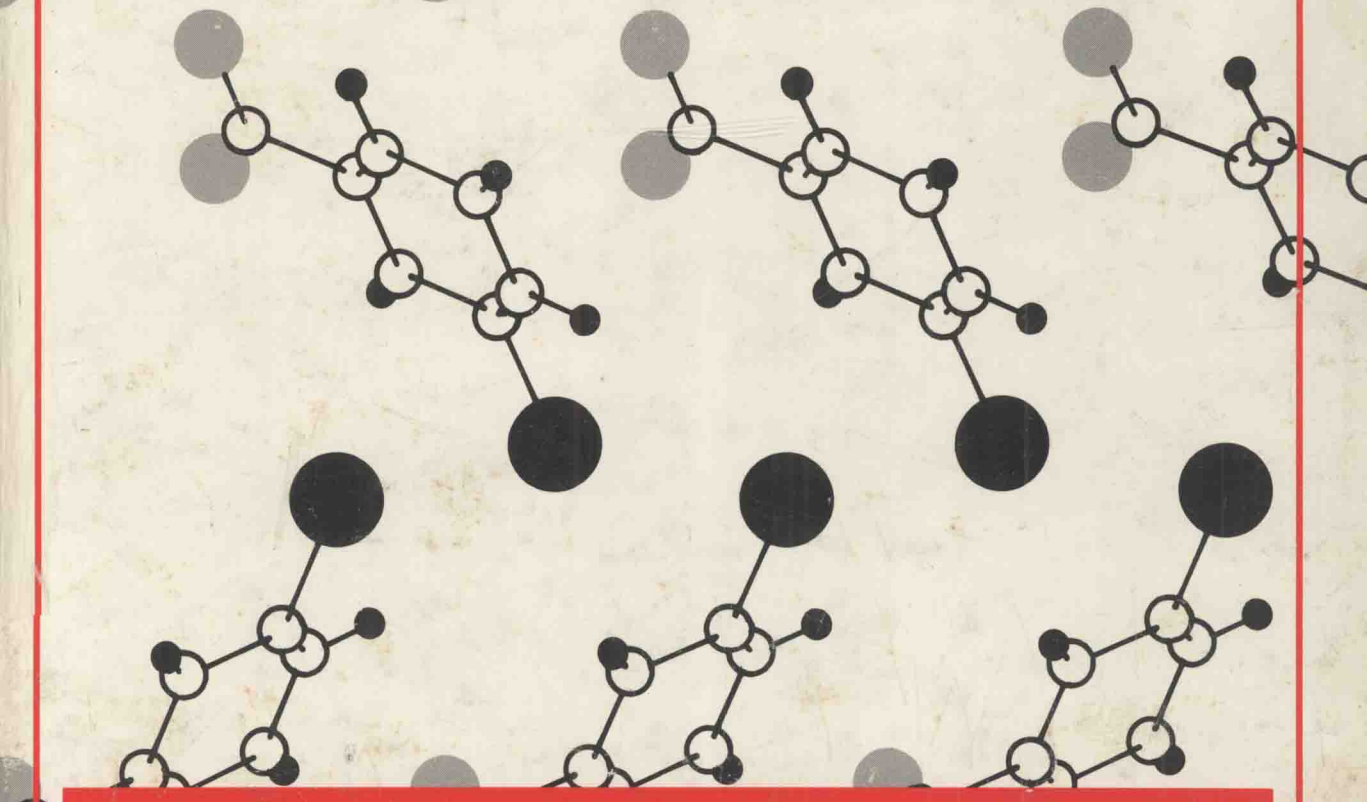
# *Advances in*

# INDUSTRIAL CRYSTALLIZATION



J.GARSIDE • R.J.DAVEY • A.G.JONES

# Advances in Industrial Crystallization

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# FOREWORD

It has been said that crystallization is the oldest and least understood separation and purification technique in the chemical industry. True as this may be, it is now going through a quite remarkable renaissance. More research than ever is being undertaken, increasing numbers of applications are being recognized and the opportunities for further developments are vast in fields as diverse as new metallic, ceramic and polymeric materials, fine and speciality chemicals, and in medical, biochemical and biotechnological products.

It is just thirty years since the first edition of John Mullin's book *Crystallization* was published and in its preface he said 'crystallization is still referred to as more of an art than a science'. Although we would all recognize that the art is still important, the last thirty years have seen a transformation into what is now an overwhelmingly science-based subject. Credit for much of this achievement can be attributed to the work of John Mullin. His retirement from the Ramsay Memorial Chair of Chemical Engineering at University College London in September 1990 provides a fitting occasion to celebrate his continuing contribution to the field of industrial crystallization.

Although dwarfed in size by the second edition, the first edition of *Crystallization* was unmistakeably a major landmark in the field. It was the first text that brought together those areas that are now recognized as forming the foundations of industrial crystallization – physical chemistry, the kinetics of nucleation and growth, and chemical engineering – highlighting the interactions between them and describing their complexities with a precision and clarity of style that has always been a hallmark of John's writing.

From the 1960s, the Crystallization Research Group at University College, London developed an international reputation and attracted research workers and students from around the world. The international links and collaborations that now exist between so many workers in the field of crystallization owe much to the common bond of having worked with John at UCL. For us the editors, who were privileged to be a part of that Group, the enthusiasm for the subject that he generated has persisted and enriched our professional lives. For this we owe John an enormous and lasting debt.

The meeting from which this book is derived was held to celebrate John's achievements. It brought together a group of speakers, many of whom have worked with John as students and colleagues. Four main aspects of industrial crystallization were highlighted, *Precipitation and Nucleation, Crystallization Kinetics, Habit Modification,* and *Crystallizer Design and Operation,* thereby embracing both the scientific and engineering aspects of the subject. The contributions combine state of the art reviews with reports of recent and original research, looking both backwards to the achievements and forwards to the new opportunities. We are especially grateful for the efforts of the contributors and hope that this book will provide a timely compilation of current thinking and form the basis for future research and development in industrial crystallization. John has helped lay the foundations of much of the work included in this volume and the willingness with which the contributors responded to the plans for the meeting and for this volume is a measure of their respect for his achievements and their thanks for his friendship. We trust it will form a lasting and fitting acknowledgement of his continuing work.

*JG*
*RJD*
*AGJ*

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# CONTENTS

## CRYSTALLIZER DESIGN AND OPERATION

# PRECIPITATION AND NUCLEATION

# STUDIES ON THE EARLY STAGES OF CRYSTAL NUCLEATION

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## INTRODUCTION

The understanding of dynamics of the phase transformation from a supersaturated solution into a crystalline solid, requires knowledge of the solution structure at the onset of crystallization. Indication for the existence of large molecular clusters in supersaturated solutions was presented by the pioneering studies of Mullin and Leci [1]. The authors reported that isothermal columns of supersaturated solutions of citric acid developed concentration gradients. Larson and Garsides [2,3] obtained similar results for aqueous solutions of electrolytes ($NaNO_3$, $K_2SO_4$) and non-electrolytes (urea). The phenomenon was explained by assuming the formation of molecular clusters in the size range of 4-10 nm ($10^3$ molecules). Khamskii [4] reported that light transmision through supersaturated solutions decreased continuously prior to the onset of crystallization. Meyerson et al. [5] determined the diffusion coefficients of various solutes in concentrated and saturated solutions using Gouy interferometry. The observed decrease in the diffusion coefficient with increase of concentration implied once again the formation of aggregates in the supersaturated solution. While these macroscopic methods provide important experimental proof for the existence of clusters at the onset of crystal nucleation, they, however, yield little information on the structure of these clusters and the role they play as intermediates in the crystallization process.

We shall discuss here a complementary approach which is stereochemical in nature to provide knowledge on the molecular level, on the structure, dynamics of growth and dissolution in different environments of these clusters. The methodologies applied include oriented crystallization at the air/solution interface as a tool for detecting and

probing the structure of molecular clusters of insoluble and soluble amphiphiles. The packing arrangement and the orientation of the molecules within some of the clusters have been determined using the methods of grazing incidence X-ray diffraction (GIXD), and second harmonic generation (SHG). Time resolved aggregation in two-dimensions of some surfactants has been also monitored by the GIXD technique. The stereochemical approach has been used for the design of "tailor-made" polymers as additives to control crystal polymorphism and resolution of enantiomers by crystallization.

## EPITAXIAL CRYSTALLIZATION UNDER AMPHIPHILIC MOLECULES

Oriented crystallization of α-glycine by soluble hydrophobic α-amino acids [6,7]

The crystalline structure of the monoclinic α-form of glycine is composed of hydrogen bonded layers in which the molecules are related in the *ac* plane by translation symmetry only (Fig.1). The area per molecule within such a layer is *ac* sinβ = 25.9Å$^2$. The layers are interlinked by N-H...O bonds via centers of inversion to form centrosymmetric bilayers. Since each layer is chiral, the replacement of the C-H group of glycine molecule, which emerges from the (010) crystal surface, by an alkyl

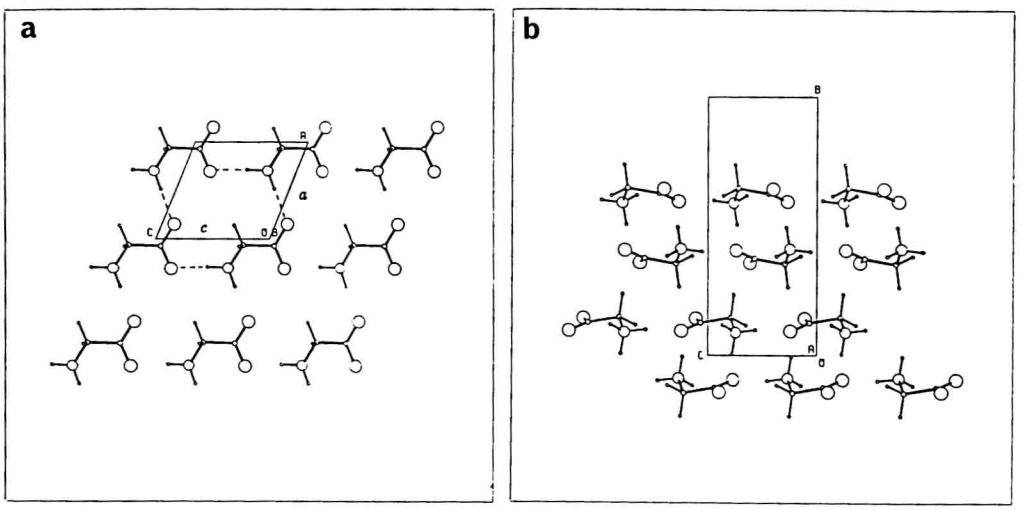


Figure 1 Packing arrangement of α–glycine viewed : a) perpendicular to the *a c* layer of molecules; b) along the *a* axis, displaying the bilayer of molecules.

group for example, would generate a chiral α-amino acid surface layer of *R*-configuration. By virtue of the glide or inversion symmetry of the crystal, a layer of glycine molecules at the opposite ($0\bar{1}0$) crystal surface may be replaced by a chiral layer of (*S*)-α-amino acids.

The hydrophobic optically pure α-amino acids valine, leucine, norleucine, isoleucine, phenylalanine and α-amino octanoic acid, all pack in hydrogen-bonded layer structures similar to that of α-glycine. The area per molecule within each layer ranges from 25.1 to 26.6Å$^2$, close to that of α-glycine. Surface tension measurements of aqueous solutions of these amphiphilic molecules, both pure as well as saturated in glycine, indicated a positive surface accumulation parameter, implying that these molecules aggregate at the solution surface. It is our hypothesis that the molecules at the surface may form ordered 2-D aggregates stabilized by the hydrogen bonds formed between their polar head groups. The proof for this proposed lateral ordering involved the design of structured surfaces which may act as a template at the air/solution interface for an epitaxial like crystallization of 3-D crystals such as glycine .

With this idea in mind, we investigated the oriented crystallization of glycine in the presence of low concentrations of optically pure hydrophobic α-amino acids. We took advantage of the fact that one class of the hydrophobic α-amino acids form crystalline layer structures similar to that of glycine, while the other class was selected so that its hydrophobic moieties are too bulky to allow the formation of a similar layer structure. Indeed, the crystal packing arrangements of compounds such as *t*-butyl glycine and neopentyl glycine show the formation of a hydrogen-bonded layer that occludes solvate water since the bulky hydrophobic groups impose too large separation distances between neighbouring molecules (Fig.2). Consequently, we expected that only the first class of α-amino acids, used in minor concentrations as cosolutes can induce an oriented crystallization of glycine at the air/solution interface. The *R*-α-amino acids should trigger glycine nucleation from the (010) face and the *S*-α-amino acids from the ($0\bar{1}0$) face. Indeed, addition of as little as 0.1-1% of the optically pure hydrophobic α-amino acid induced a fast oriented crystallization at the interface . In contrast, as expected, addition of α-amino acids with bulky side chains, such as *t*-butyl glycine, neopentyl glycine, or hexafluorovaline did not induce α-glycine crystallization at the solution surface. The oriented nucleation does not occur despite the high aggregation of additive at the air/solution interface which was determined from surface tension measurements. This result is in keeping with a mismatch between the proposed

2-D packing of the bulky α-amino acids at the water surface and the layer structure of glycine.

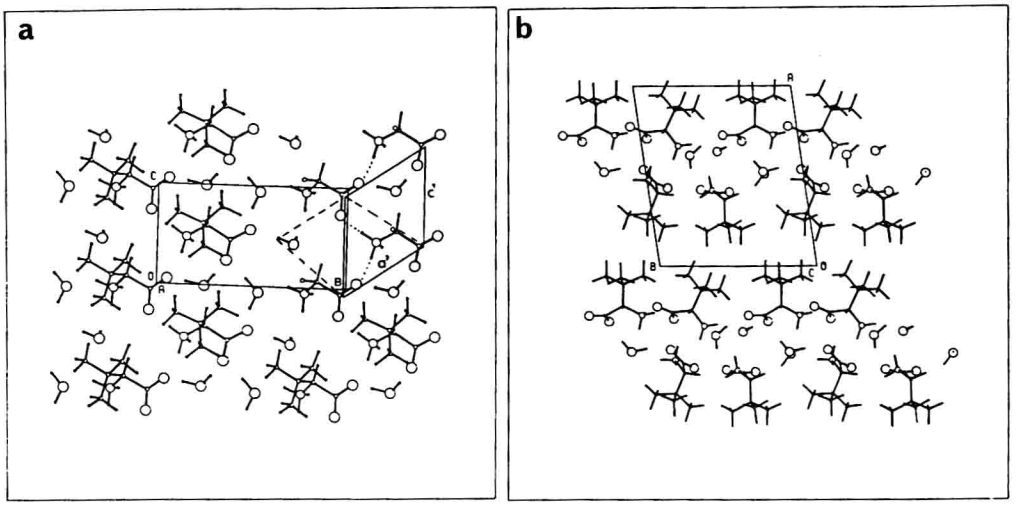


Figure 2 Packing arrangement of (S) t-butyl glycine monohydrate crystal viewed : a) perpendicular to the layer of molecules; b) along the *c* axis. The water molecules form strands separating the ribbons of *t*-butyl glycine molecules.

Oriented crystallization of α-glycine under α-amino acid monolayers [8,9]

In order to obtain more direct information on the structure of molecular aggregates formed at the air/solution interface, we extended our studies on the induced crystallization of glycine by insoluble amphiphilic α-amino acids. These surfactant molecules, in contrast to the short chain α-amino acids, are amenable to surface analysis such as surface pressure-area isotherms. Only very recently, with the advent of intense, highly collimated and monochromatic X-ray beams from synchrotron sources, it became possible (in cooperation with K. Kjaer and J. Als-Nielsen) to probe the structure of the crystalline domains formed by these amphiphiles at the air/solution interface. Crystallization experiments of glycine underneath amphiphilic molecules with a surface molecular area of ~ 25Å$^2$, close to that of glycine at the {010} face, yield results akin to that of the corresponding hydrophobic α-amino acids. This behaviour is expressed both for the compressed or non-compressed monolayer. Thus, for example, monolayers of palmitoyl-*R*-lysine , stearyl-*R*-glutamate yield complete oriented crystallization of glycine. On the other hand, optically pure α-amino

acid monolayers which bear a fluorocarbon tail, imposing a molecular area of 28.5Å$^2$, induce crystallization of glycine with both (010) and (0$\bar{1}$0) orientations. An α-amino acid monolayer with a bulky steroid side chain of surface molecular area of 38Å$^2$ does not induce, as expected, crystallization of glycine. The structure of two of these monolayers was determined by GIXD measurements .

Figure 3 depicts the experimental in-plane diffraction pattern obtained from the palmitoyl-*R*-lysine monolayer [10]. The monolayer proved to be a 2-D powder with a "coherence length" (in other words, a perfect crystalline domain size) of about 500Å and unit cell dimensions $a$=5.03, $b$=5.46Å, $\gamma$=117.8°, implying a molecular area of 24.3Å$^2$. The molecular layer thickness was determined from X-ray reflectivity measurements and compares well with that provided by the molecular model deduced from the GIXD data and X-ray powder diffraction data of 3-D crystalline palmitoyl-*R*-lysine. It was deduced that the hydrophobic chain axis of the monolayer molecule is tilted by 30° from the vertical, such an orientation being favorable for hydrogen-bonding between neighbouring amide groups (Fig 4).These bonds fix the chain

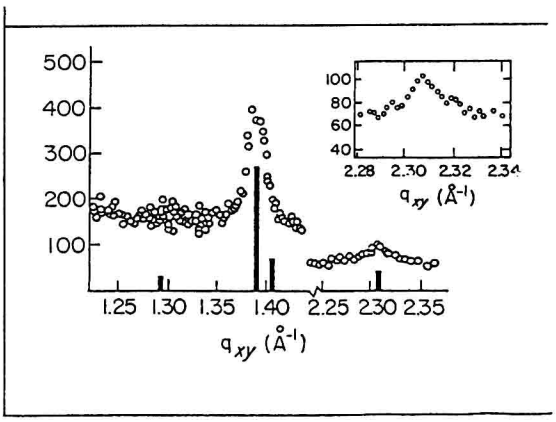


Figure 3 GIXD in-plane diffraction pattern of the palmitoyl-*R* -lysine monolayer.

orientation and packing. On these bases, a model was proposed (Fig. 4) in which the packing arrangement of the α-amino acid head groups is very similar to that of an *ac* layer of glycine in its own crystal structure. We propose that this similarity in packing arrangement is responsible for the epitaxial crystallization of glycine at the air/solution interface. In contrast, GIXD data for the fluorinated α-amino acid $CF_3(CF_2)_9(CH_2)_4OCOCH_2CH(NH_3^+)CO_2^-$ (PFA) in the compressed state yielded a cell

which differs significantly from that of α-glycine [11]. Attempts to observe in-plane diffraction at room temperature of uncompressed monolayer of palmitoyl-*R*-lysine was unsuccessful. Nevertheless, uncompressed monolayer of the fluorinated α-amino acid PFA at room temperature [12] and amphiphiles such as alcohols, acids and amides at low temperature form crystalline clusters according to GIXD measurements [13].

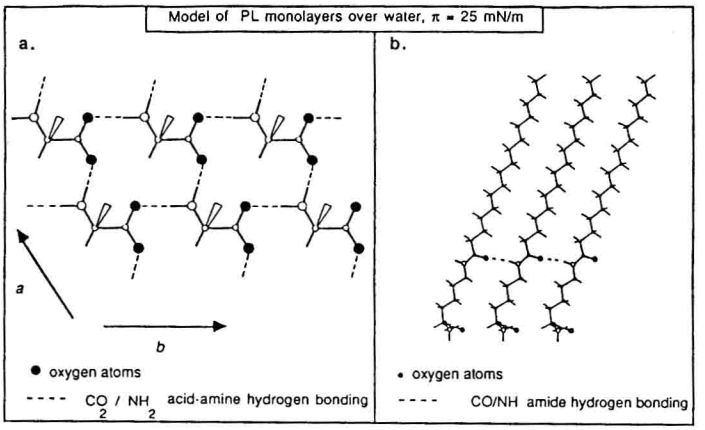


Figure 4 Model of the palmitoyl -*R* - lysine monolayer packing arrangement viewed : a) perpendicular to the layer; b) 'edge-on'.

Growth of 2-D PFA crystallites monitored by GIXD [12]

The grazing incidence X-ray diffraction technique provides an analytical tool to study time-resolved crystallization of amphiphilic molecules in two dimensions. Time-resolved GIXD measurements of the growth of PFA crystallites on pure water at room temperature were not feasible because the measuring time was too long compared to the time required for crystalline self-aggregation. On the other hand, growth of crystallites over a solution of glycine was substantially impeded so that crystallite formation could be monitored in real time. Ten minutes after deposition of the surfactant, no GIXD signal could be detected . The integrated peak intensity reached a plateau about 50 minutes after deposition (Fig.5), implying a saturation of the number of ordered molecules; the coherence length took more time (150 minutes) to reach a value ≥1500Å. These studies might provide some clues on aging of supersaturated solutions before crystallization begins, a process which has been inferred for many organic and inorganic materials.

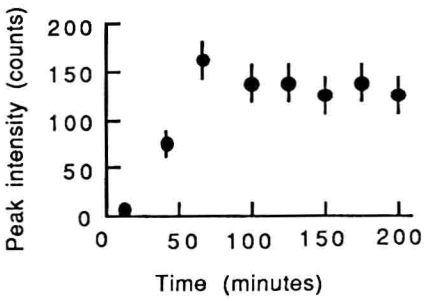


Figure 5 Integrated peak intensity of PFA on glycine subphase as a function of time .

Crystallization of NaCl under monolayers [14]

In the α-amino acid surfactant/glycine system, the polar head groups of the molecules in the 2-D aggregates at the air/solution interface may be regarded as forming the first layer of the to-be-grown glycine crystal. In principle, one may extend this approach for designing surfaces which will induce organization of layers of atomic or molecular ions in solution. Such structured ionic layers may be similar or complementary to the layer structure of the to-be-nucleated crystal. In order to probe the feasibility of this approach, we studied the nucleation of sodium chloride underneath several monolayers at different pH values [12].

Sodium chloride precipitates from aqueous solutions in the cubic space group Fm3m, $a$=5.64Å, exhibiting six {100} crystal faces. When crystallized under specific conditions, two other less stable faces {110} and {111} can be expressed. The {110} face (Fig. 6a) is composed of alternating rows of $Na^+$ and $Cl^-$ ions, separated by 2.82Å. On the other hand, the {111} face is composed of ions of the same kind (i.e,$Na^+$ or $Cl^-$) (Fig 6b). The juxtaposed layers of opposite charge neutralize the system.

When monolayers of arachidic or stearic acid were spread over NaCl solution, 70-90% of the sodium chloride crystals nucleated from their {111} faces. Since the 111 layer is comprised of ions of one type only, were the $Na^+$ ions aligned underneath a layer containing carboxylate head groups, they would, in an ordered system, pack in an identical hexagonal net in order to conserve charge neutrality. The hexagonal lattice of the {111} face of NaCl is $a'=b'=3.99$, $\gamma'=120°$, with an area of 14.5Å$^2$. Thus, there can be no structural match between the layer of $Na^+$ ions attached to the monolayer with

an area/molecule of approximately 20Å$^2$ and the underlying 111 layer of $Cl^-$ ions of area 14.5Å$^2$. Thus, the observation that up to 90% of the NaCl crystals are attached with their {111} faces to the monolayer may be explained by electrostatic attractions. Amphiphilic acids, with a large surface area per molecule, such as cholesteryl succinate ( ~38Å$^2$), do not induce crystallization of NaCl at all. This is in keeping with the expectation that the double layer of $Na^+$ ions below the carboxylate layer is more diffuse, thus reducing the chance for induced nucleation of NaCl attached with its {111} face at the interface.

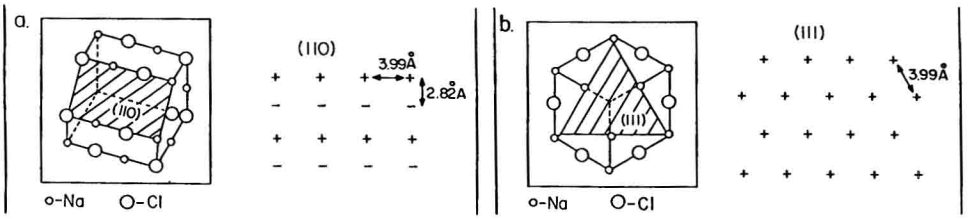


Figure 6 Schematic representation and point charge distribution of: a) the {110} face ;b) the {111} face of NaCl crystal.

Monolayers of zwitterionic α-amino acids, in the pH range of 3 to 10, induce a fast nucleation of NaCl. At neutral pH, many NaCl crystals nucleate from the {110} face. We may account for the preference of the {110} face on the following grounds: the distribution of $Na^+$ and $Cl^-$ ions at the {110} face of NaCl and that of the $NH_3^+$ and $CO_2^-$ moieties of the polar head groups of the monolayer are complementary to one another. The distance between adjacent rows of $Na^+$ and $Cl^-$ ions on the {110} face is 2.82Å (Fig. 6) matching fairly well the 2.6 Å separation distance between adjacent rows of $NH_3^+$ and $CO_2^-$ moieties in the monolayers.

A systematic study has been carried out on the induced crystallization of NaCl by PFA at different pH values. At neutral pH, the monolayer induces crystallization of NaCl from the {110} face and at pH >11.1, from the {111} face. We could deduce that the $Na^+$ ions bound to the anionic $H_2N\text{-}CH\text{-}CO_2^-$ head groups of the monolayer expose to the solution an equipotential ionic layer suitable for NaCl nucleation. GIXD studies of PFA monolayers spread over highly basic KOH subphases (pH=11.5) yielded results in favour of a laterally ordered PFA-$K^+$ bilayer. The study was carried out with $K^+$ ions which are stronger X-ray scatterers than $Na^+$ ions. The presence of $K^+$ ions induces all PFA molecules to be assembled into 2-D crystals, even in the uncompressed state, with