

Typical STM images of (R)-1 and (S)-1 physisorbed independently at the 1-phenyloctane-graphite interface are shown in Figure 3. A bright (dark) contrast reflects an increased



Fig. 3. STM images of **1** physisorbed at the 1-phenyloctane-HOPG interface. (**A**) (*R*)-**1**, large area with multiple domains ($I_{set} = 0.05$ nA, $V_{set} = 1.04$ V). (**B**) (*R*)-**1**, high-resolution image ($I_{set} = 0.03$ nA, $V_{set} = 1.00$ V; $I_{HOPG} = 1.09$ nA, $V_{HOPG} = 0.02$ V). (**C**) (**S**)-**1** ($I_{set} = 0.02$ nA, $V_{set} = 1.04$ V; $I_{HOPG} = 0.27$ V). The periodicity perpendicular to the double rows D is indicated by white arrows. The inset shows the corresponding graphite image. The white solid lines in the insets indicate the direction of the major symmetry axes of HOPG (<-12 - 10>, <11 - 20>, and <2 - 1 - 10>). The black dashed line in the insets and main images, running perpendicular to one of the main symmetry axes, is a reference axis selected to evaluate the orientation of the monolayer with respect to the substrate. Yellow solid lines indicate the propagation direction of the double rows. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Fig. 4. STM images of (*R*)- and (*S*)-1 mixture (ratio 1:1) physisorbed at the 1-phenyloctane-HOPG interface. (A) Large area with multiple domains ($I_{set} = 0.06$ nA, $V_{set} = 1.04$ V). (B) Smaller-scale image containing both types of domains ($I_{set} = 0.05$ nA, $V_{set} = 1.02$ V; $I_{HOPG} = 1.09$ nA, $V_{HOPG} = 0.02$ V). The inset shows the corresponded graphite image. The white solid lines in the inset indicate the direction of the major symmetry axes of HOPG (<12 - 10>, <11 - 20> and <2 - 1 - 10>). The black dashed lines in the inset and main image, running perpendicular to main symmetry axes, are reference axes selected to evaluate the orientation of the monolayer with respect to the substrate. Yellow solid lines are the propagation direction of molecular double rows.[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(decreased) tip-sample distance, due to higher (lower) topographical features and/or a higher (lower) tunnelling efficiency.

The STM images are composed of double rows of bright spots separated by often less bright lines running perpendicular to these double rows. The bright spots in the double rows are attributed to the phenoxy propionic acid head groups which potentially dimerize through hydrogen bonds. Note though that the contrast along the double rows is not always constant, indicating a variation or flexibility in the orientation and the interaction of the phenoxy propionic groups. The lines running almost perpendicular to the double rows correspond to the alkyl chains. They are adsorbed adopting an all-trans conformation, and those of adjacent rows are interdigitated. Due to the variation in image contrast in many of the images, it is not possible to determine the distance between two adjacent phenoxy propionic units in a straightforward manner. Alternatively, the distance between nextnearest-neighbour interdigitating alkyl chains was determined to be 0.98 ± 0.03 nm. The periodicity perpendicular to the double rows (D) is easier to determine and measures 3.7 \pm 0.2 nm. The insets in Figure 3 illustrate the graphite substrate (not to scale with the STM image of the monolayer) where the main symmetry axes are indicated by white lines. The alkyl chains run parallel to one of the main symmetry axis of graphite.

The chirality of the enantiopure monolayers was analyzed evaluating the orientation of a molecular row with respect to graphite. Therefore, for each domain a reference axis was selected, running perpendicular to one of the major symmetry axes of graphite, to evaluate the orientation of the monolayer with respect to the substrate. The reference axis selected is the one which forms the smallest angle with the lamellae. The angle between the graphite reference axis and the tape axis of the monolayer is on average $-3.7^{\circ} \pm 2.1^{\circ}$ for (*R*)-1 (Fig. 5A) and $+4.5^{\circ} \pm 2.9^{\circ}$ for (*S*)-1 (Fig. 5B). A similar relationship is observed in all domains probed for both enantiomers. This fact indicates clearly that the stereogenic centres influence strongly the molecule-surface interaction.

When an equimolar solution of the (R)-1 and (S)-1 in 1phenyloctane was deposited onto HOPG domains similar to the ones observed to the single enantiomers were registered (Fig. 4).

To investigate the possibility of spontaneous resolution^{20,21} of the racemic mixture (R)-1/(S)-1, the chirality in each domain formed was analyzed. Both domains with positive and negative θ angles were found, i.e., $-3.0^{\circ} \pm 2.3^{\circ}$ and $+3.4^{\circ} \pm$ 2.5° (Table 2). The results of the analysis of chirality in different domains are presented in the histograms in Figure 5 for both enantiomers and the racemic mixture. These domains are not evident in large scale images, because the difference in angle of the domains is only $\sim 6^{\circ}$ and the resolution and correction of the images in large areas is not possible, their appearance is similar to the large areas of the enantiopure compound shown in Figure 3. Close-up images of domains with reliable graphite reference axes must be taken to identify the domains with different chirality, as shown in Figure 4B. These data indicate the spontaneous resolution of the racemic mixture at the surface.

In the 2D adsorbed structure **1** is arranged in a slightly different way from that in the 3D crystal while the gross supramolecular structure – head to head carboxylic groups and interdigitated alkyl chains – is similar. The main difference is the presence of solvent molecules in the crystal which are between two (S)-**1** molecules forming hydrogenbonds, whereas in the 2D structure dimers of (S)-**1** presum-

TABLE 2. Monolayer descriptors: D is the repetitive row to
row distance (see Fig. 3)

	<i>D</i> (nm)	θ (°)	Ν
(<i>R</i>)-1	3.7 ± 0.2	-3.7 ± 2.1	13
(S)-1	3.7 ± 0.1	$+4.5\pm2.9$	21
(R)-1+(S)-1 (1:1)	3.8 ± 0.1	-3.0 ± 2.3	28
	3.8 ± 0.1	$+3.4\pm2.5$	21

 θ is the angle between the graphite reference axis and the row propagation axis. N is the number of domains analyzed.



Fig. 5. Histograms of the angle \ominus observed for physisorbed monolayers formed of solutions of (A) (*R*)-1; (B) (*S*)-1; (C) racemic (*R*)-1/(*S*)-1. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ably interacts with itself by forming hydrogen-bonded dimers. The distance between two alkyl chains in the 3D crystals is ~ 4.1 Å, in the 2D crystal on graphite this distance is 5 ± 1 Å. These results demonstrate that both the 2D closest packing principles, related to the minimization of the surface free energy, and hydrogen bond play a role in the adsorption process. The final adsorption structure is determined by the balance of these two forces.

Modeling has been used to unravel the role played by supramolecular interactions and chirality on the formation of monolayers at HOPG surfaces, examining the specific case of (S) enantiomer (the (R) enantiomer is expected to give similar results of opposite handedness, only the orientation of the layer inverted with respect to the HOPG symmetry axis). The initial structure corresponds to the model proposed from the STM data, i.e., a monolayer composed of double rows of phenoxy groups forming hydrogen bonds, separated by interdigitated alkyl chains.

The modeling of the (*S*)-1 monolayer has been performed in two stages: in the first step, we investigate the internal organization of the assembly, as well as its orientation with respect to graphite symmetry axes. To do so, we analyse the stability of starting models upon comparison of the geometrical parameters obtained by STM with the predicted MD values. The simulations are carried out on a graphite layer (19.5 \times 19.5 nm²), with 40 molecules of (*S*)-1 arranged as indicated in Figure 6 on top. The second step consists in assessing the relative stability of monolayers featuring different ori-



Fig. 6. Modeling result for (*S*)-**1** assembly at the HOPG surface: internal organization of the monolayer (top) and orientation of the layer with respect to graphite (bottom). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Graphite

Scheme 2. Representation of the angle between rows of molecules and the <-1 1 0 0> symmetry axis of graphite upon molecular displacement.

entations with respect to the symmetry axes of the graphite surface. To do so, we consider a smaller system (16 molecules of (*S*)-1 on top of a $12.1 \times 12.1 \text{ nm}^2$ graphite sheet), as represented at the bottom of Figure 6. The analysis of the energy-minimized geometries extracted from these MD simulations, and the comparison to the experimental data allows pinpointing those interactions that are responsible for the specific orientation of the monolayers on graphite, i.e. the chiral signature of the assembly.

The starting models of the monolayers were built on the basis of STM parameters. The construction process *per se* already gave us some hint on the origin for the rotation of the rows formed by the molecular cores with respect to graphite: it has been observed that a small displacement between repeating units in one row promotes more favourable (Van der Waals) interactions among molecules belonging to the same row. However, due to the presence of the chiral group, the repeating units in one row are displaced with respect to each other in a specific direction, which depends on the molecular chirality: by \sim +0.5Å along the alkyl chain axis for (*R*)-1, as sketched in Scheme 2.

The geometrical parameters obtained from the modeling are found to be overall in good agreement with experiment, see Table 3. Thus, the model proposed for the organization of the molecules within the monolayers accounts well with most of the salient features extracted from the STM images. Slight differences between theory and experiment probably arise from not accounting for solvent effects in the calculations. Namely, the MD simulations tend to overestimate the interactions between alkyl chains yielding lower intermolecular distances compared to the measured values.



Fig. 7. Potential energy profile for the rotation of the layer of (*S*)-1 molecules with respect to the <-1 1 0 0> reference graphite axis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

A closer look at the supramolecular structure within the monolayers of (*S*)-**1** shows that the formation of hydrogen bonds between facing resorcinol "heads" leads to a rather large separation between adjacent molecules in a given row. As a result, the empty space between the alkyl chains along one row can be filled through interdigitation with the alkyl tails of the molecules belonging to the neighbouring rows.

The second set of MD simulations aimed at investigating the energy of (*S*)-1 monolayer as a function of rotation over graphite revealed that the alignment of the alkyl chains along one of the main symmetry axes of graphite also determines the global orientation of the stack. This is shown in Figure 7, where we see that the equilibrium angle of the (*S*)-1 monolayer (that amounts to $\sim +2^{\circ}$ in our simulations) allows for optimal Van der Waals interactions between the (*S*)-1 tails and the graphite surface. This equilibrium rotation angle for the chiral domains is in reasonable agreement with the experimental value of $\sim +4.5^{\circ}$.

Monolayers of 1 at the Air-Water Interface

Langmuir monolayers of the enantiomers and racemic forms of amphiphile **1** were prepared by placing drops of a chloroform solution of the samples on deionised water and then compacting them with the barrier in the Langmuir trough. To produce the most compact Langmuir layers the influence of the pH on the Langmuir monolayers of the three samples were studied by surface pressure-area isotherms (Fig. 8). Surface pressure-molecular area isotherms have been proven to be a sensitive way of studying the chiral dis-

TABLE 3. Geometrical parameters typical of the (S)-1 monolayer

	<i>d</i> /nm	a/nm	b/nm	c/nm	D/nm
Theoretical (DRIEDING–FORCITE) Theoretical (MM3 Tinker) Experimental	$\begin{array}{c} 0.54 \pm 0.07 \\ 0.50 \pm 0.04 \\ 0.49 \pm 0.02 \end{array}$	$\begin{array}{c} 1.1 \pm 0.08 \\ 0.90 \pm 0.07 \\ 0.98 \pm 0.03 \end{array}$	$\begin{array}{c} 1.2 \pm 0.02 \\ 1.22 \pm 0.11 \\ 1.23 \pm 0.10 \end{array}$	$\begin{array}{c} 0.85 \pm 0.22 \\ 0.92 \pm 0.07 \\ 1.11 \pm 0.13 \ \mathrm{nm} \end{array}$	$\begin{array}{c} 3.78 \pm 0.17 \\ 3.98 \pm 0.22 \\ 3.68 \pm 0.21 \end{array}$

d refers to the alkyl–alkyl separation; *a*, *b*, and *c* refer to the distances between the cores of the (*S*)-1 molecules; *D* is the distance between two (*S*)-1 stacks. *Chirality* DOI 10.1002/chir



Fig. 8. Pressure-area isotherms for monolayers of (*R*)-1, (*S*)-1, and (*R*)-1/(*S*)-1 1:1 mixture at subphase pH value of (A) 2, (B) 5.6, (C) 7.8. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

crimination effects of enantiomeric and racemic monolayers. $^{\rm 22-24}$

The shape of the isotherms at pH 2 and 5.6 – which show no appreciable surface pressure below 40 Å² per molecule and then a very steep rise—are typical of an amphiphile that forms a tightly packed monolayer with the alkyl chain of neighbouring molecules interacting strongly. The increase of the pH value to 7.8 results in a shallower isotherm and a shift to a bigger area per molecule value, resulting in a Langmuir monolayer with a bigger molecular area requirement. The isotherm relative to the racemic mixture is further shifted with respect to that of the enantiopure samples. It is clear how the subphase pH conditions influence the ionic state of the head group and so the intermolecular interactions. At pH 7.8 the carboxylic groups are in the anionic state and repulsive electrostatic forces between the head groups dominate their packing.

There is no substantial difference between the slopes of the isotherms at subphase pH 2 and 5.6 meaning that there is not a big difference in the packing at the air-water interface of the two enantiomers and of the racemic mixture in either condition. Although there are slight differences between the racemic modification and the enantiomers over the whole isotherms, the only difference at both pH values was observed around the collapse point of the isotherm, and this effect could depend on factors other than the chirality. While for the pure enantiomers there is a decrease of pressure after the collapse, for the racemic the pressure stays constant indicating a different behavior of the racemic monolayer at the higher pressure.

The limiting molecular area in the condensed phase at either pH 2 or 5.6 at zero pressure, which is obtained by extrapolating from the slope of the solid phase to zero surface pressure, is 33 Å² per molecule for both the enantiopure and racemic compounds and represents the hypothetical area occupied by one molecule in the condensed phase at zero pressure. This value is of the order of that expected for the head-group of the compound.

Figure 9 shows the hysteresis of two successive compression/expansion cycles of the racemic and enantiomeric monolayers of the amphiphilic resorcinol derivative. For the enantiomers, the first and second compression isotherms are identical and practically no hysteresis was observed even during subsequent isotherms. For the racemic compound the isotherms exhibited hysteresis and a decrease in limiting mean molecular area on successive compression was observed. The limiting molecular area goes from 33 Å² per molecule to 27 Å² per molecule.

The smaller limiting area per molecule of the racemic mixture could be partially attributed to the reorientation of the molecules during the decompression and recompression steps, forming a better packed monolayer after the cycle. Other explanations are plausible, such as the formation of nonmonolayer aggregate regions within a monolayer host, the dissolution of the monolayer into the aqueous phase or the partial overlapping of the molecules in the monolayer films leading to a multilayer stacks on the surface of water. On the other hand it was found that during the experiments on the racemate when the moving barrier was stopped at 22 mN m⁻¹ the molecular area decreases about 25% after 15 min relaxation. This phenomenon suggests that a stereoselective kinetic process must occur upon film compression. The Langmuir layers are not very stable and confirm the



Fig. 9. Surface pressure/area isotherms for the compression/expansion cycle of (A) enantiomeric and (B) racemic 1 monolayers at 25° C on a pure water subphase (pH 5.6). Rate of compression/expansion was 5 Å²/molecule per minute.



Fig. 10. BAM images of (R)-1 taken at pH 5.6, 25°C: (A) after spreading; (B) at the liquid-phase; (C) at the solid phase; (D) after collapsing.

tendency of the molecules to find a more stable interaction state. This big difference in behavior between enantiomers and racemate is further evidence of the formation of a racemic compound at the interface.

The visualization of the monolayers from zero pressure to collapse pressure was registered by a Brewster Angle Microscope (BAM) to observe the homogeneity and the domain structure of the monolayers. In Figure 10 the images of the monolayer of (R)-1 at pH 5.6 during the course of its compression are shown. The areas of different brightness arise from different molecular layer densities.

After spreading the enantiomeric amphiphile in chloroform on the water's surface, a monolayer of scattered, lace-like structure appears. During compression, homogeneous structures with smaller and larger hole are formed (liquid-condensed phase). Further compression results in a homogeneous thin film (crystal-like solid phase) without any black spots (which represents the water subphase). Then at higher surface pressure the monolayer undergoes a transformation, and, because of the collapse of the film,²⁵ a few white spots appear. The images suggest well shaped condensed phase domains, which mean a highly ordered molecular packing is found for the enantiomers and the racemic mixture.

The images of (*R*)-1, (*S*)-1 and the racemic (*R*)/(*S*)-1 at the two-dimensional gas phase (before compression) were compared and no substantial difference was noted between the structure of the domains (Fig. 11).

The morphology of the domains at subphase pH 2 was found to be similar to the ones at pH 5.6, whereas clear differences were found between the enantiopure and the race-*Chirality* DOI 10.1002/chir mic compounds at subphase pH 7.8 (Fig. 12). Both enantiomers form three tipped star-shaped structures during compression, whereas the racemic mixture forms more acicular and inhomogeneous structures of larger domain dimensions. That confirms the different interactions existing in the racemic mixture which were found during the observation of the isotherms and the isocycles for the deprotonated amphiphile.

After the correct choice of subphase pH (5.6) stable monolayers of (R)-1, (S)-1 and their racemic mixture at the air/ water interface were produced and deposited by vertical lifting onto normal glass, mica and hydrophobic glass. The molecular packing orientation and arrangement within the LB films was further investigated by sum-frequency vibrational spectroscopy. The sum-frequency ssp spectra of (R)-1, (S)-1 and (R)-1/(S)-1 (1:1) monolayers deposited onto glass by the Langmuir-Blodgett technique are shown in Figure 13. The good signal-to-noise ratios of the sum-frequency spectra clearly indicate that the transfer of ordered monolayers to the glass substrates was successful. The sum-frequency spectra of the monolayers of the (S)-1 and (R)-1 enantiomers (bottom and middle traces in Fig. 13, respectively) in the C—H stretch region (2800–3000 cm^{-1}) are very similar. The spectrum of the monolayer of the racemic mixture (top trace in Fig. 13) exhibits the same peaks but with somewhat different intensity ratios and a slightly lower signal-to-noise ratio as compared with the enantiopure samples.

The assignment of the major peaks in the spectra is well established in the literature.²⁶ The spectra are dominated by the symmetric methyl stretch (r^+ mode) at 2878 cm⁻¹, and the Fermi resonance of the same mode at 2940 cm⁻¹ ($r_{\rm FR}^+$).



Fig. 11. BAM images of (A) (R)-1; (B) (S)-1; (C) Racemic (R)-1/(S)-1 taken at pH 5.6, 25°C after spreading.

The antisymmetric methyl stretch (r⁻) shows up as a shoulder at 2956 cm⁻¹. The broad peak at 2850 cm⁻¹ arises from the symmetric methylene stretch (d⁺ mode). The I(r⁺)/I(d⁺) intensity ratio of the methyl and methylene symmetric stretch modes in the spectra of the monolayers prepared from the pure enantiomers indicates rather high conformational order of the alkyl chains, with a only a small fraction of *gauche* conformations.²⁷ The relative intensity of the methyl and methylene symmetric stretch peaks of the racemic (*R*)-1/(*S*)-1 (1:1) monolayer is lower than for the pure enantiomers indicating a somewhat lower conformational order of the alkyl chains. The sum-frequency spectra thus suggest slightly different structures in the Langmuir-Blodgett monolayers of the pure (*R*)-1 and (*S*)-1 enantiomers as compared to the racemic monolayer.

CONCLUSIONS

The self-assembly of the racemic amphiphile **1** at the 1phenyloctane-graphite interface results in spontaneous resolution of the enantiomers, because of the angle that the enantiomers form with the graphite axis and the preference for the lactate group to induce a certain angle. On the other hand, π/A isotherms and BAM imply that when racemic mixtures of the amphiphiles are spread on water and compressed then it seems that there is no spontaneous resolution. The racemic mixture domains are not as stable as the enantiopure ones and an overlapping of the monolayers happens during the second compression in a compression/



Fig. 12. BAM images of (A) (R)-1; (B) (S)-1; (C) Racemic (R)-1/(S)-1 taken at pH 7.8, 25°C during compression.



expansion cycle and when keeping a pressure for few minutes. These results illustrate the key role that orientation and substrate have upon chiral separation processes in low dimensions, and are consistent with results on the curtailed spontaneous resolution of a bis-lactate on a metal surface reported recently.²⁸ Together with the observation that the bulk material forms a racemic compound, the observations infer that more than a subtle change in head group of the amphiphile is necessary to generate surfactants that will resolve spontaneously under any condition, a challenge particularly relevant for studies of chirality at the nanoscale²⁹ and one we are pursuing.

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