MANCHESTER 1824

The University of Manchester

Molecular routes to Nucleation Control.
Roger Davey

Content: 1. Catalysis - Heterogeneous processes
2. Inhibition - additives

MANCHESTER 1824

The University of Manchester

Democratic means of political control: an historic moment.

MANCHESTER 1824

The University of Manchester

Speeding up : slowing down. What does CNT say?

$$J = AS \ln S \exp(-\frac{B}{\ln^2 S})$$

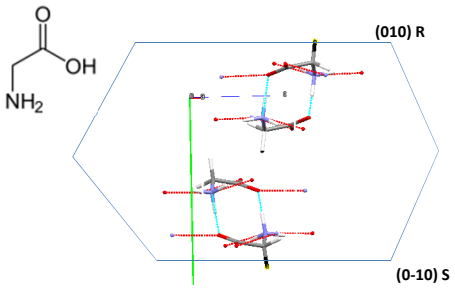
$$A = \frac{f_0 C_0}{\sqrt{12\pi B}} \qquad B = \frac{16\pi v_0^2 \gamma^3}{3(kT)^3}$$

Modifying the attachment kinetics **Changing the interfacial tension.**

MANCHESTER 1824

The University of Manchester

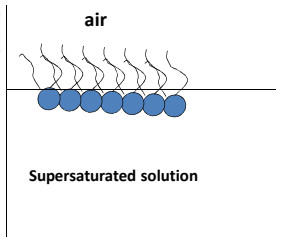
Speeding up - Reducing the interfacial tension. a Glycine.

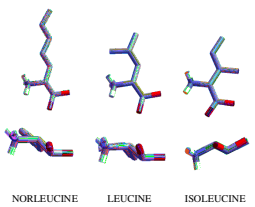


MANCHESTER 1824

The University of Manchester

Reducing γ using monolayers – templating.

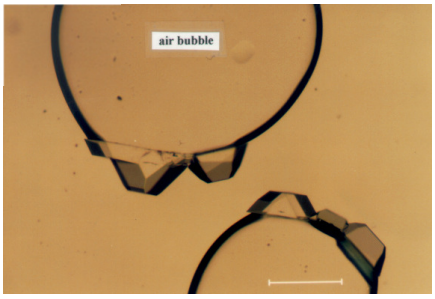


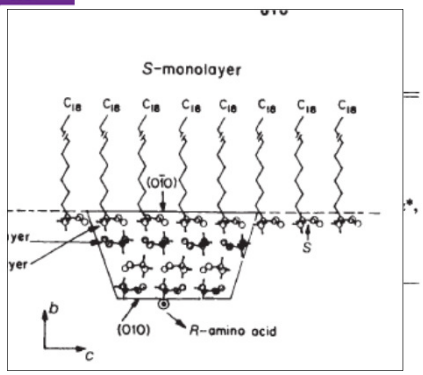


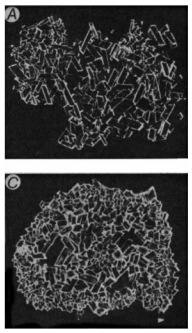
MANCHESTER 1824

The University of Manchester

Glycine templated at an interface







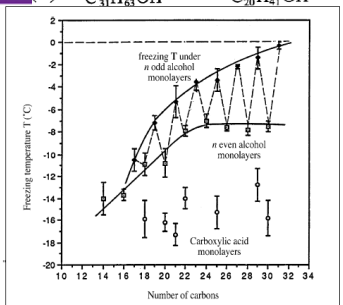
(010)

$2\ R\text{-}CH_3\text{—}(CH_2)_{17}\text{—}OCO\text{—}CH_2\text{—}CH\text{—}(NH_3^+)\text{—}CO_2^- \uparrow$
$S\text{-}CH_3\text{—}(CH_2)_{17}\text{—}OCO\text{—}CH_2\text{—}CH\text{—}(NH_3^+)\text{—}CO_2^- \uparrow$

(0-10)

Ice

(b) $C_{31}H_{63}OH$ $C_{20}H_{41}OH$



CRYSTAL GROWTH & DESIGN 2003 VOL. 3, NO. 2 125–150

Figure 21. Freezing temperatures (T) of supercooled water drops covered by monolayers of amphiphilic alcohols $C_nH_{2n+1}OH$ (rhombs and squares) and carboxylic acids $C_nH_{2n+1}COOH$ (open circles). Curves are drawn separately for alcohols with n odd (filled rhombs) and n even (open squares).

Toward
Understa
Isabelle We

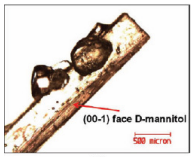
Reducing Υ - Crystal on crystal – epitaxy

Cryst. Growth Des. 2012, 12, 1159–1166

Toward the Rational Design of Crystalline Surfaces for Heteroepitaxy: Role of Molecular Functionality

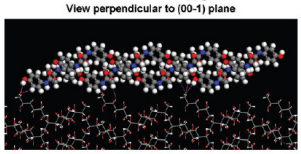
Keith Chadwick, Jie Chen, Allan S. Myerson, and Bernhardt L. Trout*

paracetamol



(b)

View perpendicular to (00-1) plane



View along the (00-1) plane

Figure 10. The most energetically favorable orientation of AAP (100) upon D-mannitol ($00\bar{1}$).

Table 1. Average Induction Times, τ, for AAP Form I from Ethanol ($\sigma = 0.36$) with Various Crystalline Substrates

substrate	average induction time, τ (mins)	R^2 (linear regression)
none (bulk)	1930 ± 85	0.9699
α-LMH	410 ± 11	0.9788
D-mannitol	390 ± 8	0.9795
graphite	1080 ± 32	0.9731
sodium chloride	905 ± 19	0.9925
L-histidine	1910 ± 95	0.9781

The degree of lattice registry between the AAP and substrate crystal faces was evaluated using EpiCalc Version S.[26–28] EpiCalc calculates the degree of lattice match between two 2D lattices as a dimensionless potential energy, V/V_0. V/V_0 represents a "goodness-of-fit" between the overlayer and substrate lattices and can only take a value between $-0.5 \leq V/V_0 \leq 1$. The different modes of epitaxy are represented by

time of AAP as either D-mannitol or α-LMH. Therefore it is reasonable to conclude that, for AAP Form I, the surface functionality of the substrate is more important than achieving a lattice match when promoting nucleation. This conclusion is

Extension to non crystalline solid surfaces: self assembled

CRYSTAL GROWTH & DESIGN

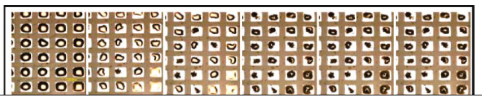


Table 3. The Polymorph Outcome of Glycine for Different pHs and Island Sizes

pH	concentration (M)	size of island (μm)	total samples	crystallization time (min)[a]	α-form (%)	β-form (%)	γ-form (%)
3.40	3.20	250	3000	10	11.6	14.1	73.3
		500	2000	25	66.0	7.8	26.2
5.90–6.20	3.20	250	3000	5	94.5	5.4	0.1
		500	3000	10	92.2	2.9	4.9
10.10	3.20	250	2000	60	52.4	17.1	30.5
		500	2000	450	83.8	4.9	11.3

[a] The crystallization time corresponds to the time when crystals are observed on 99% islands on the substrate.

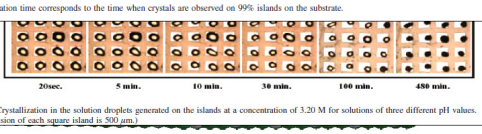


Figure 3. Crystallization in the solution droplets generated on the islands at a concentration of 3.20 M for solutions of three different pH values. (The dimension of each square island is 500 μm.)

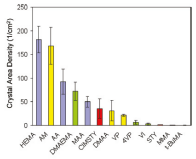
Extension to polymers

Langmuir 2011, 27, 5324–5334

Surface Design for Controlled Crystallization: The Role of Surface Chemistry and Nanoscale Pores in Heterogeneous Nucleation

Ying Diao, Allan S. Myerson, T. Alan Hatton, and Bernhardt L. Trout*

inducing nucleation. The nucleation induction time study revealed that poly (4-acryloylmorpholine) and poly(2-carboxyethyl acrylate), each cross-linked by divinylbenzene, significantly lowered the nucleation induction time of aspirin while the other polymers were essentially inactive. In addition, we found the presence of nanoscopic pores on certain polymer surfaces led to order-of-magnitude faster aspirin nucleation rates when compared with surfaces without pores. We studied the preferred orientation of aspirin crystals on polymer films and found the nucleation-active polymer surfaces preferentially nucleated the polar facets of aspirin, guided by hydrogen bonds. A model based on interfacial free energies was also developed which predicted the same trend of polymer surface nucleation activities as indicated by the nucleation induction times.



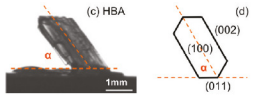


Figure 2. Nucleation density of aspirin on polymer films. Columns representing polymers from groups a, b, c, d, and e are colored blue, yellow, green, pink, and red, respectively. Error bars were derived from three repeats.

Loads of related examples!

Regulating Nucleation Kinetics through Molecular Interactions at the Polymer–Solute Interface

Cryst. Growth Des. 2014, 14, 678–686

Efrem Curcio,[†,‡] Vilmalí López-Mejías,[§] Gianluca Di Profio,[+] Enrica Fontananova,[‡] Enrico Drioli,[†,‡] Bernhardt L. Trout,[§] and Allan S. Myerson*[,§]

Self-Association during Heterogeneous Nucleation onto Well-Defined Templates

Langmuir 2014, 30, 12368–12375

Samir A. Kulkarni,*[,†] Cameron C. Weber,[‡] Allan S. Myerson,[‡] and Joop H. ter Horst[†]

Geometric Design of Heterogeneous Nucleation Sites on Biocompatible Surfaces

Cryst. Growth Des. 2013, 13, 3835–3841

Vilmalí López-Mejías, Allan S. Myerson, and Bernhardt L. Trout*

Langmuir **2002**, *18*, 5886–5898

Crystallization of Amino Acids on Self-Assembled Monolayers of Rigid Thiols on Gold

Alfred Y. Lee,[†,‡] Abraham Ulman,[†,§] and Allan S. Myerson*[,‡]

Slowing down – reduction of the attachment frequency – f*

(we don't know how to enhance f* -solvents?)

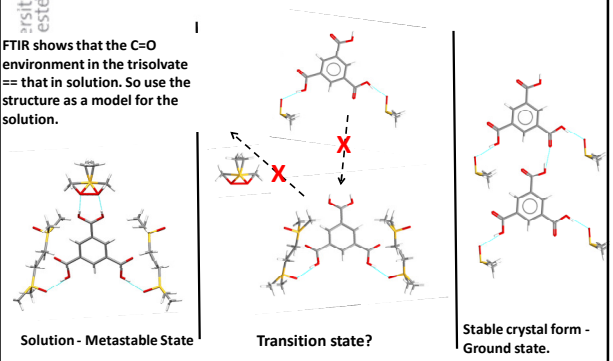
+

→ Rate determining step?

- Incorporation into a surface lattice site
- Desolvation of both surface and growth unit.
- Diffusion to the cluster.

A molecular transition state – DMSO/TMA

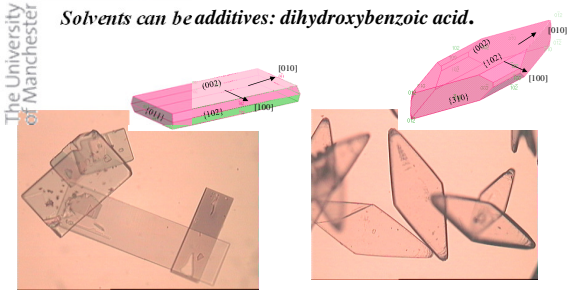
FTIR shows that the C=O environment in the trisolvate == that in solution. So use the structure as a model for the solution.



Solution - Metastable State | Transition state? | Stable crystal form - Ground state.

Can we use solvents to enhance or reduce f* - we know that solvent can determine rates:

Solvents can be additives: dihydroxybenzoic acid.



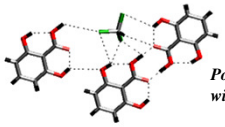
(a) toluene **(b) chloroform**

Effect of solvent: 2,6-dihydroxybenzoic acid

toluene

{310} surface

chloroform

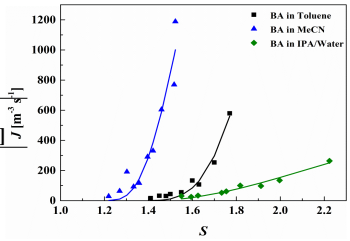


Possible $CHCl_3$ interaction with {310} face

So this could be rate determining

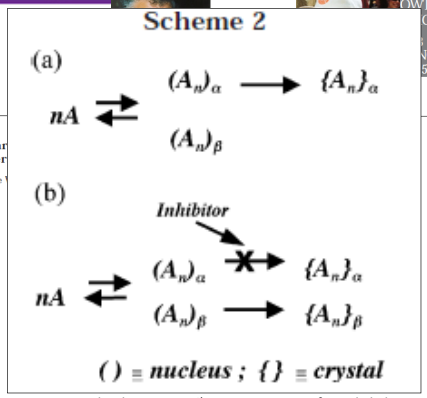
Benzoic Acid Non-linear Fit

	f_0C_0/M [mol·l⁻¹s⁻¹]	γ [mJ/m²]
toluene	8.40	4.5
acetonitrile	4.07	3.0
Ipa water	1.58	4.4

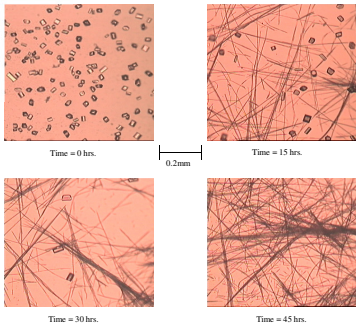


So we know solvent is important but we don't know the rules about selection

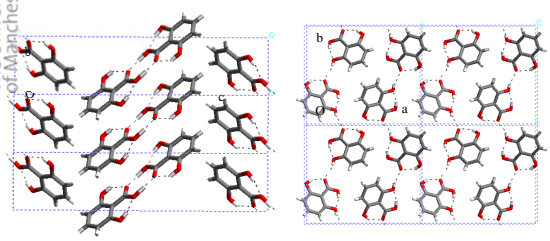
Scheme 2



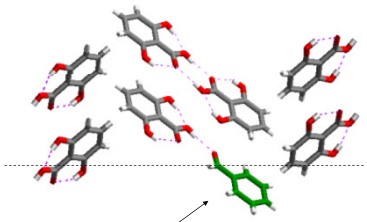
Choosing an additive: 2,6 dihydroxybenzoic acid



The structures

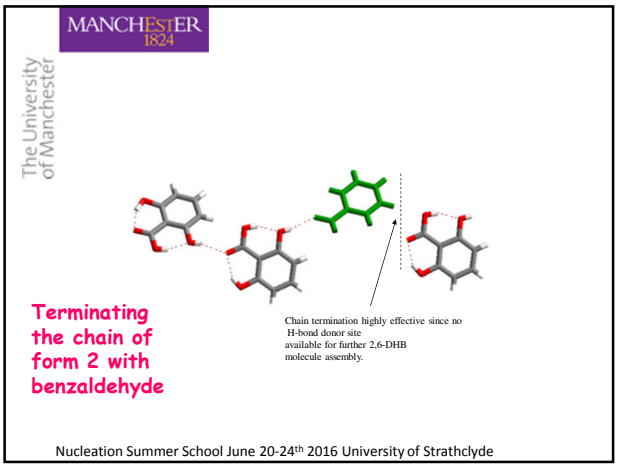


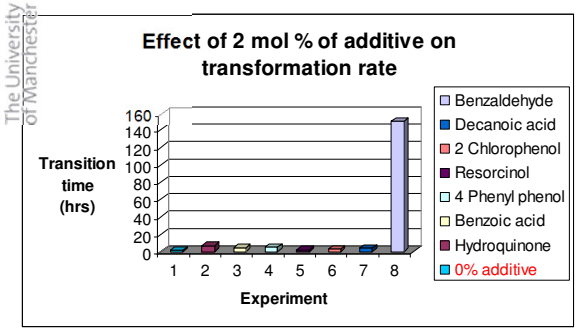
Form 1 **Form 2**



Benzaldehyde as an imposter in form 1

Benzaldehyde additive molecule replaces a 2,6-DHB molecule within the structure and growth not affected.





As crystal growers we want to see if this structural method is consistent with kinetics of nucleation and growth.

The key question is this – when we perform these experiments does the macroscopic crystal that we harvest tell us anything about nucleation or is it only a reflection of the growth process?

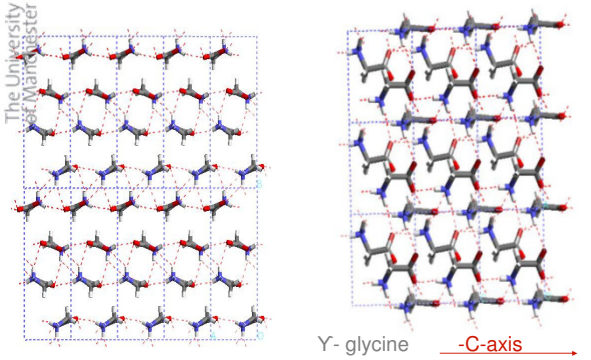
Nucleation

$$J = AS\exp(-\frac{B}{\ln^2 S}) \quad \text{(CNT)}$$

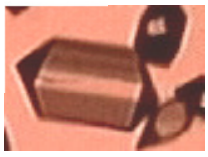
Growth

$$R = \beta\Omega n_0 \nu \exp(-W/kT)\,(\sigma^2/\sigma_1)\tanh(\sigma_1/\sigma), \text{(BCF)}$$

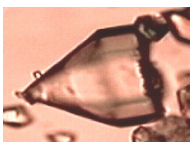
Glycine revisited now with kinetics



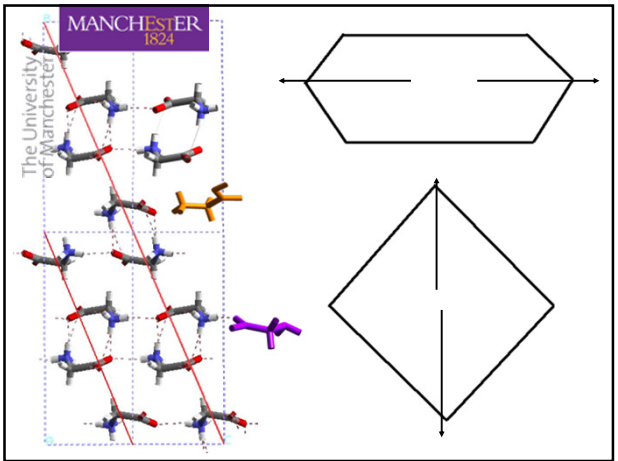
α and ϒ forms – crystal morphologies
Both forms zwitterionic



α metastable
Centrosymmetric



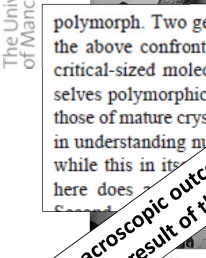
- γ
- most stable
- acidic/basic solution
- polar morphology
- flat end COOH rich, grows fast



MANCHESTER 1824

The University of Manchester

polymorph. Two general observations ca… e. First, the above confrontation of data wit… mes that the critical-sized molecular clusters … lution are themselves polymorphic, having … cteristics that mirror those of mature crystals. T… n has proved to be useful in understanding nu… ange of other systems[4,31] and while this in its… stify the assumption its success here does … eight to validity of the hypothesis.



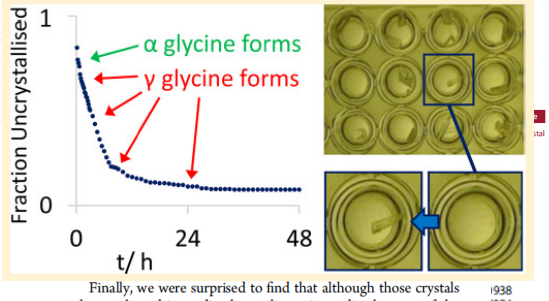
…and ethylenediamine on the appearance and morphology of α and γ glycine: (a)1 wt % malonic acid pH 5.02; (b) 2 wt …1% ethylenediamine pH 8; (d) 10% ethylenediamine.

The macroscopic outcome is in line with expectations but is it really the result of the additive interfering with nucleation?

MANCHESTER 1824

The University of Manchester

Nucleation



Finally, we were surprised to find that although those crystals that nucleated immediately or almost immediately were of the expected α polymorph[4–17] those that nucleated later were of the γ polymorph. It is possible that if seeding is excluded then the nucleation rate of the γ polymorph is higher than that of the α polymorph. If so, then we may need to rethink our understanding of why the α polymorph is usually obtained.

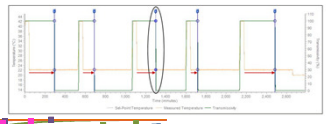
MANCHESTER 1824

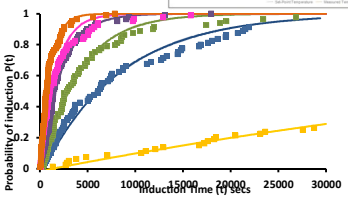
The University of Manchester

Measurements of nucleation rate are not routine.

S. Jiang, J. H. ter Horst, *Cryst. Growth Des.* **2011**, *11*, 256-261.

Crystal 16.





Induction time distributions

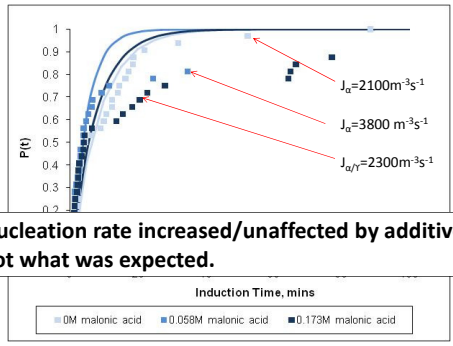
$$P(t) = 1 - exp(-JV(t - t_g))$$

33

MANCHESTER 1824

The University of Manchester

Effect of malonic acid on the nucleation rate of α.



Nucleation rate increased/unaffected by additive – not what was expected.

Induction time probability P(t) for glycine nucleation in malonic acid solution σ= 0.41

MANCHESTER 1824

The University of Manchester

Chem. Commun., 2010, 46, 5924–5926

COMMUNICATION

Acceleratio… tailor-made

Richard Dowling, Guangjun Han,

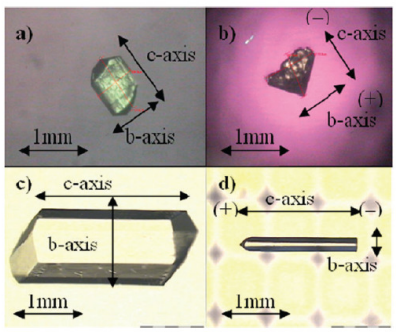


Fig. 1 (a) Measured axes of α-glycine (Manchester), (b) measured axes of γ-glycine (Manchester), (c) measured axes of α-glycine (Singapore) and (d) measured axes of γ-glycine (Singapore).

MANCHESTER 1824

The University of Manchester

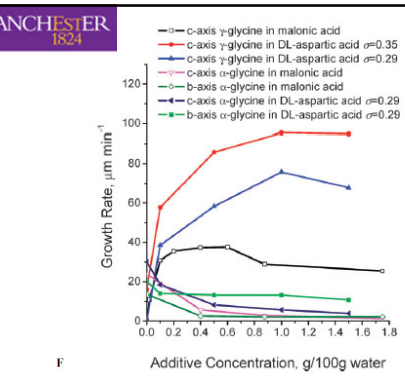


Fig. 3 Effect of DL-aspartic acid (Singapore) on γ-glycine and α-glycine growth in supersaturated solutions of σ = 0.29 and σ = 0.35 and effect of malonic acid (Manchester) on γ-glycine and α-glycine growth at a concentration of 28 g glycine per 100 g water.

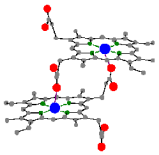
And so microscopically things are not what they appear macroscopically:

	Macro	Micro	Additive kinetic effect
Nucleation	α only	α and ϒ	No change to rates
Growth	α only	Low S α>ϒ High S α ~ϒ	α inhibited ϒ accelerated

1. Everything we want to explain we can do via a growth only model
2. The additives favour ϒ not only by inhibiting α but also by catalysing ϒ
3. The macroscopic experiments tell us nothing about nucleation.

Kinetics and structure are interlinked – the full story requires both.

Plenty of opportunity for crystal growers to collaborate with crystallographers.



The student -Ronnit Buller

Reading the literature

letters to nature

The structure of malaria pigment β-haematin

Silvina Pagola*, Peter W. Stephens*, D. Scott Bohle†, Andrew D. Kosar† & Sara K. Madsen†‡

* Department of Physics & Astronomy, State University of New York, Stony Brook, New York 11794-3800, USA
† Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071-3838, USA
‡ Present address: Department of Biologic and Materials Sciences, University of Michigan, Ann Arbor, Minnesota 48109, USA

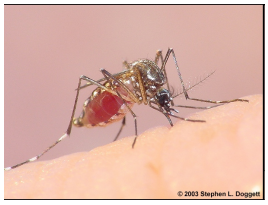
Despite the worldwide public health impact of malaria, neither the mechanism by which the *Plasmodium* parasite detoxifies and sequesters haem, nor the action of current antimalarial drugs is well understood. The haem groups released from the digestion of the haemoglobin of infected red blood cells are aggregated into an insoluble material called haemozoin or malaria pigment. Synthetic β-haematin (Fe^{III}-protoporphyrin-IX)$_2$ is chemically[1,2], spectroscopically[2,3] and crystallographically[4] identical to haemozoin and is believed to consist of strands of Fe^{III}-porphyrin units, linked into a polymer by propionate oxygen–iron bonds. Here we report the crystal structure of β-haematin determined using simulated annealing techniques to analyse powder diffraction data obtained with synchrotron radiation. The molecules are linked into dimers through reciprocal iron–carboxylate bonds to one of the propionic side chains of each porphyrin, and the dimers form chains linked by hydrogen bonds in the crystal. This result has implications for understanding the action of current antimalarial drugs and possibly for the design of new therapeutic agents.

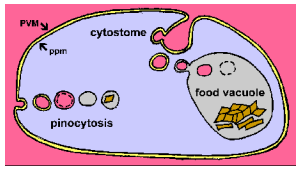
NATURE | VOL 404 | 16 MARCH 2000 | www.nature.com

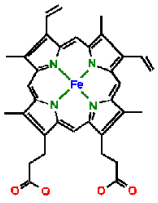
Back to malaria

Quinine was the only known prophylactic against malaria which in 1850 killed 2M people per year (and still does).

Perkins -mauve







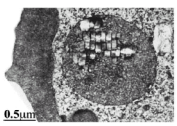


Figure 15. Electron micrograph of the digestive vacuole (dv) of a *Plasmodium falciparum* trophozoite inside an erythrocyte, showing a cluster of hemozoin crystals (bar = 0.5 μm). [Study by Goldberg et al.[9] Reproduced with permission from the author.]

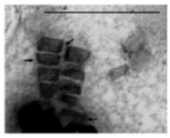


Figure 5. SEM micrograph of digestive vacuole in cultured parasite of *P. falciparum*, where representative arrows point to the more denser regions of the hemozoin crystals, indicating excess location of [^{3}H]chloroquine at their {001} faces. (Bar = 0.5 μm.) From ref 25. Copyright (1996) National Academy of Sciences, USA.

Quinoline Binding Site on Malaria Pigment Crystal: A Rational Pathway for Antimalaria Drug Design

Rosit Buller,*,† Matthew L. Peterson,† Ora Almarsson,† and Leslie Leiserowitz*,‡

Department of Materials and Interfaces, The Weizmann Institute of Science, Rehovot 76100, Israel, and Transform Pharmaceuticals Inc., 29 Hartwell Avenue, Lexington, Massachusetts 02421 USA

Received July 2, 2002

CRYSTAL GROWTH & DESIGN 2002 VOL. 2, NO. 6 553–562

Colloids, Crystals & Interfaces Research Group

556 Crystal Growth & Design, Vol. 2, No. 6, 2002

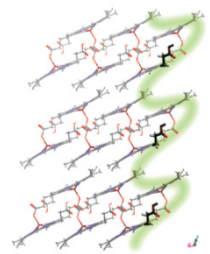


Figure 3. β-Hematin, viewed along the *a*-axis, showing the molecules exposed at the corrugated {001} face, with crevices outlined in green.

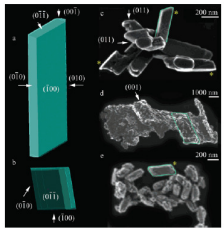
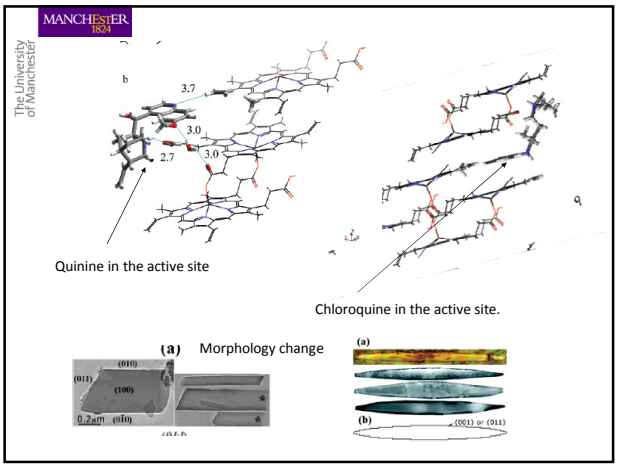


Figure 2. (a, b) Theoretical growth form of β-hematin viewed along the *a* and *c* axis, respectively. {*h,k,l*} indices of some faces are indicated. Figure 2. Field emission inlens scanning electron microscopy micrographs of hemozoin purified from (c) *P. falciparum*, (d) *S. mansoni*, (e) *H. columbae*. Representative crystals in (c–e) that strongly resemble the theoretical form are delineated, including one among the horizontally juxtaposed crystals in (d). From ref 28. Copyright (2001) with permission from Elsevier Science.



MANCHESTER 1824

The University of Manchester

Molecular routes to Nucleation Control.
Roger Davey

Content: 1. Catalysis - Heterogeneous processes
2. Inhibition - additives

Nucleation Summer School June 20-24th 2016 University of Strathclyde