Institution: University of Oxford

Unit of Assessment: 8 Chemistry

Title of case study: UOA08-07: Understanding solid-liquid reactions to improve manufacturing processes for agrochemicals at Syngenta

1. Summary of the impact

The cost of goods is an especially important issue in developing commercially available agrochemicals, which must be manufactured on a large scale. Richard Compton's research at the University of Oxford has led to a step change in the understanding of heterogeneous reaction mechanisms for liquid - organic solid or liquid - inorganic solid processes involved in large-scale manufacturing processes. Compton's work has had particular impact on optimising the processes used by Syngenta AG in its manufacturing of agrochemicals. Since 2008 the insights gained on inorganic-base dissolution have been of great benefit to Syngenta in its development of scalable robust manufacturing processes, particularly in relation to production of its fungicide Amistar and insecticide Actara, which are two of the world's largest selling products of this type. In 2012 Syngenta achieved total sales of over $ 14 billion, $ 4.8 billion of this from fungicide and insecticide revenues.

2. Underpinning research

Science & methodology

The fundamental science underpinning this case study involves the study of solid-liquid mass transfer and coupled chemical reactions. The work described has been carried out since 1993 under the supervision of Richard Compton at Oxford University. It has involved development of experimental and modelling methodologies to interrogate and quantify chemical and physical processes occurring directly at the solid-liquid interface rather than inferring them from remote indirect methods. Examples of the methods developed include the channel flow cell with numerous *in situ* analysis methodologies (this has been adopted and adapted by others, but was conceptualised and developed first by Compton), dynamic *in situ* AFM [1] and numerous novel electrochemical techniques. Modelling of the mass transfer processes between detector and solid-liquid interfaces under controlled and defined fluid-dynamic regimes has enabled direct measurement of the solid-liquid interfacial processes involved. Importantly, the new methods enable classes of differentiated mechanisms to be quantified, varying from those where reaction occurs solely in the solution phase following dissolution, through processes occurring in the interfacial regime, to true heterogeneous reactions that occur directly either at or within the solid surface. The methodology has been applied to both reactive dissolution processes and precipitation processes. Examples of particular value to Syngenta include:

(i) Studies on sparingly soluble organic molecules reacting with solubilised reactants

Cyanuric chloride (CC) is used in the manufacture of dyestuffs and agrochemicals at the thousands of tonnes per annum scale. CC is sparingly soluble in water. The Compton group has quantified the reactive dissolution of CC with amines including competitive hydrolysis [2], which occurs in parallel with dissolution. Similarly, a mechanistic understanding of the reaction of the insoluble *p*-chloranil with amines has been developed. In this case, the mechanism is further complicated by formation of a product of even lower solubility which "coats" the reactant, inhibiting the process [1]. The hydrolysis of crystalline trityl chloride has also been quantified and shown to be truly interfacial, driven by the specific orientation and concentration of C-Cl bonds at the substrate crystal surface; this is an unambiguous example of how Compton's methodologies can clearly characterise surface reactivity that is dependent upon the specific crystal face exposed to the reacting liquid medium [3]. This research was carried out in collaboration with Zeneca Ltd (who merged into Syngenta AG in 2000).

(ii) Studies on sparingly soluble inorganic bases in polar aprotic solvents

A significant extension of Compton's work was to refocus the research from organic to inorganic solids. Inorganic bases such as K_2CO_3 are used routinely with solvents such as DMF to generate the reactive anion of an acid in solution for subsequent reaction with a solubilised electrophile. The research conducted on K_2CO_3 clearly showed that very low base solubility can, and indeed does, lead to the dissolution of the base into the solvent becoming rate limiting, rather than any subsequent chemical step. Establishing this fact has had significant impact on operation at full scale. Work by Compton (in collaboration with Syngenta AG) quantified the dissolution rates of inorganic bases and how they vary depending upon conditions, between related structures (e.g. K^+ vs Na^+ base), and the crystal structure [4]. The methods developed were readily transferable to Syngenta's processes for agrochemical production (see Section 4) and had a major impact on their choice of base in manufacturing processes.

(iii) Targeted removal of metal ions from waste streams
Metal catalysed processes, especially using palladium, are becoming increasingly important in industry. The detection, removal and recovery of pollution from waste streams is important for cost reasons and to minimise environmental impact. The Compton group developed methods using simple functionalisation of cheap carbon to recover precious metals such as palladium from water, including detailed characterisation of the surface physical properties that control the removal processes [5].

3. References to the research

Asterisked outputs denote best indicators of quality; University of Oxford authors are underlined.

1. * Booth, J., Compton, R.G., Atherton, J.H. Mechanism of solid/liquid interfacial reactions. Atomic force microscopy studies of the self-passivating reaction between solid p-chloranil and aqueous phase N,N-dimethylphenylenediamine. J Phys Chem B, 1998, 102, 3980. DOI: 10.1021/jp980895q
   The hydrodynamic flow cell was used to measure the rate of a soluble reaction with the surface of an organic solid and to simultaneously image the formation of the insoluble product on the solid surface so providing a kinetic model for a process used by Syngenta.

2. Compton, R.G., Harding, M.S., Atherton, J.H., Brennan, C.M. Mechanism of a solid/liquid interfacial reaction. The reaction of an aqueous solution of an aromatic amine with cyanuric chloride. J. Phys. Chem., 1993, 97, 4677. DOI: 10.1021/j100120a020

3. * Tam, K.Y., Compton, R.G., Atherton, J.H., Brennan, C.M., Docherty, R. Mechanism of solid/liquid interfacial reactions. The hydrolytic dissolution of solid triphenylmethyl chloride in aqueous solution. JACS, 1996, 118, 4419. DOI: 10.1021/ja9529145
   Channel flow cell measurements, as pioneered by the Compton Group, were used to show that the rate of chemical reaction (hydrolysis) changed markedly between different crystal faces of an organic solid so providing a key stimulus for Syngenta to characterise reactivity at the individual crystal face scale.

4. * Forryan, C.L., Compton, R.G., Klymenko, O.V., Brennan, C.M., Taylor, C.L., Lennon, M. Comparative solubilisation of potassium carbonate, sodium bicarbonate and sodium carbonate in hot dimethylformamide: Application of cylindrical particle surface-controlled dissolution theory. Phys. Chem. Chem. Phys., 2006, 8, 633. DOI: 10.1039/b512463h

5. Abiman, P., Wildgoose, G.G., Crossley, A., Compton, R.G. Removal of palladium ions from aqueous systems by chemically modified cysteine carbon powder. J. Mater. Chem., 2008, 18, 3948. DOI: 10.1039/b805804k

4. Details of the impact

Since 2008 the research of the Compton group in the field of heterogeneous reaction mechanisms has had a significant impact at Syngenta AG, the company with which it has collaborated. Syngenta is the world's biggest manufacturer of crop chemicals and a major global supplier of insecticides, fungicides and herbicides. In 2012 it achieved sales of $ 14.2 billion [6]; fungicides alone accounted for 23% - over $ 3 billion - of total revenues [7] and insecticides for $ 1.8 billion [8]. Azoxystrobin, sold by Syngenta principally under the trade name Amistar, is the world's leading fungicide by sales, while thiamethoxam is the active ingredient developed by Syngenta and used in its product Actara, the best selling insecticide worldwide. Manufacturing processes for both these products, as well as others made by Syngenta, have benefited from important changes as a result of the Compton group research. In the words of a Senior Fellow at Syngenta UK, "*The fundamental science behind the processes described above has been key to the development of scalable, robust, optimised manufacturing processes where, although the chemical fundamentals (rate constant, equilibrium constant, etc.) are scale insensitive, the mass transfer components are not. The overall thinking and methodology used is the primary scientific value (transferable to all and any solid-liquid system, helping to direct technology exploitation and raising the awareness of the need for such methodology). However, the specific systems studied have proved of particular value to Syngenta since 2008 in terms of process changes, and have helped our process chemists from laboratory synthesis to include more physical quantitative chemistry in the development process.*" [10]

Impact of studies on sparingly soluble inorganic bases in polar aprotic solvents

Research by the Compton group in this area clearly showed that key processes, especially at full scale, can be controlled by the physical process of inorganic base dissolution, and drew attention to the fact that organic chemistry transformations cannot be studied in isolation from the inorganic transformations. As such, care needs to be taken when designing, scaling and running larger scale manufacture of the specific base used, the physical form of the base used and the processing conditions. This had substantial impact for Syngenta since 2008. They manufacture Amistar (the world's largest selling fungicide) via a sequence, the final step of which employs K_2CO_3 to deprotonate an acid, HA, in a polar aprotic solvent, to produce a nucleophilic A^-K^+ salt. This subsequently reacts with an electrophilic chloro-heterocycle to produce the active ingredient (Ai). The rate limiting 'step' in the overall process can switch from being the covalent-bond-forming reaction to the rate of carbonate dissolution, depending on the carbonate salt being used. Understanding this has allowed Syngenta to optimise the robustness of the process and appreciate fully the potential impact of using alternative carbonate sources.

The production of Actara, Syngenta's world-leading insecticide, also uses K_2CO_3 in the final Ai stage in an analogous manner. For environmental reasons, Syngenta desired to switch from K_2CO_3 to Na_2CO_3, but Na_2CO_3 failed in process development with much lower rates, lower conversions, longer cycle times and increased by-products. Compton's work showed that the solubility of Na_2CO_3 and rate of dissolution into polar aprotic solvents is an order of magnitude less than K_2CO_3. With this insight, Syngenta found that the solution-phase reactivity of the A^-K^+ and A^-Na^+ salts were comparable (slight differentiation due to ion-pairing effects) and that the failure with Na_2CO_3 was due to the process being controlled by the slow rate of dissolution. With this knowledge in hand, alternative processes were rapidly developed.

In both of these examples, water can be produced. In some cases the system then switches from involving solid-liquid mass transfer to solid-liquid-liquid transfer as the water produced becomes saturated in the inorganic base and phase separates from the polar aprotic solvent. This produces a gelatinous mass, which at full production scale requires control of agitation and active removal of the water. Otherwise, again, the rate of inorganic base mass transfer from the solid phase through the aqueous liquid phase to the continuous organic solvent (in which the reactant resides) becomes rate limiting. The methods devised by Compton have been used by Syngenta to study and control precisely such a process for an important recently-developed herbicide. A conversion of >98% without rate-limiting mass transfer is now obtained in manufacture, versus a previous figure of ~75% [10].

Impact of studies on sparingly soluble organic molecules reacting with solubilised reactants

Triazine-based herbicides such as Atrazine (used in Syngenta's product Gesaprim) are crucial to agriculture; it is estimated triazine-based herbicides currently save US consumers >$ 3 billion p.a. in decreased producer costs and increased yield and support 85,000 US jobs [9]. Cyanuric chloride forms the basis of triazine-based herbicides, and within Syngenta the science behind the research of the Compton group has subsequently been used to optimise the process for manufacture of herbicides like Gesaprim. Prior to the research of the Compton group, this had suffered from scale up issues; the work helped identify that the root cause of the problems was coating of the reactant solid with an even more insoluble product. [10]

Targeted removal of metal ions from waste streams

Homogeneous Pd catalysis is important in major industrial coupling reactions. The downside of large scale Pd use beyond the laboratory-scale is the large amounts of solubilised Pd that have to be recovered and removed from waste streams – for both cost and environmental reasons. The methods and concepts developed by the Compton group have been used by Syngenta since 2008 to plan how to address the issue and optimise recovery. [10]

The cost of goods is an especially important issue in the agrochemical industry [11]. Syngenta are unable to quantify the precise financial benefits to them of the Compton research concerning individual steps in multi-stage overall manufacturing processes. However, in the context of yearly revenues of billions of dollars, the financial impact for the company is likely to be very substantial. According to the Senior Fellow at Syngenta UK, *"Overall the research of the Compton group has been of great benefit to Syngenta, enabling significant improvements in the company's development of processes, and sustainably increasing its capability in quantitative physical chemistry. The extension of this has been broad impact into Syngenta's production processes*." [10]

5. Sources to corroborate the impact

[6] Syngenta webpage confirming the company's sales profile: http://www.syngenta.com/global/corporate/en/investor-relations/company-profile/Pages/key-facts.aspx (downloaded 06-11-2013).

[7] Bloomberg news item corroborating the percentage of Syngenta sales represented by fungicides: http://www.bloomberg.com/news/2013-04-17/bayer-claims-syngenta-s-fungicide-appear-infringes-patent.html (downloaded 06-11-2013).

[8] Syngenta webpage corroborating sales of its products: http://www.syngenta.com/global/corporate/en/investor-relations/company-profile/Pages/products-and-brands.aspx.

[9] Syngenta webpage corroborating statistics relating to Atrazine: http://www.atrazine.com/AtraMain.aspx (downloaded 11-10-2013).

[10] The Senior Fellow at Syngenta UK will corroborate impacts relating to process changes for manufacture of fungicide, insecticide and herbicide products at Syngenta and the consequent benefits to Syngenta. He will also corroborate impacts in relation to targeted removal of metal ions from waste streams.

[11] A recent article by Syngenta scientists highlights the importance of agrochemical costs in addressing food security for an estimated world population of 9 billion by 2050. http://www.sciencemag.org/content/341/6147/742.abstract