

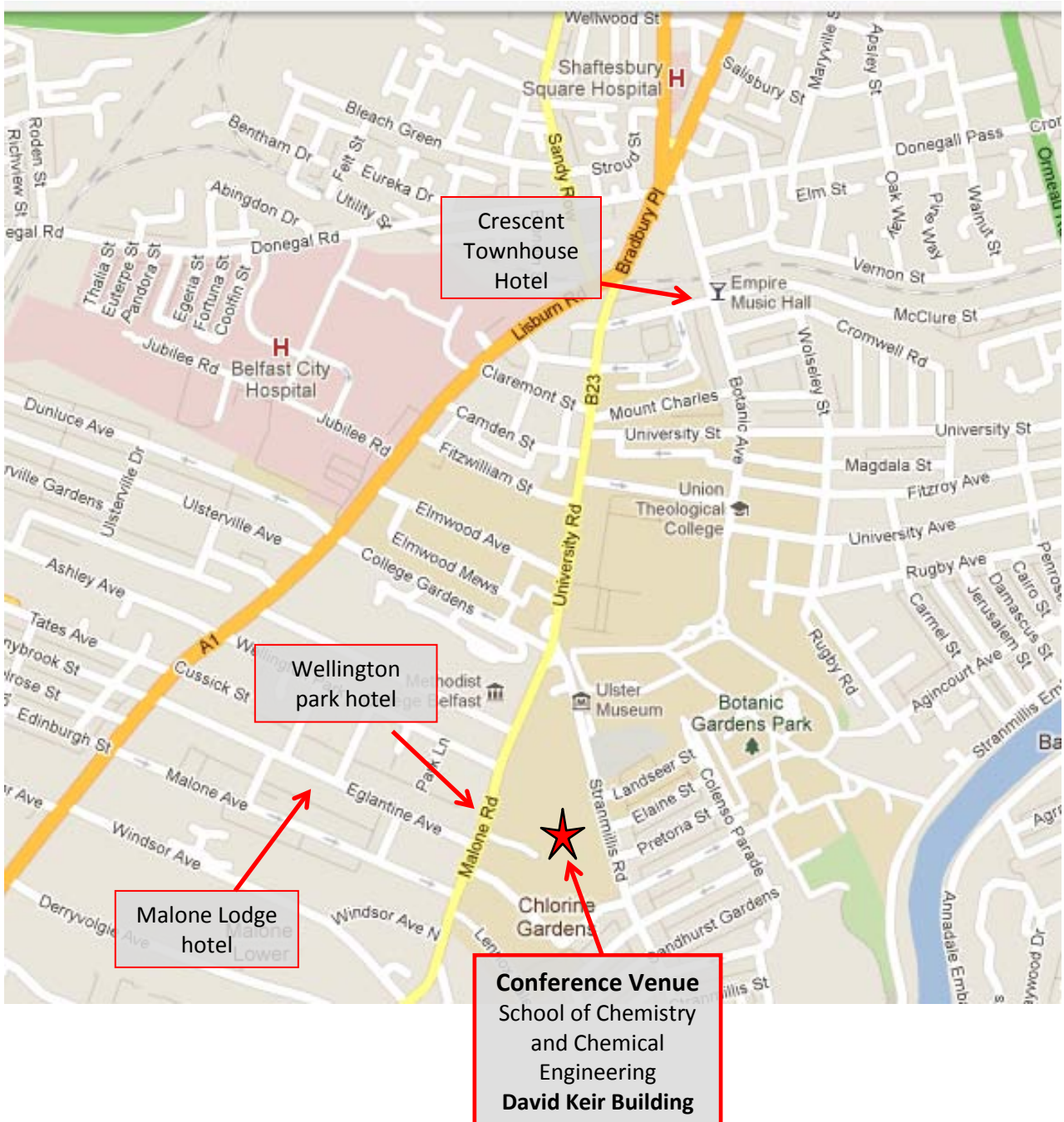
The 2nd Symposium on Mechanochemistry and Solvent-free Synthesis

Queen's University of Belfast

18th – 19th August 2011



Map of Queen's University of Belfast and its Vicinity



We are grateful to Retsch and ASEP (Analytical Services and Environmental Projects) for their sponsorship of the symposium.



Day 1: Thursday 18th August

12.30 – 1.30 **Sandwich buffet lunch** available in the Asquith Room (LG.432).

Session I (Room 01.403)

Chair: Stuart James

1.30 Peter Baláž, Košice

Mechanochemistry in technology: From lab-scale to industrial application

1.50 Elena Boldyreva, Novosibirsk

Mechanochemical synthesis in inorganic / organic systems: what is similar, what is different?

2.10 Rebecca Taylor, Belfast

Green catalyst preparation

2.30 Dario Braga, Bologna

Solid-state transformations of crystal forms

2.50 Coffee break (Asquith Room, LG.432)

Session II (Room 01.403)

Chair: Mark Muldoon

3.30 Fabrizia Grepioni, Bologna

Solid-state preparation of ionic co-crystals

3.50 Tomislav Friščić, McGill

Ion- and liquid-assisted grinding: MOFs, metallodrugs and mechanisms

4.10 Stuart James, Belfast

Mechanochemical synthesis and the resulting properties of MOFs

4.30 Lee Brammer, Sheffield

Characterising products of solid state syntheses and reactions

4.50 Kenneth Harris, Cardiff

Structural characterisation of new materials prepared by solid-state mechanochemistry

5.10 Posters and wine reception (Asquith Room, LG.432)

7.30 Dinner (Lanyon Building, Council Chamber and Canada Room)

Day 2: Friday 19th August

Session III (Room 01.403)

Chair: Dario Braga

9.20 Teresa Duarte, Lisbon

Diversity in mechanochemistry: Green synthesis of catalysts, new pharmaceutical forms and bio-inspired metal coordination compounds

9.40 Len MacGillivray, Iowa

Supramolecular catalysis in the organic solid state via dry grinding

10.00 Achim Stolle, Jena

Alkynes as building blocks for synthesis in ball mills

10.20 Coffee break (Asquith Room, LG432)

Session IV (Room 01.403)

Chair: Gary Sheldrake

10.50 James Mack, Cincinnati

Bizzarro world: Understanding the rules that govern mechanochemical reactions

11.10 Guan-Wu Wang, Hefei

Mechanical milling-promoted solvent-free reactions of [60]fullerene and beyond

11.30 Francesco Ravalico, Belfast

Rapid synthesis of nucleotide pyrophosphate linkages in a ball mill

11.50 Carsten Bolm, Aachen

Asymmetric organocatalysis in a ball mill

12.10 - 12.30 Opportunity for general discussion including joint activities

12.50-2.00 Sandwich lunch (Asquith Room, LG.432)

Lecture Abstracts

MECHANOCHEMISTRY IN TECHNOLOGY: FROM LAB-SCALE TO INDUSTRIAL APPLICATION

Peter Baláž

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This contribution deals with application of mechanochemistry in extractive metallurgy, materials engineering, crystal engineering, pharmacy and waste treatment. In extractive metallurgy the most commercially attractive potential applications will be illustrated. Mechanochemical approach in material and crystal engineering will focus on the non-equilibrium processing of materials and their current and potential applications. In pharmacy, the selected examples of fine milling application will show the improved bioavailability of drugs. The examples of fine milling in waste treatment are also given.

The main advantage of the mechanochemical processing is that it is a quantity process permitting kilograms of materials to be produced at an ambient temperature, easy handling operation conditions in a solvent – free mode and in a very short processing time. Nanoparticles are often formed by this technological approach which add value to the processed solids. Simplification of the processes, ecological safety and the product extraordinariness characterize the mechanochemical approach in technology.

More information on the topic can be found in the following monographs:

- P. Baláž, Mechanochemistry in Nanoscience and Minerals Engineering, Springer, Berlin Heidelberg 2008
- O. I. Lomovskij, V.V. Boldyrev, Mechanochemistry for Solving Environmental Problems, GPNTB SO RAN, Novosibirsk 2006 (in Russian)
- G. Kaupp, Organic Solid-State Reactions with 100 % Yield, Vol. 254 in: Topics in Current Chemistry, Springer, Berlin Heidelberg 2005
- C. Suryanarayana, Mechanical Alloying and Milling, Marcel Dekker, New York 2004
- E. G. Avvakumov, M. Senna, N. Kosova, Soft Mechanochemical Synthesis. A Basis for New Chemical Technologies, Kluwer Academic Publishers, Boston, 2001
- D. Braga, F. Grepioni, A. G. Orpen, Crystal Engineering: From Molecules and Crystals to Materials, Kluwer Academic Publishers, Dordrecht 1999.

MECHANOCHEMICAL SYNTHESIS IN INORGANIC / ORGANIC SYSTEMS: WHAT IS SIMILAR, WHAT IS DIFFERENT?

Elena V. Boldyreva^{1,2}

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Mechanochemical synthesis is being widely applied in inorganic chemistry since quite a long time, and mechanochemistry of inorganic solids is a well-established field. In the last decade mechanical treatment is becoming more and more popular for achieving selective and "greener" synthesis also in organic systems. New groups and researchers enter the field of mechanochemistry, and many of the facts and effects, which have been already known, are re-discovered, and at the same time some important concepts are often neglected. The author of this contribution is involved in mechanochemical research both in inorganic and organic systems since a long time. The aim of the contribution is to overview the basic concepts of mechanochemical synthesis in "solid + solid" systems in general, and to consider how they work when applied to inorganic and organic systems.

I shall first consider the general features of a "solid + solid" synthesis, not necessarily related to mechanical treatment, and discuss the problems of bringing reagents in contact (mixing), the phenomena at the interfaces, the role of diffusion, several variants of positive and negative feed-back in "solid + solid" reactions. I shall also consider the cases, when a reaction, although initiated in a mixture of solid reagents, occurs actually between gases, liquids, a solid and a liquid, or a solid and a gas.

Mechanochemical synthesis will be then considered in relation to the "solid + solid" synthesis in general. The role of mechanical treatment in bringing reagents in contact, intensifying the diffusion, modifying the interface and bulk properties and in this way affecting the chemical processes will be discussed. I shall consider the importance of selecting the optimum ratio of the particle size of the components, as well as of their relative hardness and brittleness, in addition to paying attention to chemical properties of reagents. The role of liquid and solid additives to the reagent mixture, as well as the effect of temperature on the outcome of the mechanochemical synthesis will be discussed. The importance of selecting the optimum type of mechanical treatment will be considered. A special attention will be paid to the consequences of the fact, that a mechanical action is not continuous, but is applied as pulses of a particular energy and frequency.

Boldyreva E.V., Boldyrev V.V. Mechanochemistry and mechanical activation of solids. In: *Experimental and Theoretical Studies in Modern Mechanochemistry* (Ed. G. Mulas & F. Delogu) 2010, Transworld research network: Kerala, p. 1-39.

GREEN CATALYST PREPARATION

Rebecca Taylor, Christopher Hardacre, Cristina Lagunas, Stuart James

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The conventional method for synthesis of heterogeneous catalysts is a multi-step reaction (seven steps) that produces large amounts of waste. In this project we have been looking at alternative methods of catalyst production which eliminate or lower the amount of steps and therefore waste produced.

2 wt % Ag/Al₂O₃ catalysts have been prepared by means of solvent-free mechanochemistry using a ball mill. They show a remarkable increase in activity for the reduction of nitrogen oxides with octane by lowering the light off temperature by up to 150 °C compared with a 2 wt% Ag/Al₂O₃ catalyst prepared by wet impregnation. The best catalyst prepared from silver oxide (Ag₂O_BM) showed 50% NO_x conversion at 240 °C and 99% at 360 °C (figure 1).

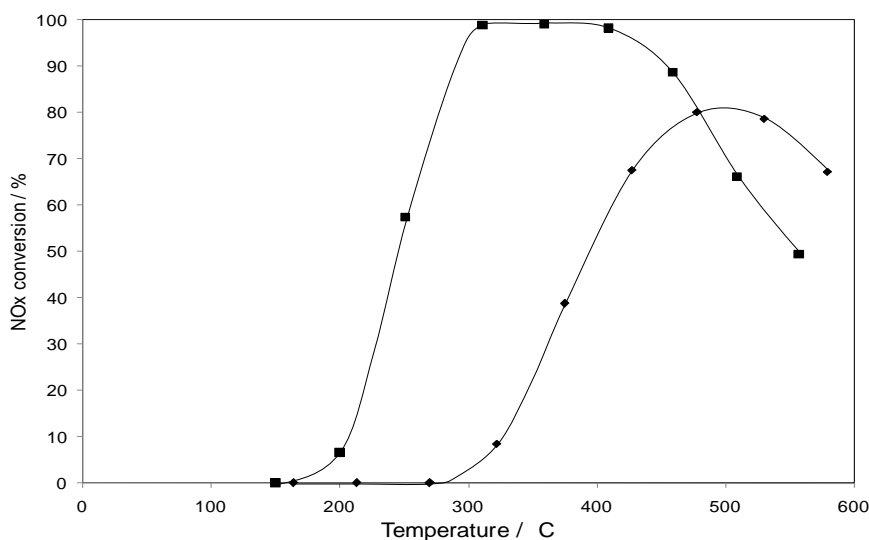


Figure 1. NO_x conversion as a function of catalyst temperature for the SCR of NO_x reaction with *n*-octane over Ag catalysts. (■ Ag₂O_BM; ◆ AgSTD)

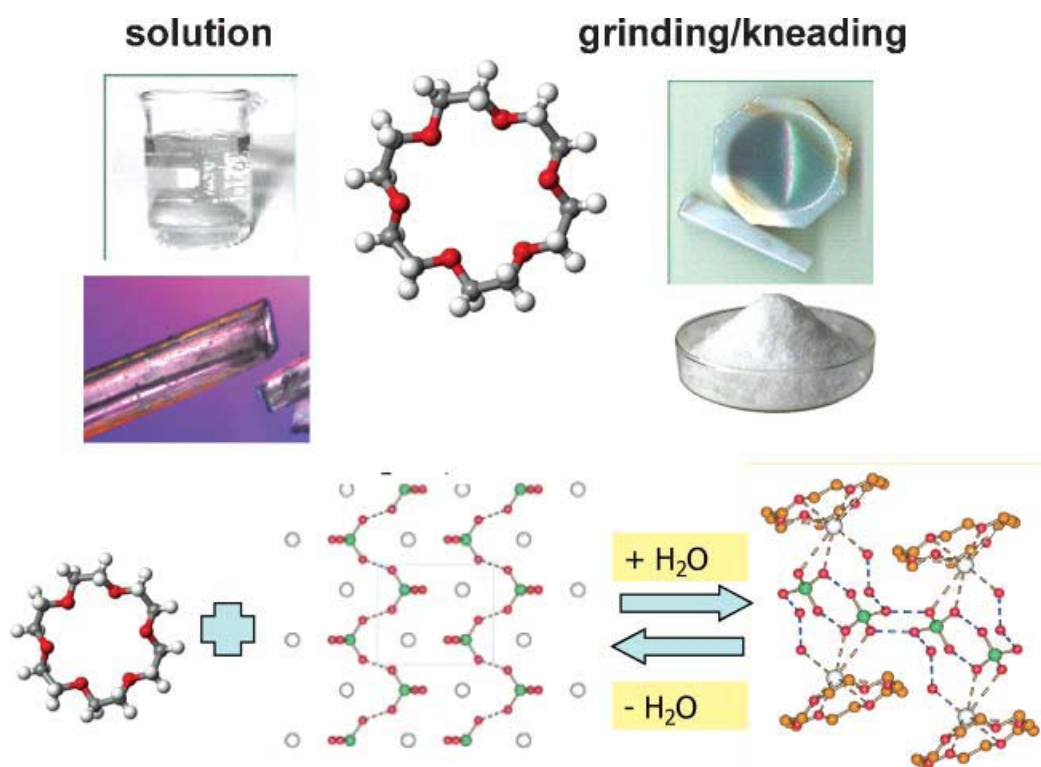
SOLID-STATE TRANSFORMATIONS OF CRYSTAL FORMS

Dario Braga

Dipartimento di Chimica G. Ciamician, Università degli Studi di Bologna.

15-crown[5] or 18-crown[6] complexes of alkali, transition metal and ammonium cations together with polyprotic inorganic and organic anions can be used to construct crystalline molecular salts based on hydrogen bonded anionic networks. This new class of organic-inorganic complexes displays a variety of crystal-to-crystal transformations, mainly associated to the loss/uptake of water molecules and/or to the ionic reorganization accompanying phase transitions on varying the temperature. The dehydration and phase transition processes have been investigated by DSC, TGA and variable temperature X-ray powder diffraction. Most of the complexes described herein have been prepared by solid state mixing of the solid reactants.

Further examples of solid-state transformations investigated at UniBo will be discussed.



SOLID-STATE PREPARATION OF IONIC CO-CRYSTALS

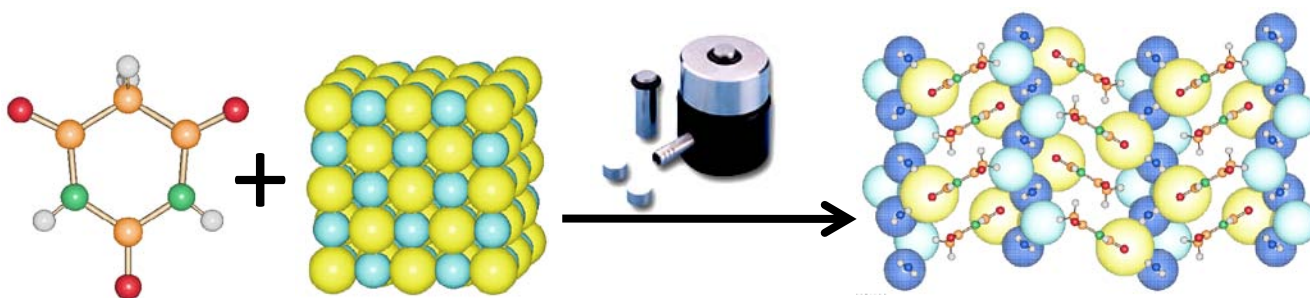
Fabrizia Grepioni

Dipartimento di Chimica G. Ciamician, Università degli Studi di Bologna.

Ionic co-crystals, i.e. crystals composed by inorganic salts and a neutral organic molecule, can be a valid route to change the physicochemical properties of the organic compound. For example, the possibility of increasing the thermal stability of an organic molecule by ionic co-crystallization or that of changing the dissolution and solubility properties have important implications in all areas, beside the pharmaceutical field, where crystal forms are investigated and utilized, e.g. pigments, explosives, agrochemicals etc.

Pressing solid barbituric acid with KBr to prepare samples for IR spectroscopy leads to formation of an *ionic co-crystal*, in which the co-former is a classical ionic salt; co-crystal formation is also obtained with the other alkali bromides (LiBr, NaBr, RbBr and CsBr) and with caesium iodide. The simultaneous presence of alkali and halide ions affects the dissolution properties of barbituric acid in water.

Further examples of co-crystalline materials recently obtained at UniBo will be presented.



ION- AND LIQUID-ASSISTED GRINDING: MOFS, METALLODRUGS AND MECHANISMS

Tomislav Frišćić

Department of Chemistry, McGill University, Montréal, Canada

This presentation will focus on the development, applications and mechanistic understanding of mechanochemical conversion of metal oxides into metal-organic materials, in particular on the recent approach of ion- and liquid-assisted grinding (ILAG).^[1] Namely, sub-stoichiometric amounts of simple ionic additives were found to significantly enhance the mechanochemical reactivity of zinc oxide towards small organic molecules, leading to a simple process for the synthesis of open and close-packed metal-organic frameworks (MOFs). Besides enhancing the rates of reactions, the ionic salt additives can also control the topology of the resulting MOFs, which was exploited for the topologically-selective synthesis of pillared metal carboxylate MOFs and zeolitic imidazolate frameworks (ZIFs).^[2] Besides MOF synthesis, the ILAG methodology was also recently applied for the synthesis of bismuth salicylate complexes, specifically bismuth subsalicylate which is the active component of the popular gastrointestinal metal-based drug Pepto-Bismol.^[3] Structural characterization of mechanochemically synthesized bismuth disalicylate from synchrotron X-ray powder diffraction data provided the first structure of a bismuth salicylate complex without organic auxiliaries (Figure 1). The recent developments in the monitoring and the understanding of the course of ILAG reactions will also be described.

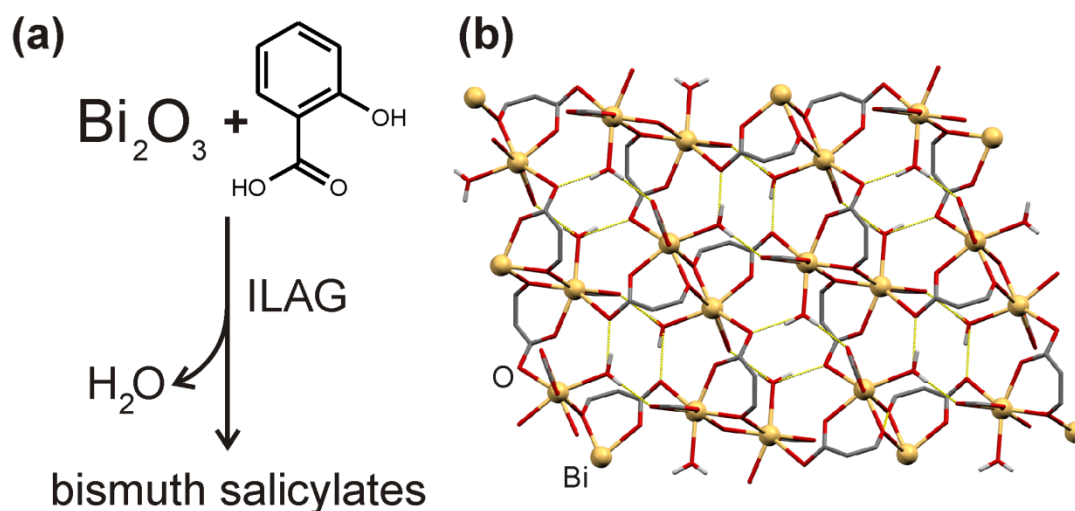


Figure 1. (a) The mechanochemical synthesis of bismuth salicylates directly from bismuth oxide and (b) fragment of the crystal structure of bismuth disalicylate coordination polymer.

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[2] *Angew. Chem. Int. Ed.* **2010**, *49*, 9640-9643.

[3] *Angew. Chem. Int. Ed.* **2011**, *50*, DOI: 10.1002/anie.201103171

MECHANOCHEMICAL FORMATION AND THE RESULTING PROPERTIES OF MOFS

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Work by several groups has established that many porous extended networks of metal ions and organic ligands (metal organic frameworks, or 'MOFs') can be prepared mechanochemically, conveniently, using either no solvent or using only minimal amounts for the synthetic step. This presentation will concentrate on aspects of reactivity as well as the critical point of the actual properties of such mechanochemically-prepared materials, and how these may differ from those of MOFs prepared by conventional solvent-based routes.

References:

1. Study of the mechanochemical formation and resulting properties of an archetypal MOF: $\text{Cu}_3(\text{BTC})_2$ (BTC=1,3,5-benzenetricarboxylate), W.B. Yuan, A.L. Garay, A. Pichon, R. Clowes, C.D. Wood, A.I. Cooper and S.L. James *CrysEngComm* 2010, **12**, 4063.
2. Mechanochemical synthesis of homo- and hetero-rare-earth(III) metal-organic frameworks by ball milling W. Yuan, J. O'Connor and S.L. James *CrystEngComm* 2010, **12**, 3515.
3. High reactivity of metal-organic frameworks under Grinding Conditions: Parallels with Organic Molecular Materials, W.B. Yuan, T. Friscic, D. Apperley and S.L. James *Angew. Chem. Int. Ed.* 2010, **49**, 3916.
4. An array based study of reactivity under solvent-free mechanochemical conditions – insights and trends, A. Pichon and S.L. James *CrystEngComm*, 2008, **10**, 1839.

CHARACTERISING PRODUCTS OF SOLID STATE SYNTHESSES AND REACTIONS

Lee Brammer, Paul Smart, Iñigo Vitorica Yrezabal, Charles Mason, Jason Loader, Ramida Rattanakam, James Wright

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Keywords: solid-gas reactions, gas and vapour sorption, coordination chemistry, metal-organic frameworks, powder diffraction, spectroscopy, computational chemistry, EXAFS

Single crystal X-ray diffraction is in most instances the definitive method of characterisation of crystalline materials, but is limited in its application to individual crystals and is usually not applicable to characterisation of the products of mechanochemical and many other solid-state reactions.

Our interests in solid state synthesis and reactions have involved studies of molecular crystals,¹⁻⁵ coordination polymers⁶ and metal-organic framework materials.^{7,8}

The presentation will focus on examples of methods used to characterize products and/or follow the progress of reactions in the solid state. These include powder X-ray diffraction, solid state and gas-phase IR spectroscopy, computational modelling and EXAFS spectroscopy.

[1] G. Mínguez Espallargas, L. Brammer, J. van de Streek, K. Shankland, A. J. Florence, H. Adams, *J. Am. Chem. Soc.* **2006**, *128*, 9584-9585.

[2] G. Mínguez Espallargas, M. Hippler, A. J. Florence, P. Fernandes, J. van de Streek, M. Brunelli, W. I. F. David, K. Shankland, L. Brammer, *J. Am. Chem. Soc.* **2007**, *129*, 15606-15614.

[3] G. Mínguez Espallargas, J. van de Streek, P. Fernandes, A. J. Florence, M. Brunelli, K. Shankland, L. Brammer, *Angew. Chem. Int. Ed.* **2010**, *49*, 8892.

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[8] C. A. Mason, P. Smart, J. Loader, A. J. Florence, M. Brunelli, L. Brammer, unpublished results.

STRUCTURAL CHARACTERIZATION OF NEW MATERIALS PREPARED BY SOLID-STATE MECHANOCHEMISTRY

Kenneth D.M. Harris

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Many new materials can be accessed only *via* mechanochemical preparation procedures, in which suitable solid starting materials are subjected to mechanical grinding. In general, materials prepared by such processes are microcrystalline powders, and the product phase usually does not contain single crystals of suitable size and quality to allow structure determination by single-crystal X-ray diffraction. Instead, the most suitable strategy for determining the structural properties of new materials prepared in this way is to use powder X-ray diffraction [1,2].

Although structure determination from powder X-ray diffraction data is significantly more challenging than structure determination from single-crystal X-ray diffraction data, the methodology for carrying out structure determination directly from powder X-ray diffraction data has advanced significantly in recent years, and this strategy can now be applied successfully to determine crystal structures of moderate complexity. The recent upsurge in the application of powder X-ray diffraction in this regard has coincided with the development of the "direct-space" strategy for structure solution [3], which is particularly suitable for structure determination of materials that are constructed from well-defined modular building units (such as metal-organic-frameworks or molecular solids). It is important to emphasize that the use of solid-state NMR in conjunction with powder X-ray diffraction data serves as a particularly powerful combined experimental approach [4], as solid-state NMR data can yield direct structural insights that can assist the analysis of the powder X-ray diffraction data.

The lecture will give an overview of current opportunities for carrying out structure determination of crystalline materials directly from powder X-ray diffraction data, giving emphasis to specific issues that arise in the case of materials prepared by solid-state mechanochemical processes. Illustrative examples [5-7] of structure determination in such cases will be presented.

- [1] K.D.M. Harris, M. Tremayne, B.M. Kariuki, *Angew. Chemie Int. Ed.*, **2001**, *40*, 1626.
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DIVERSITY IN MECHANOCHEMISTRY: GREEN SYNTHESIS OF CATALYSTS, NEW PHARMACEUTICAL FORMS AND BIO-INSPIRED METAL COORDINATION COMPOUNDS

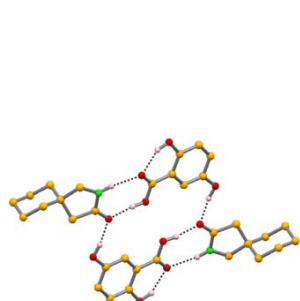
M. Teresa Duarte

Centro de Química Estrutural, Departamento de Engenharia Química e Biológica, Instituto Superior Técnico, 1049-001 Lisboa, Portugal. (teresa.duarte@ist.utl.pt)

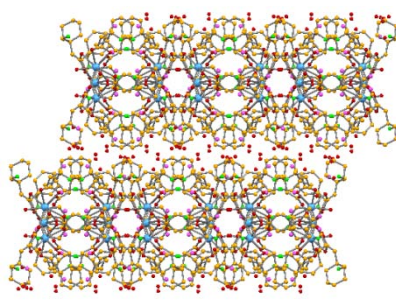
Mechanochemical techniques have been successfully employed in the synthesis of new multicomponent active pharmaceutical ingredients (API), using both liquid-assisted and neat grinding. Mechanochemistry has proved to be a feasible alternative when dealing with highly insoluble reagents and was successfully applied in the synthesis of molecular salts and cocrystals of gabapentin. Moreover, new multicomponent forms of APIs obtained by this method proved to have a more suitable solubility than the commercially available drug: we managed to both enhance (perindopril erbumine) and decrease (gabapentin-lactam) the solubility.

Bio-inspired metal coordination compounds (BioMOC²) have been obtained with the intent of improving API performance. With gabapentin we have successfully prepared coordination compounds with different lanthanides. Several pharmaceutical zinc complexes have been synthesized and are being characterized and tested.

Studies on an alternative synthetic route for the preparation of Brookhart type catalysts are under way, avoiding the 20-24 hours reactions in solution that are currently used. Promising results have been obtained with quantitative yield and will be presented.



GBPL cocrystal



GBP BioMOC²



Brookhart type catalysts

Acknowledgements are due to Vânia André, Clara Gomes, João Luís Ferreira da Silva and Pedro Teixeira Gomes. Funding is acknowledge to FCT (SFRH/BD/40474/2007; SFRH/BPD/64423/2009, PEst-OE/QUI/UI0100/2011)

SUPRAMOLECULAR CATALYSIS IN THE ORGANIC SOLID STATE VIA DRY GRINDING.

Anatoliy N. Sokolov, Dejan-Kresimir Bucar, Jonas Baltrusaitis, and **Leonard R. MacGillivray**.

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In recent years, we have been using small molecules in the form of hydrogen-bond-donor and -acceptor templates to direct [2+2] photodimerizations in the solid state. The templates isolate the reaction from effects of long-range packing so as to enable us to construct molecules in solids by design. In this presentation, we will show how the approach can be extended to the field of catalysis. We demonstrate how the reactivity can be controlled using sub-stoichiometric amounts of templates to give products in near quantitative yield. A key feature of the catalysis is an application of dry mortar-and-pestle grinding to facilitate molecular movement so as to achieve turnover.

ALKYNES AS BUILDING BLOCKS FOR SYNTHESSES IN BALL MILLS

Achim Stolle

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Chemical reactions in both laboratory and industry are nowadays not assessed by their yield and product selectivity only, but also by metrics displaying the ecological and economical footprint of the process. On the road to sustainable chemistry variables like the *E*-factor (describing the waste employed for the production of a quantity of a chemical) become important for process intensification. In synthesis, extensive solvent-use account often for low sustainability of the reaction expressed by a high *E*-factor. Thus, reduction of the solvent amount or omission are some of the possibilities for making a reaction *greener*. Although solvent-free reactions are very efficient in the liquid-phase,^[1] problems regarding mass transport, energy entry, and energy distribution come up if heterogeneous reactions are performed without solvent. One solution to overcome the mass-transport limitations is the instalment of efficient mixing devices. Regarding this, ball mills are ideal tools combining system-inherently a high mixing efficiency combined with high energy densities due to frictional forces. Thus, ball mills conquer their place among the tools for non-classical ways of energy entry (microwave, photochemistry, ultrasound, electrochemistry) favoured in organic synthesis.^[1c, 2]

The present contribution will discuss recent examples from this field of research, displaying opportunities to make an organic synthesis *greener*. The versatility of the method regarding the formation of various products from simple building blocks – alkynes – is presented. Reactions like the Sonogashira reaction,^[3] Cu-catalyzed azide-alkyne-cycloaddition (CuAAC),^[4] homocoupling of alkynes^[3c,5] and enamine formation by addition of amines to alkynes are discussed. Beside the opportunities to form different products, CuAAC for example offers the possibility to functionalize polymers in a ball mill without destruction of the polymer structure. Even directed polymerization seemed to be possible.

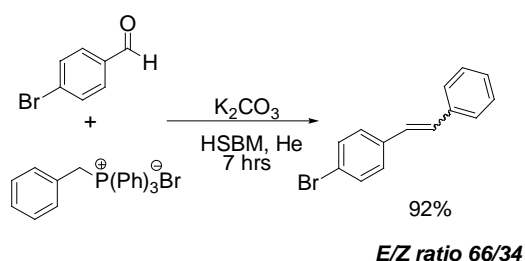
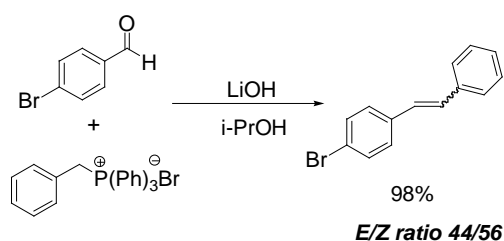
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BIZZARRO WORLD: UNDERSTANDING THE RULES THAT GOVERN MECHANOCHEMICAL REACTIONS

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The rules that govern organic chemistry in solution are known to the point that we can fully explain these rules in beginning courses to new students. Do the same rules apply when conducting chemistry in the mechanochemical world? We have investigated a number of organic reactions and will present the similarities and difference between these very different methods of performing chemical reactions.



MECHANICAL MILLING-PROMOTED SOLVENT-FREE REACTIONS OF [60]FULLERENE AND BEYOND

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The mechanical milling technique has been broadly used to produce alloys, metal oxides and other inorganic materials. Solvent-free organic reactions have drawn great interest, particularly from the viewpoint of green chemistry, because harmful organic solvents can be eliminated or reduced. Moreover, some unexpected products can be obtained only from solvent-free reactions rather than from the liquid-phase reactions. The mechanical milling technique was first applied to Reformatsky-type reaction of [60]fullerene (C_{60}) at mid-1990s,¹ in order to test the possibility of solvent-free reactions in fullerene chemistry, meanwhile avoiding the large amount of solvents for liquid-phase reactions due to the poor solubility of fullerenes in common organic solvents. The so-called “high-speed vibration milling” (HSVM) technique was then employed for other solvent-free reactions of C_{60} ,² including the synthesis of fullerene dimer C_{120} ,^{3a,b} Prato reaction,^{3c} reaction of C_{60} with 1,3-dicarbonyl compounds,^{3d-f} reaction of C_{60} with diazo compounds,^{3g} Diels–Alder reaction of C_{60} .^{3h} Subsequently, we extended the mechanical milling-promoted solvent-free reaction protocol to non-fullerene molecules, and investigated the Michael addition of 1,3-dicarbonyl compounds to chalcones and azachalcones,^{4a,b} non-reductive addition of 1,3-cyclohexanediones to *in situ* generated imines mediated by manganese(III) acetate,^{4c} reductive benzylation of malononitrile and 4-methylaniline,^{4d} aminochlorination^{4e} and aminobromination^{4f} of electron-deficient olefins, oxidative amidation of aldehydes with anilines,^{4g} synthesis of naphthopyrans by the nucleophilic addition reaction of terminal alkynes to carbonyl compounds and subsequent cyclization reaction of the synthesized propargylic alcohols with 2-naphthol,^{4h} unexpected cycloaddition of 1,3-cyclohexanediones to 1-(pyridin-2-yl)-enones mediated by manganese(III) acetate⁴ⁱ and the unexpected reaction of aldehydes with 1,3-dicarbonyl compounds promoted by iodine and DMAP leading to sipro dihydrofuran and cyclopropane derivatives.^{4j}



HSVM



Retsch MM200 mixer mill

(Guan-Wu Wang cont.)

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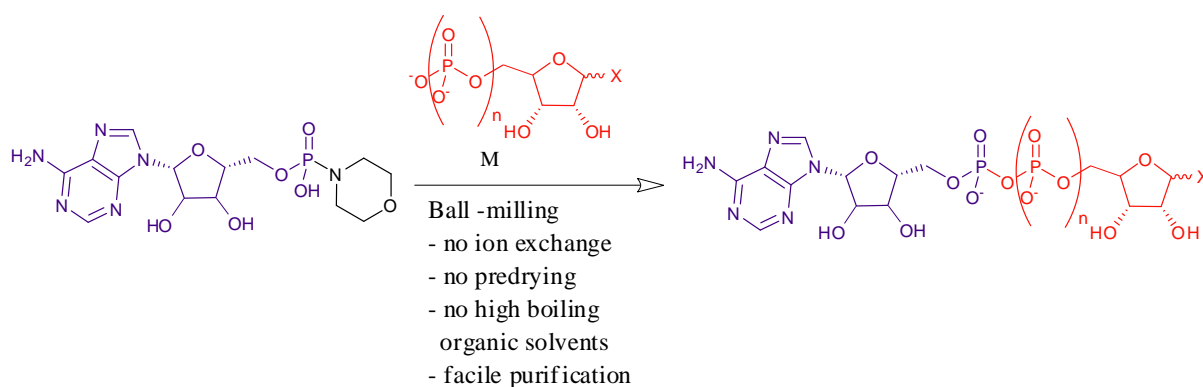
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RAPID SYNTHESIS OF NUCLEOTIDE PYROPHOSPHATE LINKAGES IN A BALL MILL

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Atom-efficient pyrophosphate coupling between a 5'-phosphoromorpholidate nucleotide donors and riboside mono-, di-, or tri-phosphate acceptors was achieved using liquid-assisted grinding in a ball-mill. This new methodology enabled the use of commercially available donors and acceptors (as their alkaline or alkaline earth salts) without extensive processing to generate organic-soluble materials, did not require anhydrous pyridine, dmf or formamide and thereby led to a dramatic reduction of the reaction time from 2 – 6 days to ninety minutes without prejudicing the yields (50 – 87% HPLC yield) and facilitated rapid purification using reversed-phase HPLC.¹

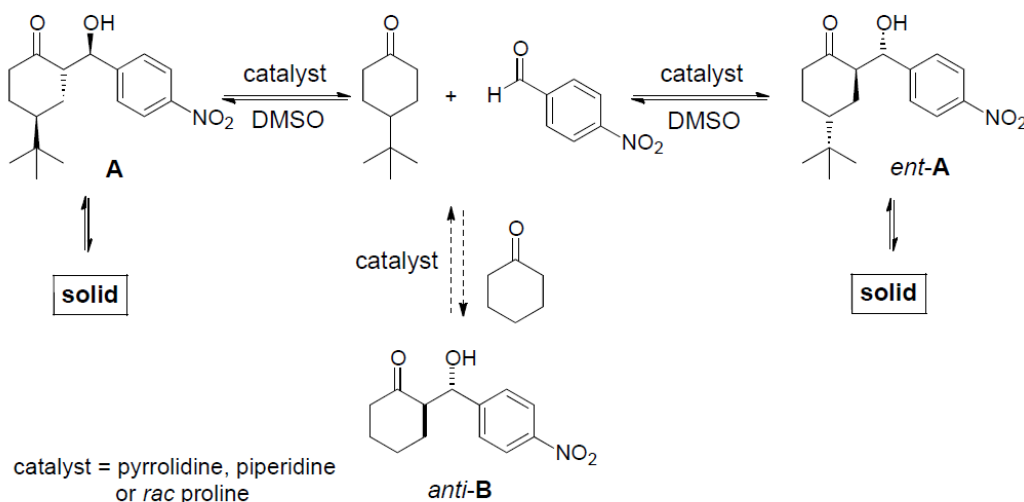


ASYMMETRIC ORGANOCATALYSIS IN A BALL MILL

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Enantioselective C-C-bond formations have been achieved by asymmetric organocatalysis in a ball mill. Alkaloids and proline served as chiral catalysts providing products with high enantioselectivities. Commonly, the reactions were performed solvent-free. With a scalemic catalyst, non-linear effects have been observed. Under appropriate conditions, enantioenrichments catalyzed by an achiral or racemic base can be observed.



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Poster Abstracts

THE FORMATION OF PHARMACEUTICAL “CO-AMORPHOUS” MATERIALS BY GRINDING

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Solubility¹ and bioavailability of an API are properties that the pharmaceutical industry strives to enhance. They may be improved by changing the solid form of the drug, such as by the formation of cocrystals and amorphous forms.^{2,3} Cocrystals have also been found to improve the physical stability of a drug⁴ via the formation of intermolecular interactions such as hydrogen bonds. Amorphous drugs are highly soluble, although usually less stable than their crystalline counterparts.⁵ Both cocrystals and amorphous materials can be formed by grinding.

Here we present studies on the combination of the concepts of cocrystals and amorphous materials to form amorphous multi-component solids, “co-amorphous” materials. In particular, we look at the co-amorphisation by ball milling of model drug compounds, theophylline and caffeine. We also report on the discovery of a metastable, second polymorph of 1:1 caffeine: citric acid cocrystal, formed via a “co-amorphous” solid phase.

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ORGANIC CHEMISTRY WITHOUT BULK ORGANIC SOLVENT – MECHANOCHEMICAL OPPORTUNITIES FOR AN ENVIRONMENTALLY-FRIENDLY RESEARCH

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In the search for a preparative method that would meet the requirements of green chemistry¹, a mechanical treatment of (in)organic reagents by simply grinding them together² has reappeared as one of the solutions to pollution related issues of the modern chemical industry. Recent advancements in the solid-state synthetic methodology, such as liquid-assisted grinding (LAG),³ allow a simple, rapid and clean synthesis of a variety of materials, including cocrystals, salts or coordination polymers. In the next level powder X-ray diffraction (PXRD), as an invaluable tool in materials characterisation, can often enable the structure determination to be carried out without using bulk solvents and the need to grow single crystals. Bearing this in mind, we now extend the previously proposed „solvent-free research“ paradigm from metal-organic chemistry⁴ to the field of organic synthesis as a part of our continuing mission in developing new principles of laboratory work.

In this presentation, we report on the quantitative synthesis of structurally diverse thiourea derivatives by automatised ball-milling of the starting material.⁵ On a selection of mechanochemically prepared compounds, we have utilised PXRD for structure determination, thus implementing the „solvent-free research“ paradigm into an organic chemistry laboratory. (Figure 1.).

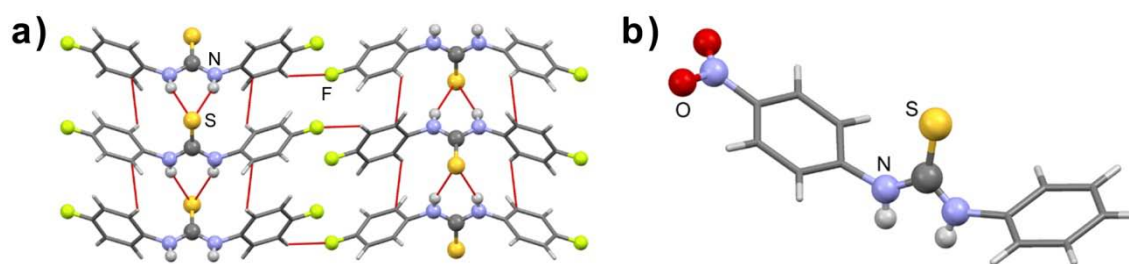


Figure 1. a) Non-covalent interactions in the crystal structure of *N,N'*-di(4-fluorophenyl)thiourea. b) The molecular structure of *N*-(4-nitrophenyl)-*N'*-phenylthiourea determined from powder X-ray diffraction data.

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