Structural Changes of Amphiphilic Aggregates at the Air–Solution Interfaces As Studied by Oriented Crystallization and Nonlinear Optics

I. Weissbuch,* G. Berkovic,* L. Leiserowitz,* and M. Lahav*

Department of Structural Chemistry
The Weizmann Institute of Science, Rehovot, Israel

Received December 20, 1989

Recently, we have provided evidence that water-soluble hydrophobic α-amino acids form ordered aggregates at the solution surface, interlinked by a two-dimensional net of hydrogen bonds.[1] These aggregates can induce fast oriented crystallization of suitable cosolute molecules when there is a match between the 2-D molecular arrangement and the structure of the face from which the crystal nucleates. We demonstrate here that this transfer of structural information from 2-D to 3-D systems can probe the structure of surface aggregates and monitor changes in orientation of 4-substituted benzoic acid amphiphiles upon addition of 4-hydroxybenzoic acid to solution. These structural changes have been independently confirmed by optical second harmonic generation (SHG).[2,3]

4-Hydroxybenzoic acid monohydrate (HBA),[4] space group $P2_1/a$, grows from aqueous solutions (usually at the bottom of the crystallizing dish) as {100} plate-like crystals elongated in the *c* direction. Adding small amounts of 4-methoxybenzoic acid (MBA) to the crystallizing solution induces a fast nucleation of HBA as floating crystals attached at the interface via their newly expressed (401) face (Figure 1).[5] Additives such as benzoic acid and 4-methyl-, 4-fluoro-, 4-isopropyl-, and 4-*tert*-butylbenzoic acids do not induce the above-mentioned effect.

In the crystal structure of HBA the molecules lie parallel to the (401) plane, forming hydrogen-bonded dimers. These dimers are interlinked within the (401) plane by hydrogen bonds involving the phenolic OH groups and water molecules. The induced crystallization of HBA at the air–solution interface can be explained by the formation of aggregates of the additive molecules whose structure mimics that of the (401) crystalline face (Figure 1). In this model the 4-oxybenzoic acid moieties lie flat on the surface so as to form the hydrogen-bonded dimers, while their aliphatic chains emerge from the solution. It is a moot point whether the hydrogen-bonded dimers, lateral aromatic H–H interactions, and partially fulfilled chain–chain contacts stabilize this 2-D motif. We thus propose that the motif is stabilized by the specific interactions with the HBA molecules in solution.

In order to support such a model, insoluble amphiphilic molecules were designed with their hydrophilic group the XC_6H_4COOH moiety (X = O, N) and used in the form of Langmuir films.[6] Three insoluble amphiphiles, 4-(hexadecyloxy)benzoic acid (**1**), 4-(hexadecylamino)benzoic acid (**2**), and 4-(hexadecanoyloxy)benzoic acid (**3**), when spread on supersaturated solutions similarly induced (401) oriented nucleation of HBA crystals at the air–solution interface. These compounds, when compressed over pure water, form monolayers consisting of molecules oriented almost perpendicular to the surface as determined from the limiting area/molecule (Figure 2) and from the SHG experiments (see below). Compression over supersaturated solutions of HBA gives more expanded π–A isotherms

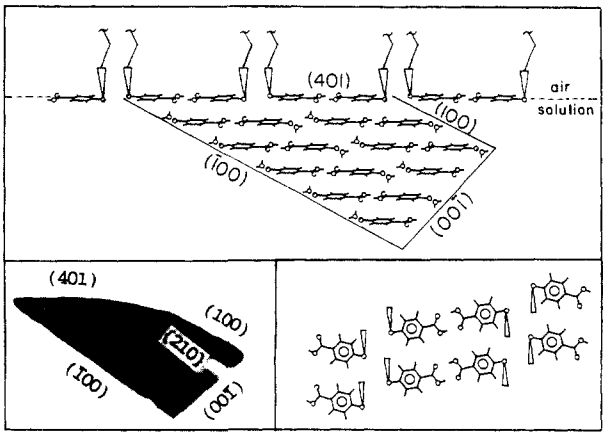


Figure 1. Packing arrangement of 4-hydroxybenzoic acid monohydrate crystal with the (401) face attached at the air–solution interface viewed "edge-on". The morphology of the crystal is represented. The layer of molecules at the interface may be either MBA or a Langmuir film. The CH_3 groups of MBA or the long hydrocarbon chains are represented schematically. Note that the O(phenol)···O(phenol) distance between adjacent molecules is 4.6 Å, thus allowing good van der Waals contacts between the chains. Inserts: photograph of a HBA crystal and a view of the molecules at the interface, perpendicular to the (401) face.

with a larger limiting area/molecule, consistent with a change in orientation of the polar moiety XC_6H_4COOH of the amphiphile molecules.

Amphiphilic molecules of a slightly different structure did not induce HBA crystallization at the interface. Thus, neither 4-(hexadecyloxy)phenylacetic acid (**4**), [4-(hexadecyloxy)-phenyl]propionic acid (**5**), nor octadecyl 4-hydroxybenzoate ($CH_3(CH_2)_{17}OCOC_6H_4OH$) (**6**) showed changes in their isotherms, nor were HBA crystals formed at the interface. Similarly, crystallization experiments under palmitic acid monolayers did not show any induction. These results indicate that only those molecules that may form hydrogen-bonded carboxylic acid dimers parallel to the water surface and similar to those of the HBA molecules are efficient nucleators, consistent with the proposed model (Figure 1).

Independent corroboration for our model has been obtained by using SHG, which can detect the presence and orientation of molecules at interfaces.[2,3] On a pure water subphase, the total SHG signals[7] from monolayers of **1**, **2**, and **6** were approximately 20, 300, and 100 times that of bare water, respectively. From the ratio of the s- and p-polarized SHG outputs,[7] the average angle θ between the surface normal and the long axis of the XC_6H_4COO group is calculated;[2,8,9] $\theta \sim 24°$ for **1**, $\theta \sim 42°$ for **2**, and $\theta \sim 47°$ for **6**, taking a value of $n = 1.5$ for the refractive index of the monolayer. Note that these θ values only refer to the orientation of the XC_6H_4COO moiety, but not necessarily to the orientation of the hydrocarbon chain.

When the subphase was a saturated HBA solution, the SHG signal from the bare air–solution interface was negligibly different from that of the bare air–water interface. Also, when a monolayer of **6** was spread on this subphase, its SHG signal and θ value were identical with those found on the pure water subphase, in complete agreement with the isotherm and crystallization experiments.

However, when a monolayer of either **1** or **2** was spread over the saturated HBA solution, the SHG signal was practically identical with that from the bare HBA subphase. This absence of a signal from the monolayer is consistent with the XC_6H_4COO groups of **1** and **2** lying almost flat ($\theta \sim 90°$) on the surface of the HBA solution, in perfect agreement with the result of the crystallization studies.[10] This change in orientation of **1** is very

(1) (a) Weissbuch, I.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1988**, *110*, 561–567. (b) Weissbuch, I.; Frolow, F.; Addadi, L.; Lahav, M.; Leiserowitz, M. *J. Am. Chem. Soc.* In press.

(2) Shen, Y. R. *Nature* **1989**, *337*, 519–525.

(3) Richmond, G. L.; Robinson, J. M.; Shannon, V. L. *Prog. Surf. Sci.* **1988**, *28*, 1–70.

(4) Colapietro, M.; Domenicano, A.; Marciante, C. *Acta Crystallogr.* **1979**, *B35*, 2177–2180.

(5) The same effect, albeit weaker, has been observed to be induced also by 4-bromobenzoic acid (or 4-chlorobenzoic acid).

(6) (a) Landau, E. M.; Grayer Wolf, S.; Levanon, M.; Leiserowitz, L.; Lahav, M.; Sagiv, J. *J. Am. Chem. Soc.* **1989**, *11*, 1436–1445. (b) Landau, E. M.; Grayer Wolf, S.; Sagiv, J.; Deutsch, M.; Kjaer, K.; Als-Nielsen, J.; Leiserowitz, L.; Lahav, M. *Pure Appl. Chem.* **1989**, *61*(4), 673–684.

(7) Dye laser pulses (612 nm, width 8 ns, energy 5 mJ, diameter 0.5 mm) polarized at 45° to the plane of incidence were directed onto the surface at 65° from the normal. Reflected SHG (306 nm) was detected via gated photon counting and averaged over 2000 pulses.

(8) Heinz, T. F. Ph.D. Thesis, University of California, Berkeley, CA, 1982.

(9) Mizrahi, V.; Sipe, J. C. *J. Opt. Soc. Am. B* **1988**, *5*, 660–667.

0002-7863/90/1512-5874$02.50/0

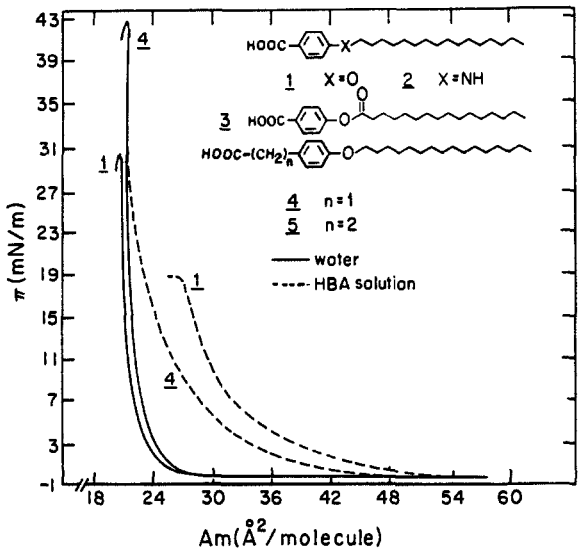


Figure 2. Surface pressure–area isotherms of compounds spread on water (full line) and on the supersaturated HBA solution, 8×10^{-2} M (broken line). Note that the isotherms for compounds **2** and **3** are similar to that for **1** and the isotherms for **5** and **6** are similar to that for **4**.

specific to the nature of the solute molecules, as was demonstrated by a further experiment in which the subphase was changed from HBA to 4-hydroxyphenylacetic acid. SHG measurements showed that the orientation of **1** was identical ($\theta \sim 24°$) with that found on water, indicating the absence of strong interactions between the molecules of the monolayer and the 4-hydroxyphenylacetic acid subphase.

Acknowledgment. We thank E. Gati-Shavit for the synthesis of compound **3** and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial assistance. G.B. acknowledges the support of the Bat-Sheva de Rothschild Fellowship.

(10) Since **1** and **2** have very different nonlinear susceptibilities, the lack of SHG over HBA solutions cannot be attributed to dimers formed between a monolayer molecule and a HBA molecule.

Total Syntheses of (−)-Histrionicotoxin and (−)-Histrionicotoxin 235A

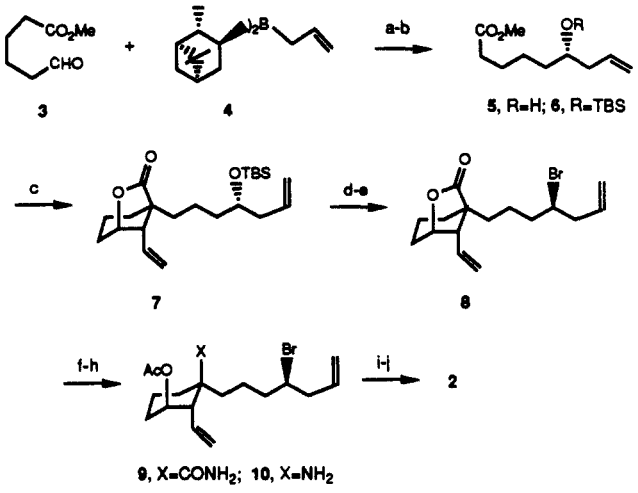
Gilbert Stork* and Kang Zhao

Department of Chemistry, Columbia University
New York, New York 10027

Received April 2, 1990

Histrionicotoxin (**1**), isolated from a family of brightly colored frogs, *Dendrobates histrionicus*,[1] found in Colombia, inhibits the function of several channels in electrogenic membranes.[2,3] Histrionicotoxin is a member of a family that revealed the first examples of an unusual class of spiropiperidine alkaloids bearing acetylenic, allenic, or olefinic side chains. Not surprisingly, this unique chemical constitution has been the target of considerable synthetic effort, but although much imaginative work has been directed toward the preparation of the relatively simple perhydro

Scheme I. Synthesis of Histrionicotoxin 235A[a]



[a](a) −78 °C to room temperature, 2 h, 44%, 86% ee; (b) *t*-$BuMe_2SiCl$, imidazole, CH_2Cl_2, cat. DMAP, 2 days, 98%; (c) LDA, HMPA/THF (6:11 v/v), *trans*-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane, −78 °C to room temperature, 2 h, 43%; (d) 5% HCl, THF, 12 h, 91%; (e) Ph_3P, CBr_4, ether, 2 h, 61%; (f) NH_4Cl, $AlMe_3$, PhH, 50 °C, 40 h; (g) Ac_2O, Py, DMAP, 56%; (h) $(CF_3CO_2)_2IPh$, CH_3CN, H_2O, 3 days; (i) Et_3N, $ClCH_2CH_2Cl$, 65–70 °C, 2 h, 40%; (j) MeOH, aqueous Na_2CO_3, 24 h, 78%.

derivative of histrionicotoxin,[2] only one group has accomplished the synthesis of (±)-histrionicotoxin itself.[4]

We now report that the "allylic epoxide cyclization" method we recently disclosed[5] allows an efficient stereocontrolled path to this group of alkaloids, whether natural histrionicotoxin itself or simpler relatives. We illustrate this by the synthesis of (−)-histrionicotoxin 235A (**2**), in addition to that of the archetype of the group, (−)-histrionicotoxin (**1**).

We describe first the synthesis of the simpler (−)-histrionicotoxin 235A (Scheme I). This began with the optically active methyl (*S*)-6-hydroxy-8-nonenoate (**5**), readily accessible by the reaction of methyl 6-oxohexanoate (**3**)[6] and *B*-allyldiisopinocampheylborane (**4**)[7] (from (−)-α-pinene, 87% ee) in 86% ee and 44% yield. The *tert*-butyldimethylsilyl ether **6** of alcohol **5** was transformed, in a single operation (alkylation, using lithium diisopropylamide, with *trans*-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane[5] was followed by cyclization), to give lactone **7**, in which three chiral centers are correctly set for eventual transformation to (−)-histrionicotoxin. Removal of the silyl protecting group with dilute hydrochloric acid was followed by formation, with inversion, of the secondary bromide (triphenylphosphine–carbon tetrabromide) (**8**)[8] of the proper configuration for subsequent formation of the required piperidine ring. The construction of that ring now required conversion of the lactone carbonyl to an amino group: This was initiated by treatment of **8** with trimethylaluminum–ammonium chloride,[9] followed by acetic anhydride, to give the acetoxy amide

(1) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.
(2) For reviews: Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, p 1.
(3) Spivak, C. E.; Maleque, M. A.; Oliveria, A. C.; Masukawa, L.; Tokuyama, T.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *21*, 351.
(4) Carey, S. C.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, *26*, 5887.
(5) Stork, G.; Kobayashi, Y.; Suzuki, T.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 1661.
(6) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.
(7) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.
(8) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

0002-7863/90/1512-5875$02.50/0