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Using solid catalysts in disulfide-based dynamic combinatorial solution- and mechano-chemistry

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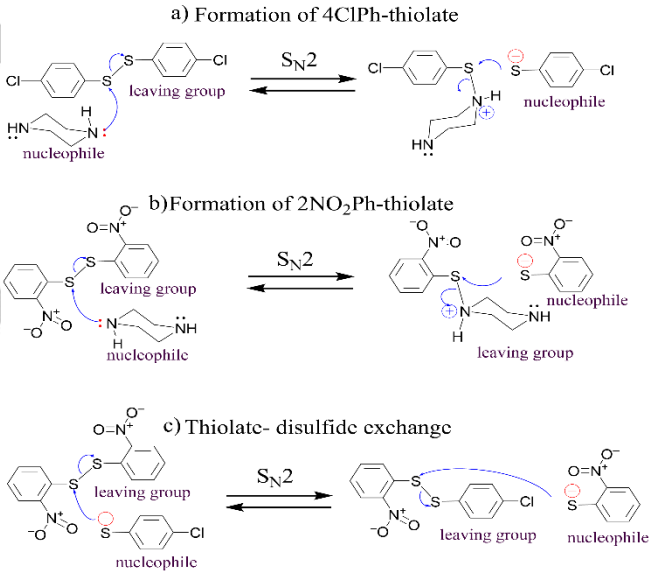
Abstract: We here show for the first time that solid amines can act as catalysts for disulfide-based dynamic combinatorial chemistry by ball mill grinding. The mechanochemical equilibrium for the two disulfide reactions studied is reached within one to three hours using ten different amine catalysts. This contrasts with the weeks to months to achieve solution equilibrium for most solid amine catalysts at 2%M at 2mM concentration in a suitable solvent. The final mechanochemical equilibrium is independent of the catalyst used, but varies with other ball mill grinding factors such as the presence of traces of solvent. The different efficiencies of the amines tested are discussed.

Introduction

In dynamic combinatorial chemistry (DCC), simple molecular units (building blocks) are held together by reversible covalent bonds. These bonds potentially generate a complex mixture of products which continuously interconvert: the composition of the mixture at equilibrium is thermodynamically controlled and is referred to as a dynamic combinatorial library. Such mixtures have been intensively explored in solution to generate complex and unexpected structures through templating and self-assembly.[1–3] The base-catalysed exchange of disulfides is one of the most successful and widely-used reactions in this field, usually involving nucleophilic attack by a thiolate anion on a disulfide bond.

We have been studying dynamic covalent chemistry in the solid-state environment of ball mill grinding, exploring whether the outcomes of reactions are the same as in solution. Our studies have also used DCC as a tool to explore the fundamental aspects of ball mill grinding. We here show for the first time that solid amines are catalysts for disulfide-based DCC by ball mill grinding, presumably by acting as nucleophiles (Scheme 1).

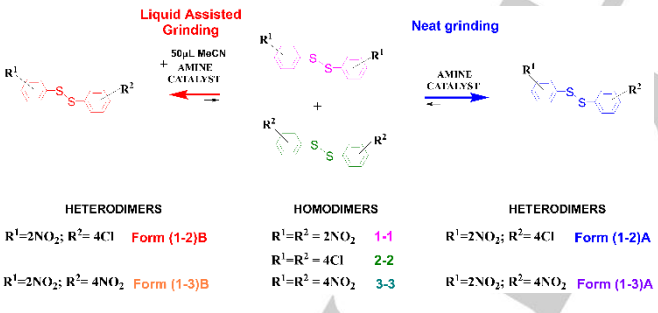


Scheme 1. Schematic diagram of the ball mill base-catalysed disulfide exchange reaction; 200mg of equimolar quantities of homodimers **1-1** and **2-2** forming the polymorphs **(1-2)B** or **(1-2)A** of the heterodimer **1-2** in the presence of typically 2-4% mol/mol of an amine catalyst under ball mill LAG conditions (left) and NG conditions (right) respectively; 200mg of equimolar quantities of homodimers **1-1** and **3-3** forming the polymorphs **(1-3)B** or **(1-3)A** of the heterodimer **1-3** in the presence of typically 2-4% mol/mol of an amine catalyst under ball mill LAG conditions (left) and NG conditions (right) respectively. With the exception of dbu, all amine catalysts were solid at room conditions.

The need for more sustainable and environmentally benign chemical synthesis methodologies is garnering increased awareness of ball mill grinding technologies. Ball milling falls under the umbrella of mechanochemistry, a technique of applying mechanical force to influence chemical reactivity. This technology was considered by IUPAC in 2019 to be amongst “the 10 chemical innovations that will change our world’.[4]

Mechanochemistry as a discipline began around the early 20th century.[5,6] The field was dominated by studies of the mechanical treatment of inorganic solids (e.g. minerals) and the preparation of alloys,[7,8] with limited examples discussing organic reactions.[9] Renewed interest in ball mill grinding technology has taken place over the past 20 years, with particular emphasis in the fields of organic[10,11] and inorganic[12,13] synthesis, material discovery (e.g. cocrystals and framework materials),[14–17] and mechanocatalysis.[18–20] However, this renewed enthusiasm for mechanochemical research remains predominantly focused on its phenomenological applications. Comparatively little research is being devoted to understanding the underlying driving forces, kinetics, and mechanism of reactions induced by ball mill grinding. This lack in fundamental understanding limits the translation of mechanochemical technologies into both academic and industrial laboratories, where well-understood solution-based methods are preferred.

Our team has been investigating the fundamentals of ball mill grinding[21–23] primarily through use of dynamic combinatorial chemistry as a probe.[24–29] Ball milling reactions generally terminate with a final equilibrium plateau wherein the phase composition does not change while the milling conditions are maintained.[23] We have demonstrated that such milling equilibria are reversible and dynamic in nature, with the stationary points corresponding to local thermodynamic minima.[26] In our earlier model disulfide exchange reactions, catalysed by a liquid amine base catalyst, the milling equilibrium comprises the heterodimer as one of two polymorphic forms, **(1-2)A** and **(1-2)B** in the case of 4-chloro-phenyl-2-nitro-phenyl-disulfide, **(1-3)A** and **(1-3)B** in the case of 4-nitro-phenyl-2-nitro-phenyl-disulfide; the outcome depends on whether the experiment is run under ball mill neat grinding (NG) or liquid assisted grinding (LAG) in the presence of 50 μL of acetonitrile per 200 mg of total powder in the milling jar (Scheme 2 and Figure 2 and Figure 3).[24–28]



Scheme 2. Proposed mechanism of disulfide exchange between two disulfide dimers. The formation of thiolate anion is promoted by an amine catalyst acting as a nucleophile on the disulfide bond. Here we depict the example of the disulfide exchange reaction of a) $(4ClPhS)_2$ and b) $(2NO_2PhS)_2$ which are promoted by the amine catalyst, piperazine. c) depicts the thiolate disulfide exchange reaction.

In both cases, the outcome of ball mill grinding reactions for the disulfides is in sharp contrast to the results of solution-based disulfide DCC libraries (Figure 4). While quantitative yields of heterodimer are obtained by ball milling for these compounds, only a statistical mixture of the starting and product phases can be obtained from solution.[28] A better understanding of the nature of these milling processes promises deeper insight into the significant differences between solution- and mechano-chemistry.

A crucial aspect of ball mill grinding is the efficiency of mixing[30–33] and the rheological properties[34,35] of the substances subjected to milling. At a fundamental level these parameters dictate the ease with which successful reactive collisions can occur at the molecular level, and hence control the probability of chemistry occurring. The addition of additives in the form of liquids or polymers can greatly facilitate mixing in many powder systems,[36] suggesting the physical state of the reactants can exert significant influence over the feasibility of a ball milling reaction. The question follows whether solid catalysts are as efficient as liquid catalysts under ball milling conditions.

Results and Discussion

We here explore the potential to replace liquid catalysts with solid catalysts in disulfide based dynamic combinatorial chemistry under ball mill grinding conditions. As the amount of catalyst added to a milling jar is typically 2-4% mol/mol we expect their ability to catalyse the reaction will depend on the powder mixing efficiency. Moreover, as the catalyst exists in the solid state at room conditions, we explore in this way the potential for molecular level mixing in a ternary system. Ultimately, we aim to demonstrate that the nature of nucleophilic amine catalyst, either sp^2 or sp^3, secondary or tertiary amine, in the solid or liquid form, does not affect the outcome of dynamic covalent mechanochemistry at milling equilibrium.

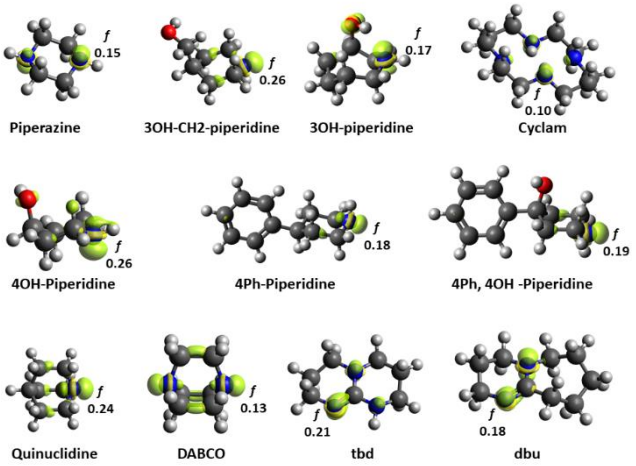


Figure 1. Reactivity surfaces (f_-) as nucleophiles for the selection of N-based catalysts examined in this work, shown as 0.01 isosurfaces. Positive (green) and negative (yellow) nodes are shown, with atoms coloured as: H- white; C- grey; N- blue; O- red

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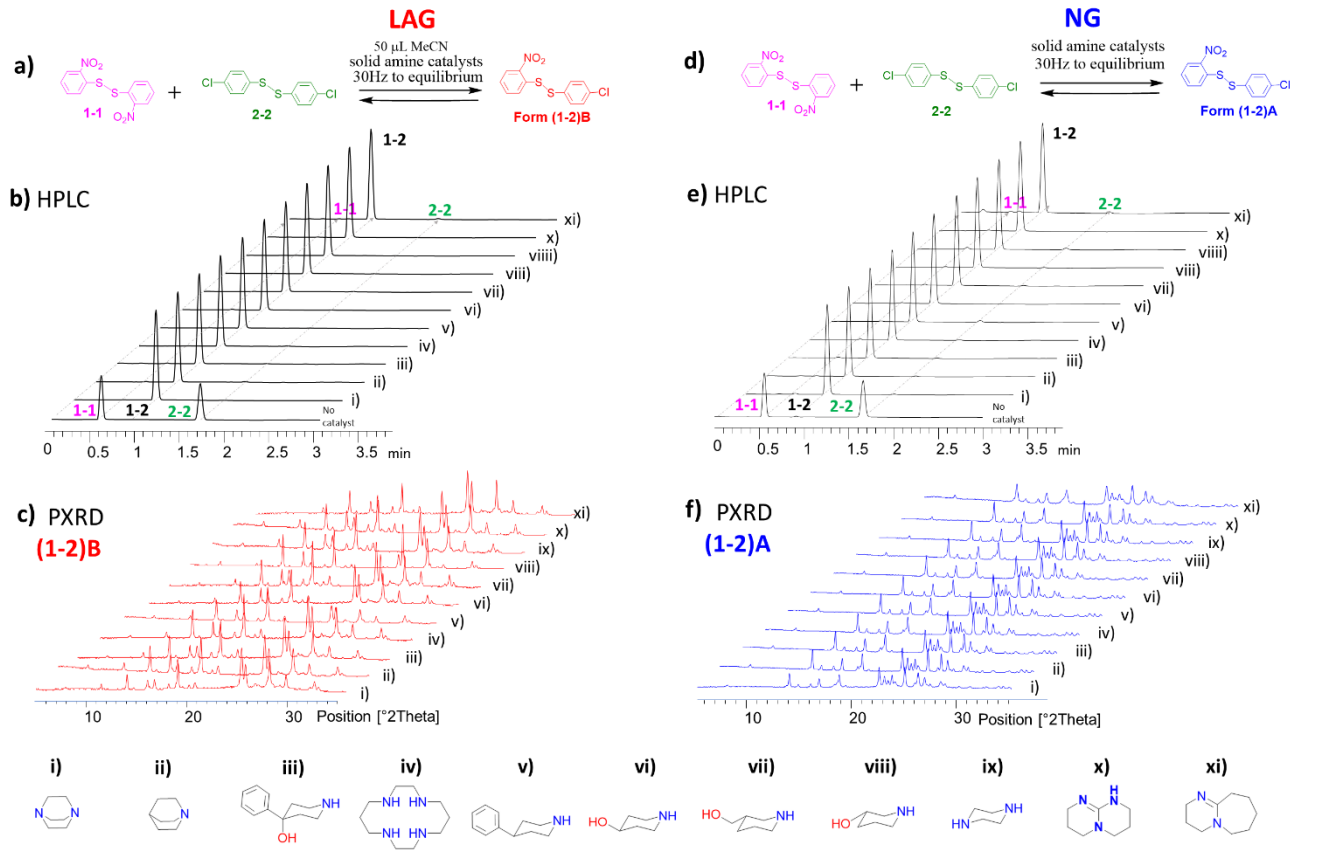

Figure 2. Experimental results of ball mill grinding to equilibrium of **1-1** and **2-2** using 10 solid-state amine catalysts and dbu, a liquid amine. The chemical structure of the amines is shown in the bottom black box. Reaction scheme and experimental grinding conditions are shown for a) LAG reactions and d) NG reactions. Framed in red, the outcome at equilibrium of the ball mill LAG reaction with the 11 amine catalyst, showing in b) their HPLC chromatograms with 97%M yield and c) PXRD scans of **Form (1-2)B**. Framed in blue, the outcome at equilibrium of ball mill NG reactions showing in e) their HPLC chromatograms with 97%M yield and f) the corresponding PXRD scans yielding **Form (1-2)A**.

Under NG conditions we obtained a 97%M conversion to **Form (1-2)A** (Figure 2, right column). Instead, 97%M **Form (1-2)B** was obtained under LAG conditions using 50 μL of acetonitrile (Figure 2, left column). In both cases, the remaining 3%M material comprised the 2 homodimers in an equimolar ratio (see ESI Section 6). For all solid amine catalysts except DABCO, equilibrium under LAG conditions was achieved within 45 minutes, as seen with dbu. In contrast, to reach equilibrium under NG typically required between 45 min and 3 h, depending on the catalyst (see ESI Section 6). There were three exceptions to this NG trend: the tertiary amines (Quinuclidine and DABCO) and 4Ph,4OH-piperidine, which all require many hours to reach equilibrium (See ESI, Section 6.9, 6.10 and 6.8). The summary of all LAG and NG experiments for 1-2 system is illustrated in Fig. S16. Importantly, the relative time required to achieve mechanochemical equilibrium under NG does not appear to correlate well with the nucleophilic strength of the amine catalyst, as indicated by f_- (Figure 1 and ESI S2), suggesting that the different activity under mechanochemical conditions is not dominated by a chemical origin. (Further discussion, see ESI Section 8).

The chemical rationale for these rate differences is not obvious. The secondary amines all possess a proton which could aid catalysis by neutralising the departing thiolate anion. However, this would not explain the slow reaction of 4Ph,4OH piperidine or the effectiveness of (liquid) dbu. Instead, we considered the possibility that these catalysts may have distinct thermal properties, potentially indicating that their behaviour under ball mill grinding conditions may differ from the other catalysts. Our differential scanning calorimetric (DSC) measurements reveal significant hygroscopicity of DABCO and quinuclidine (see ESI Section 3). We suppose that these materials may deliquesce during ball milling, thereby adversely affecting mixing efficiency, for example via the 'snowball effect',[35] wherein powder clumps into balls. However, no signs of hygroscopicity were observed in 4Ph,4OH-piperidine, which displayed one of the highest melting points (*ca.* 160 °C) of all our tested catalysts. The exceptionally poor catalytic effect of 4Ph,4OH-piperidine may correlate to other solid-state properties (e.g. hardness). This requires further investigation.

Similarly, the ten solid catalysts tested led to identical equilibrium chemical and phase compositions to liquid dbu when used in the **1-3,** 4-nitrophenyl-2-nitrophenyl-disulfide system (see Figure 3). Under LAG conditions **Form (1-3)B** is obtained above 99%M (Figure 3, left column), while under NG conditions, Form (**1-3**)A is formed between 80-85%M. In both cases, the remaining 5-20%M comprises the two homodimers in an equimolar ratio (Figure 3, right column). The nature of the solid catalyst did not play a significant role in the mechanochemical synthesis of **1-3**. Equilibrium was achieved for all solid catalysts in under 45 mins with LAG conditions. Instead, 3-4 h were generally required under NG conditions. A notable exception was DABCO, which required over 8 h to achieve

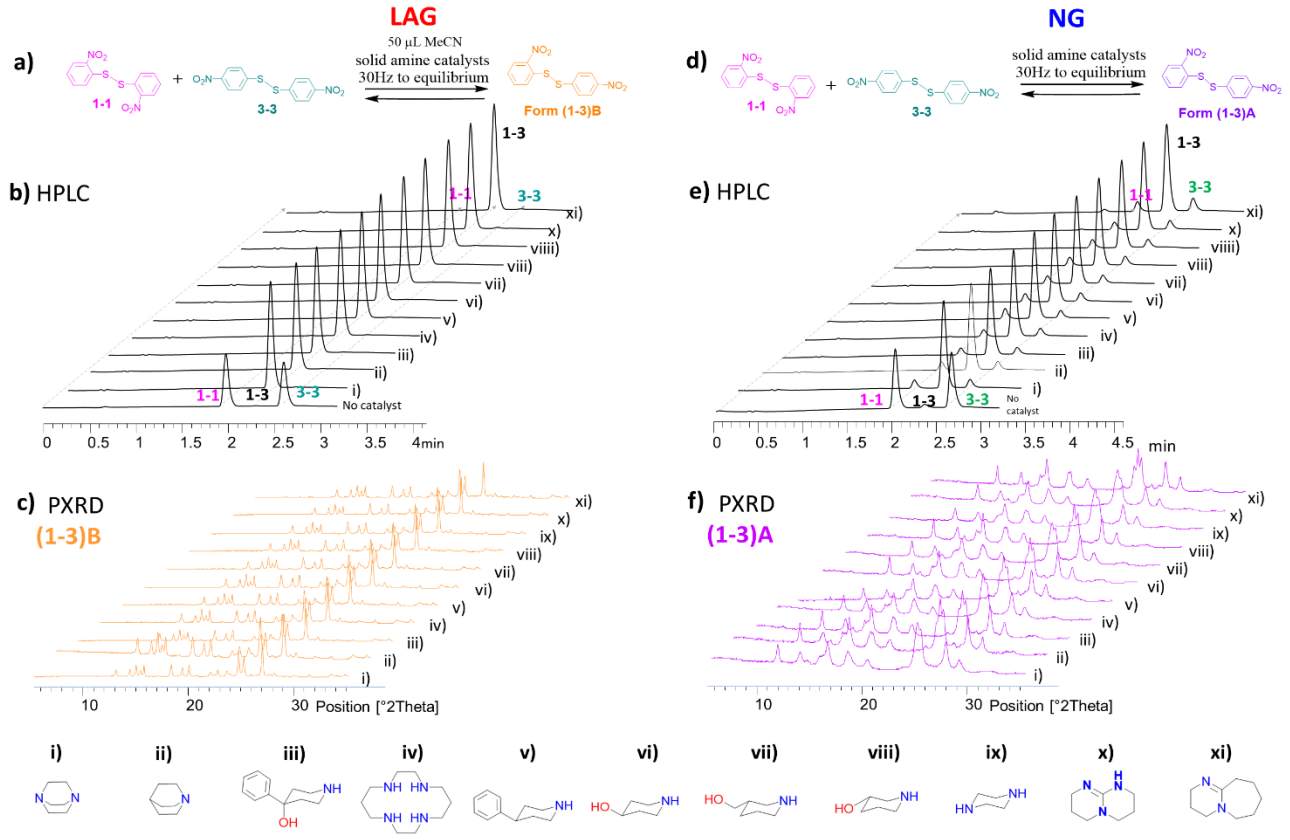

Figure 3. Experimental results of ball mill grinding to equilibrium of **1-1** and **3-3** using 10 solid-state amine catalysts and dbu, a liquid amine. The chemical structure of the amines is shown in the bottom black box. Reaction scheme and experimental grinding conditions are shown for a) LAG reactions and d) NG reactions. Framed in red, the outcome at equilibrium of the ball mill LAG reaction with the 11 amine catalyst, showing in b) their HPLC chromatograms with 99% yield and c) PXRD scans of **Form (1-3)B**. Framed in blue, the outcome at equilibrium of ball mill NG reactions showing in e) their HPLC chromatograms with 80-85%M yield and f) the corresponding PXRD scans yielding **Form (1-3)A**.

equilibrium under NG conditions, perhaps due to its highly hygroscopic nature (See ESI Section 7). The summary of all LAG and NG experiments for 1-3 system is illustrated in Fig. S30. Our experiments highlight strong differences between DCC under solution- and mechano-chemical conditions for all the amine catalysts studied here. Contrary to what was observed under milling conditions, amines are very poor catalysts for disulfide exchange in solution. We note that while near quantitative yields are obtained mechanochemically, statistical mixtures with ratios 2:1:1 of the heterodimers to homodimers is expected in solution. Yet, whereas the milling equilibrium was typically obtained within 3 h for our DCC mechanochemical reactions, equilibrium was not reached for most catalysts within four weeks under solution conditions. The difference between solution and mechanochemical reactivity is most striking for **1-1** + **2-2** (see Figure 3a), which resulted in a markedly poorer disulfide exchange yield in solution as compared to **1-1** + **3-3** (Figure 4b).

The 2mM solution-DCC experiments here presented (Figure 4) were prepared in ethyl acetate with 0.04mM of the 11 amine catalysts (2%M with respect to DCC). Ethyl acetate was selected as the ideal solvent for these experiments due to its relatively high bp at 77°C which allows the solution-DCC to be studied with minimal evaporation over the period of 1 month, the solubility of the most insoluble disulfide **1-1** in EtOAc at 4.5mg/mL is good and EtOAc does not promote disulfide.

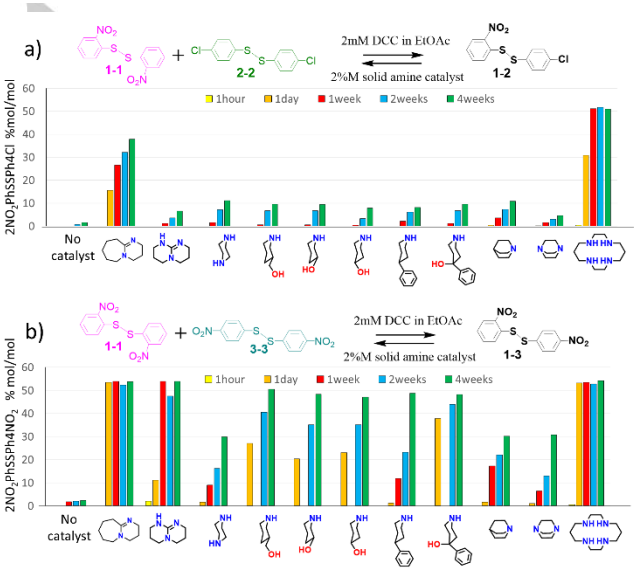

Figure 4 Progression over 1 month of the formation of heterodimer from equimolar mixtures of two homodimers in ethyl acetate solution in the presence of the 11 amine catalysts. a) 4-chlorophenyl-disulfide and 2-nitrophenyl-disulfide DCC system and b) 2-nitrophenyl-disulfide and 4-nitrophenyl-disulfide DCC system. At equilibrium, disulfide exchange in solution should reach a statistical mixture (25:25:50%M of both homodimers to the corresponding heterodimer).

Conclusion

The ability of ten solid amines to work as catalysts in disulfide based DCC was tested under solution and mechanochemical conditions on two model disulfide exchange reactions. While reaction mixtures in some solvents were still evolving after 4 weeks, DCC equilibrium is reached within 3 h under mechanochemical conditions for most solid amine catalysts studied. Many of the catalysts tested led to equilibrium in less than an hour under mechanochemical reaction. The differences in catalyst efficiency may be due to solid state properties such as hygroscopicity, melting point, or friability. Chemical equilibrium under mechanochemical conditions, which is in general different from solution equilibria, do not depend on the liquid or solid amine catalyst used. Phase and chemical milling equilibria depend on factors such as the presence, nature, of solvent in substoichiometric amounts.

In the systems studied here, the dominant formation of heterodimers rather than a statistical distribution with homodimers results from a type of dynamic combinatorial selection. We have previously shown that the selection pressure is due to the greater stability of the heterodimer crystal relative to the stability of the homodimer crystals, not to any difference in intrinsic stabilities of the hetero- or homo-dimers. The slightly more favourable crystal packing in these heterodimers could be thought of as a kind of self-templating. This raises the intriguing question, which we have not yet explored, of whether adding templates to a mixture of building blocks in a ball milling experiment could direct the selective formation of receptor cavities in the solid state in a manner that is reminiscent of molecularly-imprinted polymers.

Experimental Section

Chemicals and Materials

All solvent used for ball mill grinding experiments were obtained as follows: acetonitrile (MeCN), ethyl acetate (EtOAc) was freshly distilled in house from LR grade.

All liquid and solid catalysts and disulfide homodimers were obtained as follows:

dbu 1,8-diazabicyclo[5,4,0]undec-7-ene [6674-22-2], (MW=152.24; bp= 83°C), was purchased from Acros Organics (>97.5 % by GC); Claimed to be hydroscopic.

tbd 1,5,7-Triazabicyclodec-5-ene [5807-14-7] (MW=139.20; mp= 128.0 to 132.0 °C) was purchased from TCI (>98.0%(T)(HPLC),claimed to be moisture sensitive);

Cyclam 1,4,8,11-tetraazocyclo[2,2,2]octane (also named TACTD) [295-37-4] (MW=200.33; mp= 187.0 to 193.0 °C) was purchased from TCI (>98.0%(T), claimed to be hydroscopic) ;

DABCO 1,4 diazabicyclo[2,2,2] octane [280-57-9] (MW=112.18 ; mp= 156 to 160 °C) was purchased from .Aldrich as ≥99% and later from TCI (>98.0%(GC)(T), claimed to be hydroscopic) ;

Quinuclidine or 1-azabicyclo[2,2,2] octane (also named ABCO) [100-76-5]](MW=111.19 ; mp= 157-160°C) was purchased from Aldrich (97%) and later from TCI (>96.0%(GC)(T), claimed to be air sensitive), ;

3-hydroxy-piperidine [6859-99-0] (here named 3OH-Piperidine) (MW=101.15; mp= 60.0 to 64.0 °C) was purchased from Lancaster; claimed to be hydroscopic and air sensitive)

3-hydroxymethyl-piperidine [4606-65-9] (here named 3OHCH2-Piperidine) (MW=115.18; mp= 59.0 to 64.0 °C), was purchased from Alfa Aesar (96%, claimed to be hydroscopic);

4-hydroxy-piperidine [5382-16-1] (here named 4OH-Piperidine) (MW=101.15; mp= 85.0 to 91.0 °C) was purchased from Alfa Aesar (≥96.0%, claimed to be hygroscopic);

4-Phenyl-piperidine [771-99-3] (here named 4Ph-Piperidine) (MW=112.18 ; mp= 156 to 160 °C) was purchased from Acros Organics (97.5%, claimed to be air sensitive);

4-hydroxy,4-phenyl-piperidine [40807-61-2] (here named 4Ph, 4OH-Piperidine) (MW=177.25; mp= 157.0 to 162.0 °C) was purchased from TCI (>98.0%(GC)(T);

Piperazine anhydrous [110-85-0] (MW=112.18; mp= 156 to 160 °C) was purchased from Alfa Aesar (99%; claimed to be light Sensitive, air sensitive and hygroscopic)

Bis(4-chlorophenyl) disulfide [1142-19-4] (98+%) referred here as 2-2 was purchased from TCI,

Bis(2-nitrophenyl) disulfide [1155-00-6] referred here as 1-1 was initially purchased from Sigma Aldrich as 99% and later from TCI (>98.0%(GC)(N) which proved to be of higher purity and a more reliable chemical)

Bis(4-nitrophenyl) disulfide [1155-00-6] (98%) referred here as 3-3 was purchased from TCI.

The snap closure jars were machined in house from 316 stainless steel. The 7 mm diameter 316 stainless steel ball bearings were obtained from Dejay Distribution Ltd in UK. PXRD sample glass slides were manufactured in house. The 10 mL ZrO2 grinding jars and 10 mm ZrO_2 ball were obtained from Retsch.

Powder X-ray diffractometry (PXRD) analysis

X-ray powder diffractograms in the 2θ range 5-45° (Cu Kα radiation, step size 0.03°, time/step 100 s, 0.04 rad soller, VxA 40x40 with a total time of 13 minutes) were collected on a Panalytical X'Pert Pro diffractometer equipped with an X'Celerator detector operating in reflection geometry.

High Performance Liquid Chromatography (HPLC) analysis

HPLC analysis of the chemical composition of the powder were performed using a modular Agilent 1200 Series HPLC system composed of a HPLC high pressure binary pump, autosampler with injector programming capabilities, Peltier type column oven with 6 µL heat exchanger and a Diode Array Detector with a semi-micro flow cell (1.6µL, 6mm pathlength) to reduce peak dispersion when using short columns as in this case. The flow-path was connected using 0.12 mm ID stainless steel tubing to minimize peak dispersion.

HPLC method for the $2NO_2$PhSSPh4Cl system is:

HPLC column: 1.8µm Zorbax XDB C18, (4.6mm ID × 50 mm length)
Solvent A: Water +0.1% Formic acid;
Solvent B: Acetonitrile +0.1% Formic acid;
Gradient of 0-2 minutes 75% - 85%B with re-equilibration time of 1 minutes.
Flowrate: 2 ml/min; Column temperature of 60°C;
Injection volume of 1 µL.
1-1 eluted at 0.6 min, **1-2** at 1.0 min and **2-2** at 1.8 min.

The signal was monitored at 259 nm (8 nm bandwidth) with reference at 550 nm (100 nm bandwidth). These wavelength parameters were selected as they gave the same peak area for **1-1** and **2-2** which are added as equimolar, allowing to use the % peak area ratio (PAR) and refer the HPLC results for **1-1**, **2-2** and **1-2** as %M.

HPLC method for the $2NO_2PhSSPh4NO_2$ system is:

HPLC column: 2.0μm ACE C18-PFP, (4.6mm ID × 50 mm length)
Solvent A: Water +0.1% Formic acid;
Solvent B: Methanol +0.1% Formic acid;
Gradient of 0-2 minutes 75% to 90% B with re-equilibration time of 1 minutes. Run time of 3 minutes.
Flowrate: 1.4 ml/min; Column temperature of 50°C;
Injection volume of 0.5 μL.
1-1 eluted at 1.9 min, **1-3** at 2.2 min and **3-3** at 2.5 min.
The signal was monitored at 280 nm (8 nm bandwidth) with reference at 550 nm (100 nm bandwidth). These wavelength parameters were selected as they gave the same peak area for **1-1** and **3-3** which are added as equimolar, allowing to use the % peak area ratio (PAR) and refer the HPLC results for **1-1**, **3-3** and **1-3** as %M.

Differential Scanning Calorimetry (DSC) and Thermo-gravimetric Analysis (TGA)

Data was collected using a Mettler-Toledo TGA/DSC 3+ STAR system, with 100 µL Al crucibles. The samples (ca 5 mg) were heated at 5 $K.min^{-1}$, with a nitrogen stream blown over the sample at a flow rate of 80 $mL.min^{-1}$.

Sample preparation for $2NO_2PhSSPh4Cl$ ball mill grinding experiments

This solid state DCC reaction was prepared at a 200 mg scale by grinding 0.34 mmol of $(2NO_2PhS)_2$ crystals (104.82mg of 1-1) and 0.34 mmol of $(4ClPhS)_2$ crystals (97.66mg of 2-2) in a 14.5mL stainless steel snap-closure grinding jar (see Figure S2 a). The powder was weighed on a 5-figure balance, transferred to the bottom part of the grinding jar and both homodimers mixed with a micro-spatula. For the experiments with no catalyst, nothing else was added.

For those experiments with the liquid or solid catalysts, typically 2-4%mol/mol of the catalyst to disulfides were added and mixed well with a microspatula. Two 7 mm ID 316 stainless steel ball bearings were added on top of the powder (see Figure S2 a). For neat grinding, nothing else was added while for LAG experiments, 50 μL acetonitrile was added on top of the powder. The jar was finally snap closed and the juncture was securely sealed with insulating tape. The solid was milled at 30 Hz for the required time in a Retsch MM400 Shaker Mill.

Sample preparation for $2NO_2PhSSPh4NO_2$ ball mill grinding experiments

This solid state DCC reaction was prepared at a 200 mg scale by grinding 0.32 mmol of $(2NO_2PhS)_2$ crystals (98.67 mg of 1-1) and 0.32 mmol of $(4NO_2PhS)_2$ crystals (98.67 mg of 3-3) in a 14.5mL 316 stainless steel snap-closure grinding jar (see Figure S2 a). The powder was weighed on a 5-figure balance, transferred to the bottom part of the grinding jar and both homodimers mixed with a micro-spatula. For the experiments with no catalysts nothing else was added.

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Sample preparation for 2mM solution DCC experiments in EtOAc with 2%M amine catalysts

495 μL of the 2.02 mM stock solution of each homodimer were added to 12 HPLC vials for the 12 solution DCC experiments of the 1-2 or 1-3 system (Table S 3). 10 μL of the 4mM stock solution of each of the 11 amine catalysts were added to each of the 11 vials (Table S 4). An additional vial was prepared for the "no catalyst" experiment adding 10 μL of EtOAc instead of the stock solution of amine catalysts. These vials were well capped and stirred over 1 month period when not being analysed by HPLC.

Computational Details

Molecular geometries were extracted from available X-ray crystallographic structures. Where possible, the geometry was extracted from the mono-component crystal structure of the molecule. Where this was not possible, the geometry was extracted from a cocrystal containing the desired molecule. For this study, geometries were taken from: Cyclam,[37] 4-OH-Piperidine,[38] DBU,[39] TBD,[40] piperazine,[41] 4Ph-4OH-piperidine,[42] DABCO hydrate,[43] Quinuclidine carbon tetrabromide.[44] The structure for 3OH-piperidine was prepared manually. All ab initio electron densities were calculated using the ORCA v4.1software.[45] The input molecular geometry was optimized at B3LYP/6-311+G(d) level of theory. The electron densities were calculated with 'VeryTight' SCF integration at the B3LYP level of theory, commonly used in Fukui type analysis of organic systems.[46] The resulting electron densities were analysed using the MultiWfn software,[47] for analysis of the Fukui functions and analysis of the charge density via the Quantum Theory of Atoms in Molecules (QTAIM). Hirschfeld charges were used for the calculation of Fukui functions, shown to provide an accurate partitioning of the charge density.[46]]

Acknowledgements

The authors acknowledge COST Action CA18112 – Mechanochemistry for Sustainable Industry. We thank: C. A. Bland for the mechanical and P. Donnelly for the software design of the automation of the grinders for repeat grinding; We thank the team from the mechanical workshop at the Department of Chemistry, University of Cambridge, for the manufacture of the jars; AMB and JKMS thanks Chris Hunter research team from the Department of Chemistry, University of Cambridge for general support. G.I.L. thanks the Department of Earth Sciences of the University of Cambridge for general support. The authors thank BAM IT for access to the required computational resources.

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Keywords mechanochemistry• dynamic covalent chemistry • solid amine catalysts • disulfide exchange • ball mill grinding

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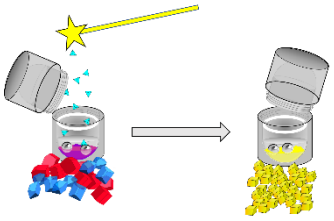

Solid state amine catalysts can be used to drive mechanochemical disulfide exchange reactions, eliminating the need for any liquid phase reagents. The solid catalysts perform significantly better under mechanochemical conditions as compared with solution conditions

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