

QUANTITATIVE SOLVENT-FREE ORGANIC SYNTHESIS

M. R. Naimi-Jamal* and G. Kaupp**

* Iran University of Science and Technology, Faculty of Chemistry,
Naarmak, 16846-11367 Tehran, Iran. naimi@iust.ac.ir

** University of Oldenburg, Faculty V, Organic Chemistry I, P. O. Box
2503, D-26111 Oldenburg, Germany. kaupp@kaupp.chemie.uni-oldenburg.de

ABSTRACT

Gas-solid, solid-solid and stoichiometric melt reactions are waste-free if they provide 100% yield of one single product. The solid-state reactions are faster according to the three-step mechanism of phase rebuilding, phase transformation, and crystal disintegration, while previous topochemistry hypothesis disallowed molecular migrations within crystals that are essential for reactivity. The new techniques are the really solvent-free procedures as they do not require auxiliaries and purifying workup. This is shown with numerous reaction examples of various reaction types both at the millimole-scale and with semi-continuous 200-gram batches.

INTRODUCTION

Sustainable benign chemical production is a major aim worldwide. Many approaches have been put forward, but really good syntheses are stoichiometric with 100% yield and thus highest atom economy. They avoid solvents and auxiliaries. The yield must be quantitative so that purifying workup can be avoided. Only these reactions are really solvent-free and do not waste energy. Many stoichiometric melt reactions or solid-solid reactions or gas-solid reactions succeed in that respect and do not require application of microwave irradiation [Kaupp G., (2003)].

The present situation in "green chemistry" is strange, as there seems to be a focus of support for the microwave application at the

in a review article that covers more than 25 reaction types [Kaupp G., (2005)].

RESULTS AND DISCUSSION

Convincing evidence about the value of organic solid-state reactions and their modern exploration is collected in Fig. 2.

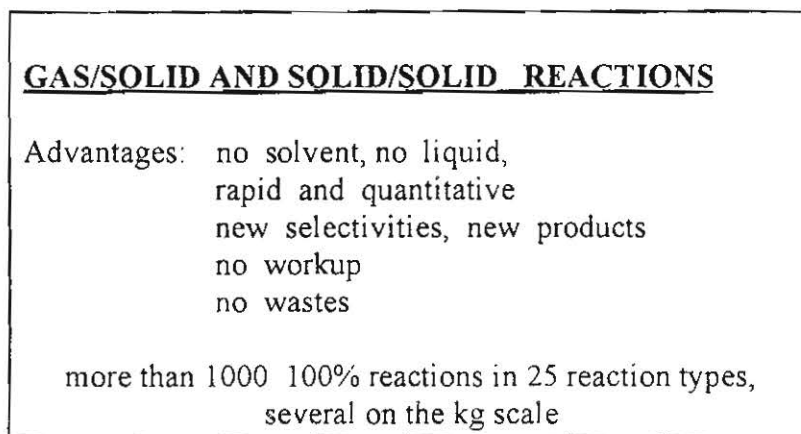


Fig. (2): The value of organic solid-state reactions.

The most striking feature is the lack of workup necessity, which would require most efforts in work and costs because the workup usually produces wastes for disposal and is a real waste of time and energy. The use of crystal effects from the starting materials is a bargain that should be profited from, rather than being neglected by dissolving crystals in mostly dangerous and expensive solvents. However, it is required that people give up the widespread belief that molecules must not migrate in crystals, which derives from the minimal atomic movement claim of the so-called topochemistry since 1964. This requirement should be facilitated by Table 1, the scale-up (Figs. 3-5) of actually occurring solid-state reactions, and the experimental evidence for far-reaching molecular migrations by AFM, SNOM, GID, and nanoscratching measurements (see below).

Table (1): 25 reaction types for more than 1000 quantitative gas-solid and solid-solid reactions without producing wastes.

Inclusion reactions	Condensation of carbonyls
Electron transfers	Cycloadditions
Proton transfers	Cycloreversions
Oxygen transfers	Substitutions with RX
Oxygenations	Aromatic substitutions
Hydrogenations	Cyclizations
Additions of RR'NH, H ₂ O, ROH	Methylations
Additions of halogens and HX	Nitrations at N and C
Eliminations	Diazotizations
Rearrangements	Azocouplings
C-C bond formations	Sandmeyer reactions
Carboxylations with CO ₂	Cascade reactions
Catalyzed reactions	

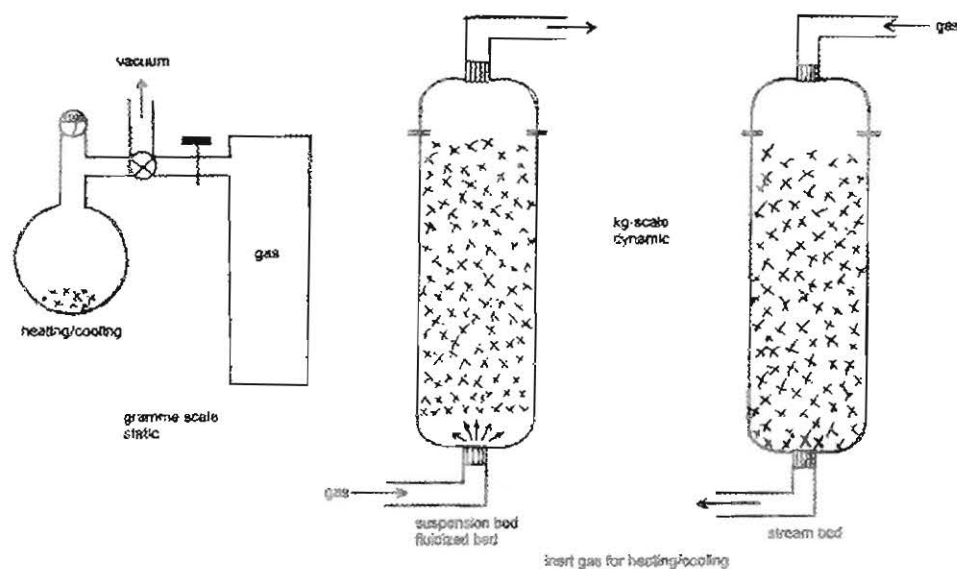


Fig. (3) : Gas-solid techniques.

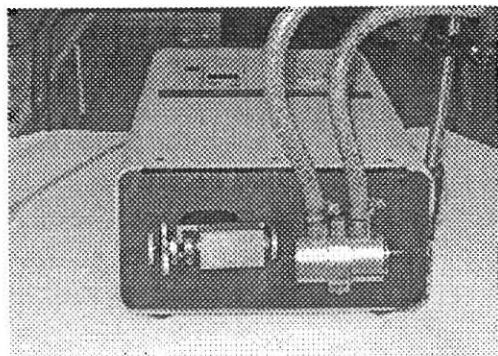


Fig. (4): Laboratory ball mill.

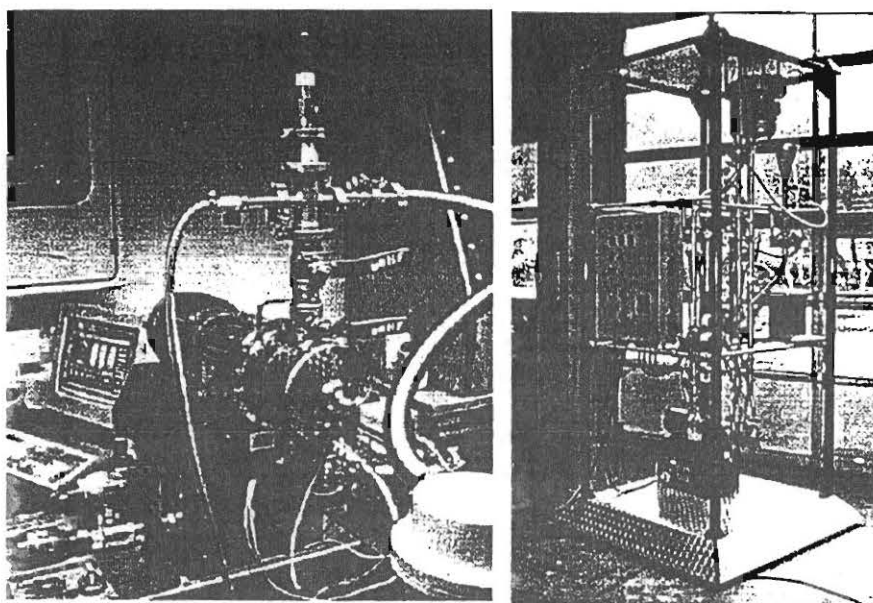


Fig. (5): Large scale ball-mill (left) and semi-continuous production unit (right).

Our most favourable reactions cover all branches of synthetic organic chemistry. Gas-solid techniques are very easy to conduct in controlled atmosphere (static gram scale and dynamic kg scale) and can be performed with slight heating or cooling if the melting points or eutectic points are low. Solid-solid reactions with mortar and pestle may be laborious but ball-mills are the preferred choice for 100% conversion and yield. Even large rotor ball-mills have been constructed and repeatedly applied in our university laboratory and semi-continuous

processes with internal gas-cycle and cyclone are of highest interest for industrial production with still larger ball mills up to 400 l milling chambers [Kaupp G. et al, (2003)].

Why were quantitative solid-state reactions and melt reactions with direct crystallization not used before our investigations? There were the theoretical concepts of solid-state photochemistry that disallowed the solid-state reactions of crystals with gases or other crystals due to the unjustified dogma of minimal atomic movement. Therefore, a new reaction theory had to be established by Kaupp with the aid of supermicroscopy since 1992 that provided opposing experimental evidences [Kaupp G., (1992)].

The blueprint of an atomic force microscope (AFM) is depicted in Fig. 6.

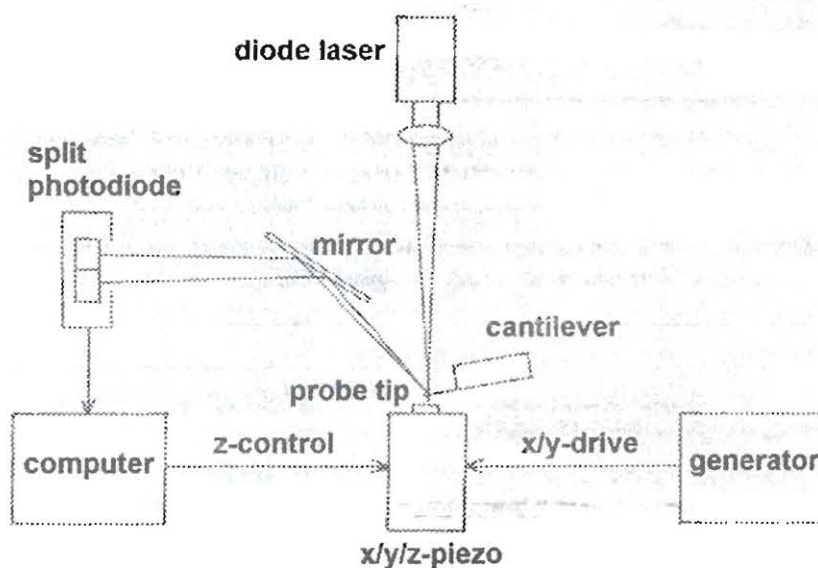


Fig. (6): Blueprint of an AFM giving submicroscopic resolution down to the molecular level.

These instruments are now readily available but this was not so when Kaupp introduced the AFM for chemical applications and initiated its application. The unprecedented mechanistic answer since 1992 may be demonstrated with a typical quantitative gas-solid diazotization reaction that definitely proves the occurrence of far-reaching anisotropic molecular migrations (Fig. 7).

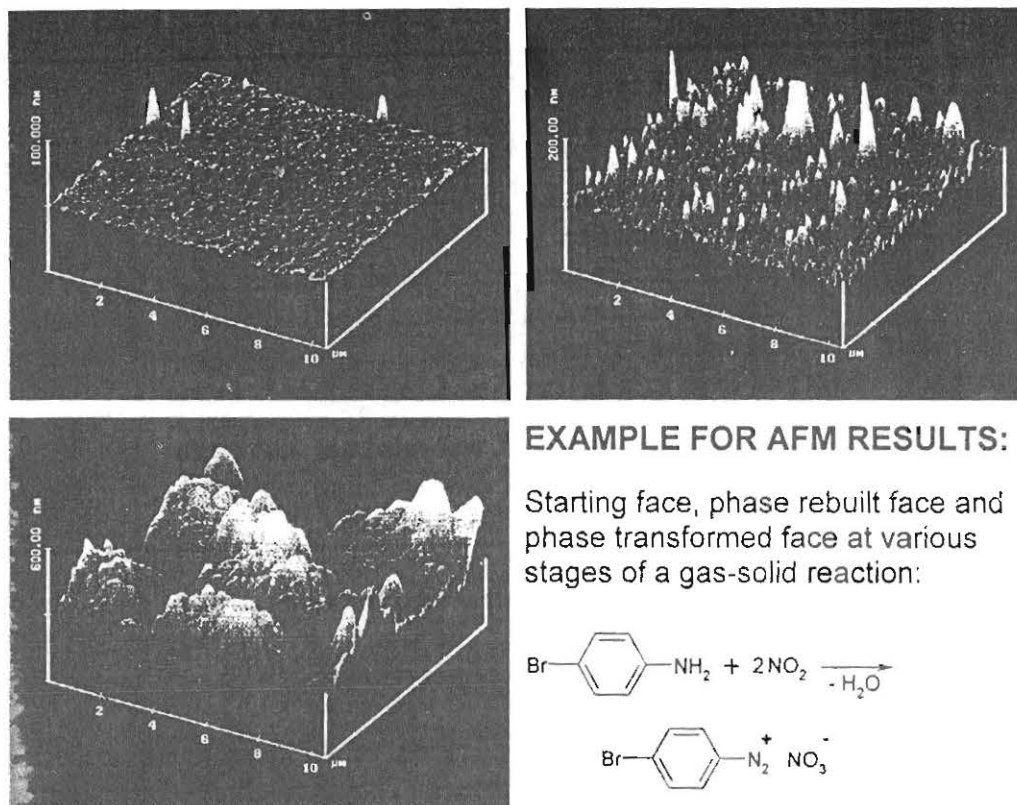


Fig. (7): AFM investigation of the gas-solid diazotization of 4-bromoaniline, showing two different stages of the solid-state mechanism.

Clearly, the surface changes and gradually forms small features in the initial stages of the gas-solid reaction. But at a certain point of exposure a very large change occurs as can be seen at the Z-scales. The interpretation is summarized in Fig. 8. We have here and in all other non-topotactic solid-state reactions (including the photochemical ones) a three-step mechanism of phase rebuilding, phase transformation and crystal disintegration with maximal anisotropic molecular migrations but not minimal movements.

AFM: what does it tell for theory?

Topotactic reactions: no geometric change, no movements, no features

Non-topotactic reactions: long-range molecular movements are essential (anisotropic, tens or hundreds of nm, guided by the crystal bulk)

Step 1: phase rebuilding

(the original lattice becomes distorted and builds features due to molecular movement on easy ways; if molecules cannot move, there will be no reaction!)

Step 2: phase transformation

(the product lattice forms usually with buildup of very large features in a sudden discontinuous event)

Step 3: crystal disintegration

(at and from grain boundaries: fresh surface is formed)

Maximal movement, not minimal movement

Fig. (8): The general solid-state mechanism as derived from experimental evidence by AFM and secured by SNOM and GID measurements.

Fig. 9 shows a typical application of AFM in the quantitative linear dimerization of 1,1-diarylethenes. They are three dimensionally interlocked in the crystal and cannot migrate. Therefore, gaseous hydrochloric acid cannot be added. However, there is overall shrinking upon linear dimerization under acid catalysis (gaseous HCl or Lewis acids) and this reaction proceeds quantitatively. Purifying workup is not necessary. The acid gases are simply evaporated in a vacuum after complete reaction [Kaupp G. et al, (1998)]. The shrinking and thus anisotropic molecular migration is directly "seen" in the AFM by the formation of tiny craters without walls at the rims.

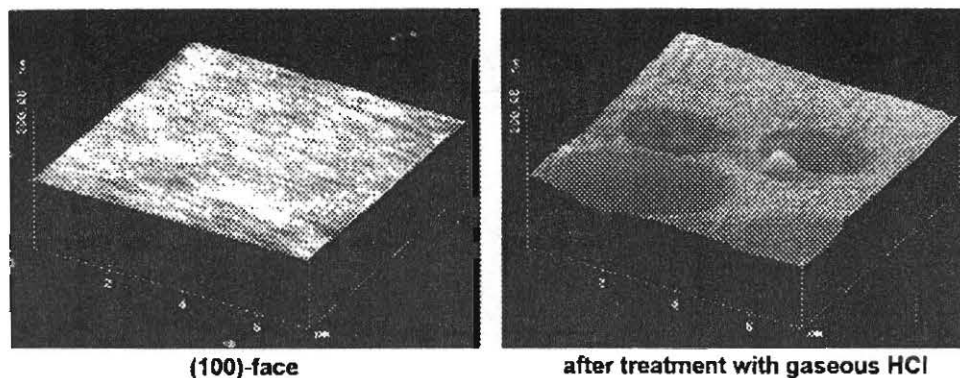


Fig.(9): Catalytic solid-state dimerization of 1,1-bis(4-tolyl)ethene; AFM analysis (X/Y: 7 μm ; Z-scale 200 nm).

Such striking success of the new paradigmatic solid-state mechanism deserves some remarks on the well-known flaws of topochemistry [Schmitt G. M. J., (1964)], which is still present in textbooks but fully disproven by AFM, SNOM, and GID for all non-topotactic reactions (only a handful of examples with no significant change of crystal structure is known [Kaupp, G., (2002)]).

Some of these flaws are collected in Fig. 10. Topochemistry principle fully neglects packing phenomena and denies molecular migrations. The limiting value for (photo)reactivity is claimed to be 4.2 \AA , but there are numerous examples for reactivity with much larger distances and also of nonreactivity with much smaller distance and reactivity despite very skew arrangement (not to speak of wrongly predicted stereochemistry; not shown here).

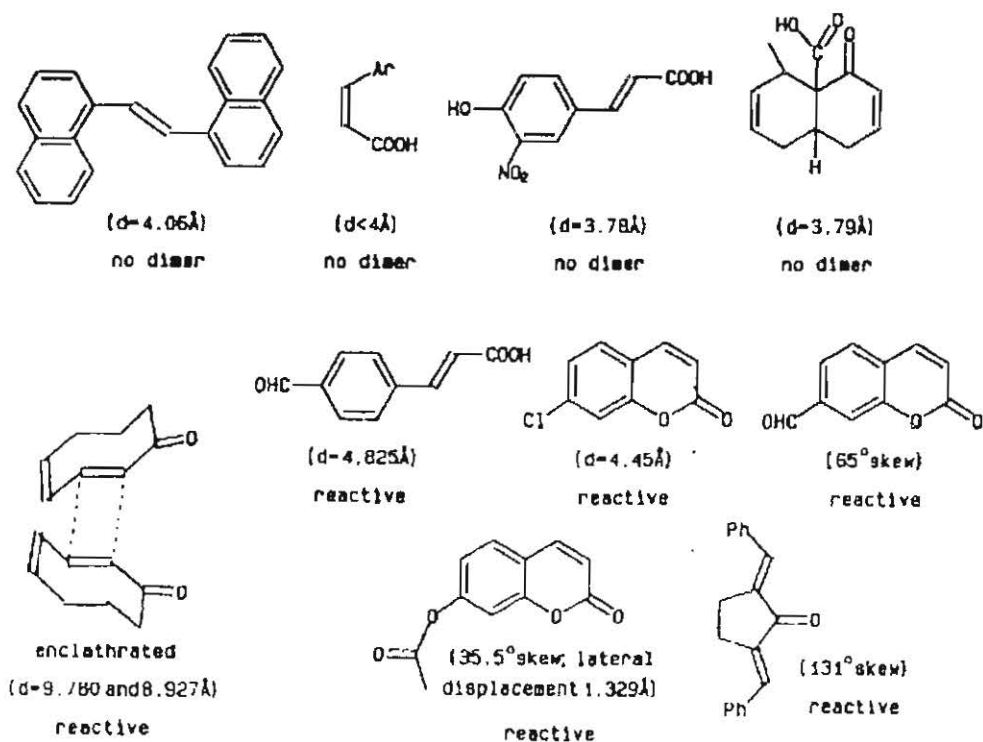


Fig. (10): Some of the well-known flaws of topochemistry claiming minimal atomic movement and reactivity only at distances $< 4.2 \text{ \AA}$.

The experimentally secured three-step mechanism can explain all of these actually non-problems just by looking at the crystal packing, which indicates the possibility or the non-possibility for long-distance migrations. It is essential that molecules that change their shape upon reaction must be able to wriggle out of the original crystal lattice by phase rebuilding and later on phase transformation followed by crystal disintegration.

As all of that is a fundamental change in paradigm we present additional support for anisotropic molecular migrations in crystals. We can induce lattice-guided molecular migrations also by mechanical stress in nanoscratching experiments [Kaupp G. et al, (2004)]. This is shown in Fig. 11.

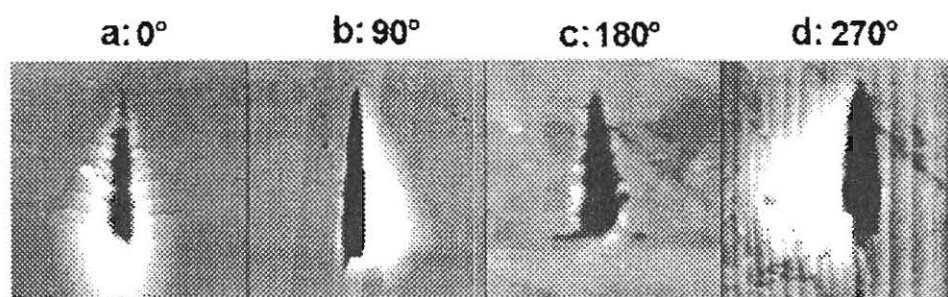


Fig. (11): AFM topographies (X/Y-scale 16 μm) of nanoscratches on the (110) surface of thiohydantoin ($P2_1/c$) in different directions.

It is clearly seen that the direction of the migrations depends on the scratching angle. In the presence of a skew cleavage plane under the (110) surface we observe either migration to both sides and in front, or only to the right side, or none but abrasion, or only to the left side. It cannot be denied that these fantastic anisotropies derive from the crystal packing.

Why do solid-state reactions proceed rapidly and completely? The reason is very favourable kinetics, usually close to zero order. An example is given in Fig.12 for the quantitative gas-solid synthesis of a highly reactive intermediate that cannot be obtained by any other technique. Zero order kinetics is very favourable for 100% conversion in a short time. In the liquid phase there is only polyvidone formation.

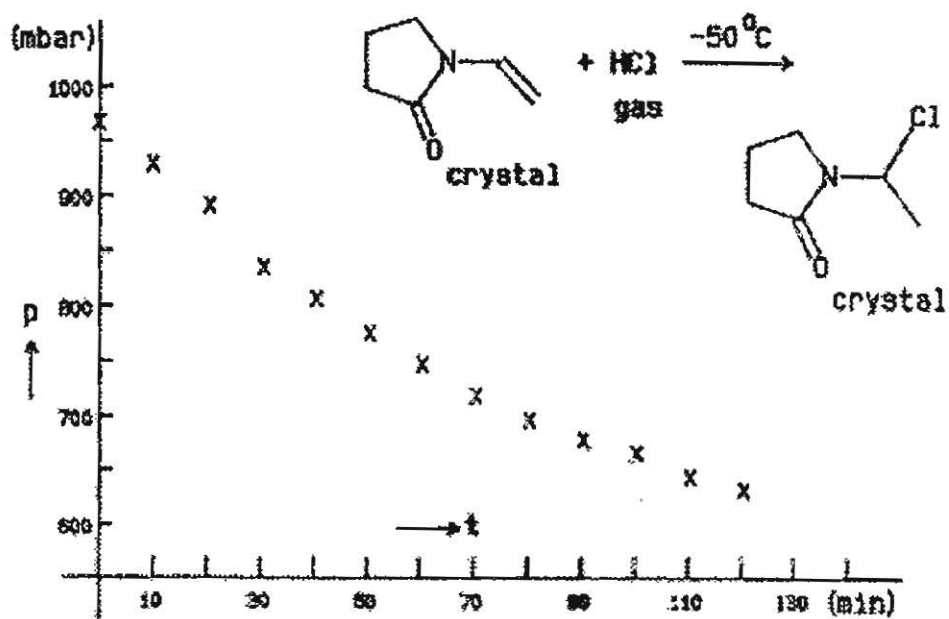


Fig. (12): Kinetics close to zero order for the gas uptake of HCl from crystalline frozen N-vinylpyrrolidone at -50°C .

The solid-state reactions are quite varied. Solid camphene quantitatively adds HBr gas with Wagner Meerwein rearrangement. However, with HCl gas only the elusive camphene hydrochloride is obtained in crystalline form at room temperature. These crystals rearrange in solution very easily and rapidly. Thus, highly labile compounds are quantitatively accessible by our technique directly in pure form (Fig. 13) [Kaupp G. et al, (2001)].

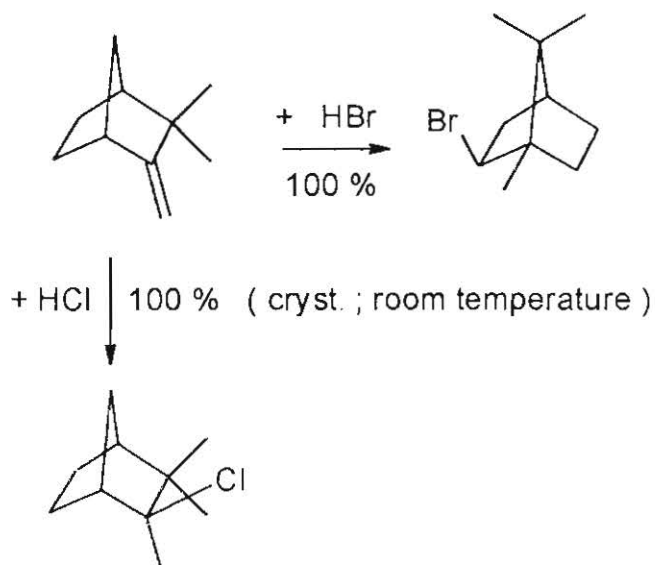


Fig. (13): Addition of gaseous HX to crystalline camphene.

Multiple regiospecific and quantitative aromatic solid-state substitutions are highly spectacular even if a drying agent ($\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$) is required in the tetranitration of tetraphenylethene. Furthermore, the tetranitration and also the tetrabromination require revolving flasks during reaction in order to achieve gas mixing (Fig. 14) [Kaupp G. et al, (1998)].

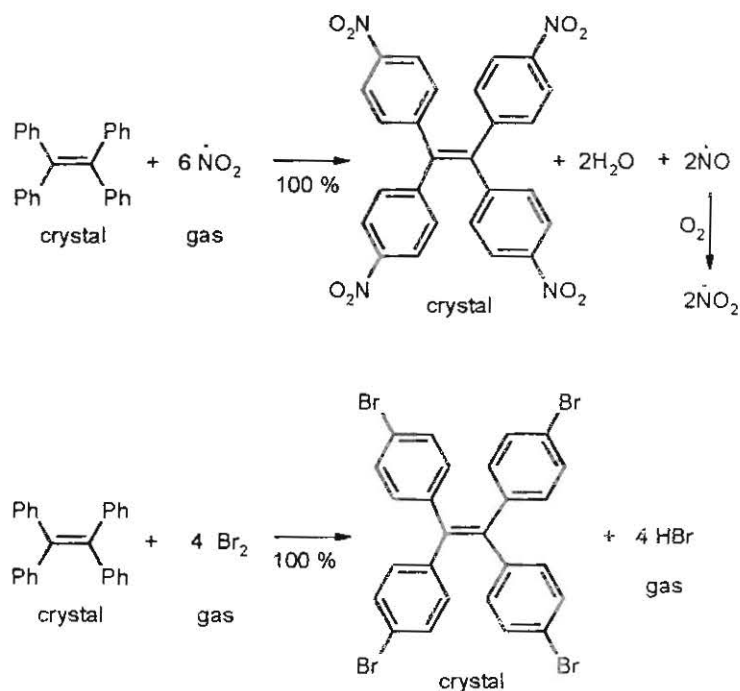


Fig. (14): Quantitative gas-solid tetranitration or tetrabromination of tetraphenylethene.

Natural products are not excluded from organic solid-state reactions if the crystal packing is favourable. For example, the gas-solid addition of bromine to cholesterol stereospecifically yields the pure dibromide that is stable, unlike the impure product that may be synthesized from solution reaction (Fig. 15).

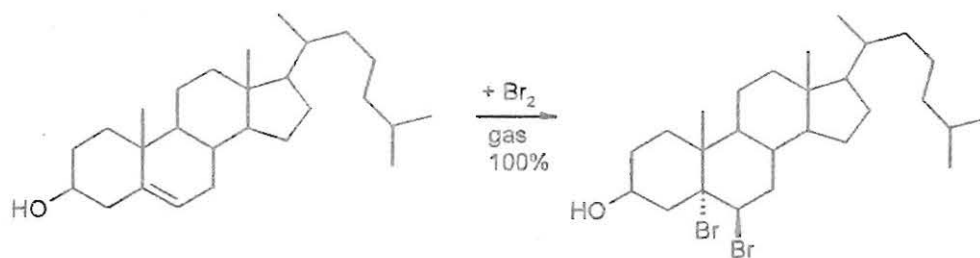


Fig. (15): Gas-solid addition of bromine to cholesterol.

Carbon-carbon bond formations belong to the most important syntheses. A large number of Knoevenagel condensations can now be sustainably performed also with milled batches of 200 g. The water of reaction becomes crystal water, but it can be removed at 80°C in a vacuum (Fig. 16) [Kaupp G. et al, (2003)].

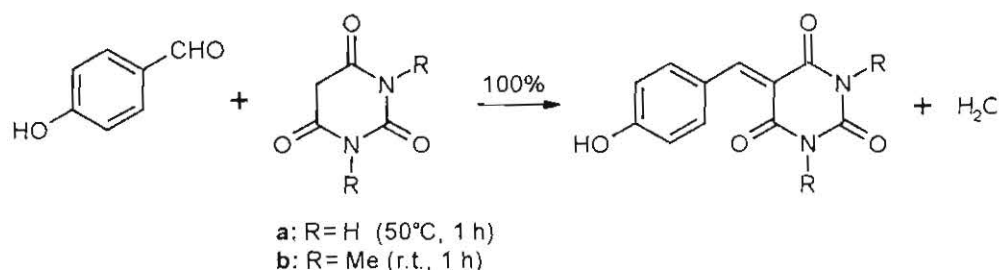


Fig. (16): Examples for waste-free Knoevenagel condensations.

Thus, Knoevenagel products are now easily obtained without catalysts, without solvents, and without microwave. The same is true for Michael additions even though the presented examples are mostly stoichiometric melt reactions with direct crystallization of the product (Fig. 17) [Kaupp G. et al, (2003)].

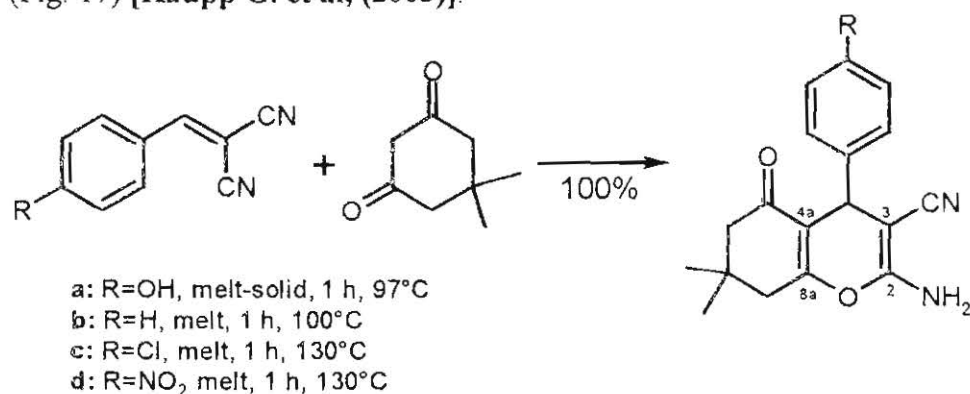


Fig. (17): Examples for waste-free Michael additions.

Amine condensations offer a large range of differing reaction types, including cascade reactions. Heterocyclic amide crystals add the vapours of aliphatic amines with ring opening and provide interesting

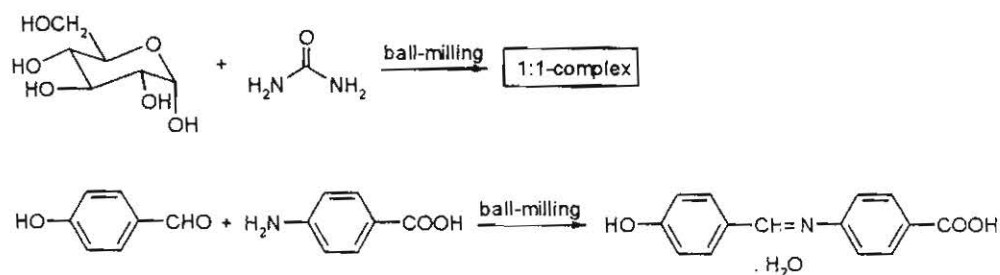
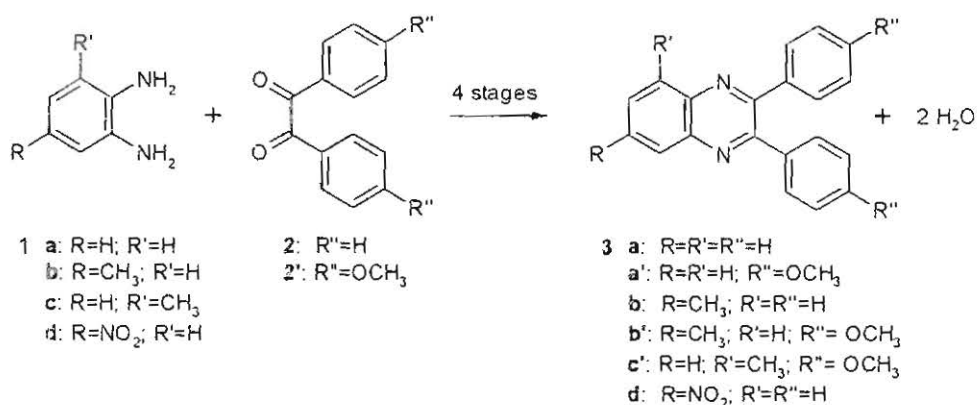


Fig. (19): Quantitative stoichiometric large-scale complexations and condensations in a 2 l ball-mill.

Solid-state quinazoline syntheses by *o*-phenylenediamine condensation are also quantitative as shown in Fig. 20 [Kaupp G. et al, (2002)]. Some of these are true solid-state reactions; others are uniform quantitative melt reactions. The solid-state reactions occur at considerably lower temperatures than the melt reactions, but some of them could not be achieved as solid-state reactions. The data reveal largely inferior yields from the corresponding solution reactions.



Yields of **3** from stoichiometric **1** + **2** mixtures under various reaction conditions

3	T (°C)	phase	yield (%)	yield (%) in solution	m.p. (°C)	lit.m.p. (°C)
a	25	solid	100	62	123	121
	100	melt	100	87		
a'	75	solid	100	85	146–147	145.5–146
	130	melt	100			
b	100	melt	100	68	109–110	111
b'	80	solid	100	–	123–125	–
	130	melt	100			
c'	80	melt	100	–	156–158	–
d	160	melt	100	57	186.5–187.5	187.5–187.9

Fig. (20): Quantitative stoichiometric syntheses of quinazoline derivatives.

The allantoin cascades in Fig. 21 are not always uniform, but the solid-state versions are superior. Milling of **1** and **2** gives only the compound **3** in Fig. 21. If the dihydrochloride is similarly co-milled, the protons intercept at the intermediate **5** and compound **7** in Fig. 21 becomes the predominant product. The melt reaction is not quantitative and the solvent reactions are poor [Kaupp G. et al, (2002)].

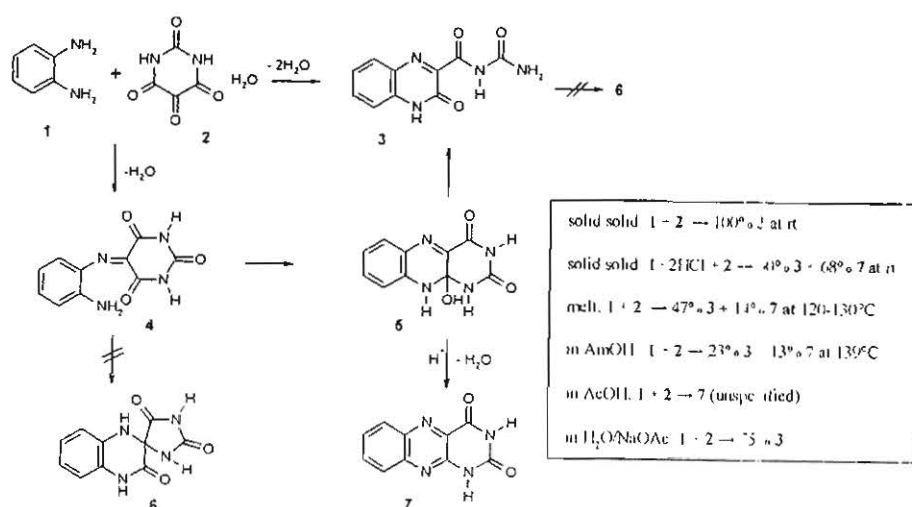


Fig. (21): Comparison of reaction conditions in allantoine cascade reactions.

Another quantitative solid-state cascade is shown in Fig. 22. The highly sensitive elusive azomethine imine is now easily synthesized by stoichiometric ball-milling in 200 g batches by substitution, elimination and decarboxylation within half an hour [Kaupp G. et al, (2002); Kaupp G. et al, (2003)]. It is not possible to imagine a comparatively efficient production technique. The difficulties in solution syntheses are very high.

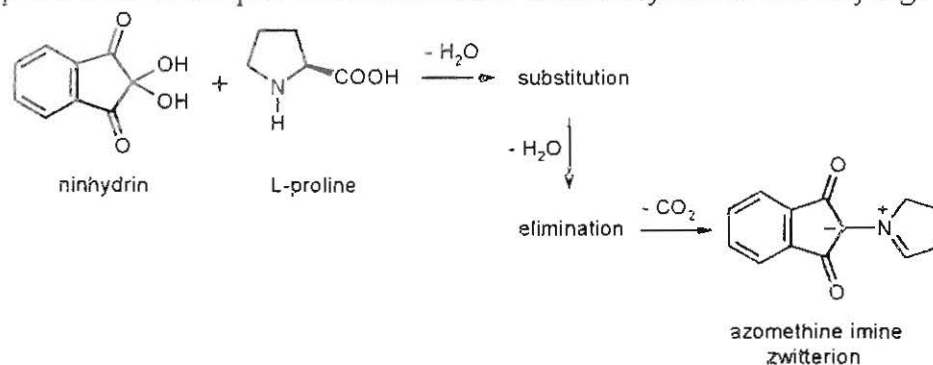


Fig. 22. Stoichiometric solid-state cascade reaction with quantitative 200 g batches in the azomethine imine synthesis.

Equally versatile are solid-state cascades in the condensation of thioureas with phenacylbromide to quantitatively give thiazolidinium salts with the special case of the bicyclic heterocycle that requires an intramolecular solid-state cyclization at rather high temperature from the stable intermediate (Fig. 23) [Kaupp G. et al, (2000)].

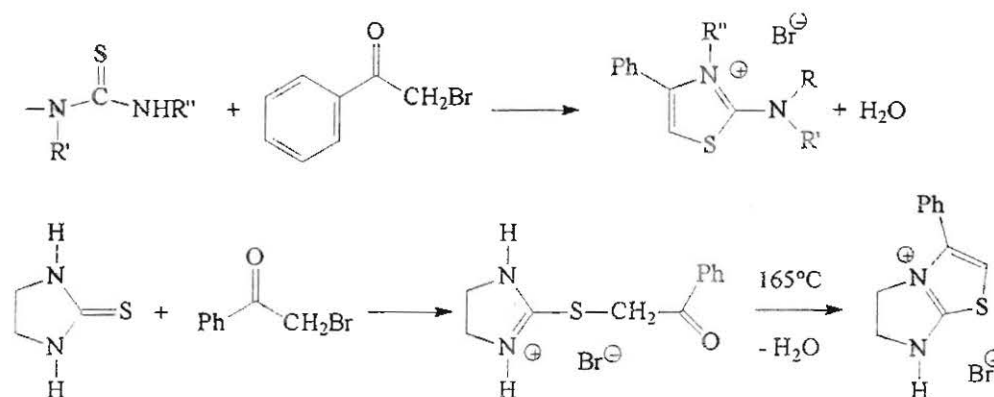


Fig.(23):Quantitative solid-state thiazolidinium salt syntheses by ball-milling at room temperature and intramolecular solid-state cyclization at 165°C of the cyclic thiuronium salt intermediate.

Importantly, the benefits of solid-state reactions can also be extended and profited from with liquid reagents, which might be crystallized at low temperatures (cf. Fig. 12) or by complexation, even though the latter technique implies auxiliary materials and thus requires purifying workup. Such complexation may nevertheless be useful, if the yields become quantitative and the auxiliary is easily removed. Thus, "solid hydrazine" may be obtained by complexation with hydroquinone and the reactions in Fig. 24 are preparatively useful [Kaupp G. et al, (2000)]. The hydroquinone is removed by sublimation or by aqueous washings.

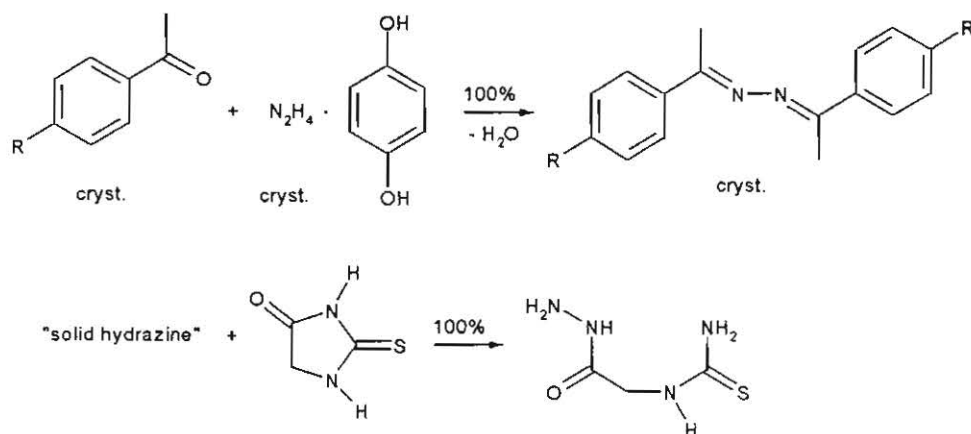


Fig. (24): Quantitative azine synthesis and regiospecific ring opening with "solid hydrazine".

CONCLUSIONS

100% yield stoichiometric reactions are better and may provide otherwise inaccessible products. Nearly comparably efficient production techniques cannot be imagined. Use of our mechanistically founded experimental technique by avoiding auxiliaries (whenever possible) provides really benign and really solvent- and waste-free reactions with unsurpassed atom economy, as no purifying workup is required in quantitative stoichiometric reactions at complete selectivity. It is thus worth to join the experimentally secured new paradigm: **molecules must anisotropically migrate in ordinary solid-state reactions**. This can always be judged or predicted by the crystal packing of the reagents. Topochemistry hypothesis might perhaps be applied to a handful of topotactic reactions where there is no geometric change by the chemical reaction.

REFERENCES

Kaupp G., Photodimerization of Cinnamic Acid in the Solid State: New Insights on Application of Atomic Force Microscopy, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 592-594; and numerous more recent papers cited in (Kaupp, G., 2003).

Kaupp G., Schmeyers J., Gas/Solid Reactions of Aliphatic Amines with Thiohydantoin: Atomic Force Microscopy and New Mechanism, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1587-1589.

Kaupp G., Kuse A., 100% Yield in 300 Gas-Solid Reactions Covering 22 Reaction Types: A Benign Option for Industrial Solid-State Production, *Mol. Cryst. Liq. Cryst.* **1998**, *313*, 361-366.

Kaupp G., Schmeyers J., Solid-state reactivity of the hydrazine-hydroquinone complex, *J. Phys. Org. Chem.* **2000**, *13*, 388-394.

Kaupp G., Schmeyers J., Boy J., Iminium Salts in Solid-State Syntheses Giving 100% Yield, *J. Prakt. Chem.* **2000**, *342*, 269-280.

Kaupp G., Green Chemical Syntheses and Processes, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 4508-4510.

Kaupp G., Schmeyers J., Boy J., Waste-free solid-state syntheses with quantitative yield, *Chemosphere* **2001**, *43*, 55-61.

Kaupp G., Solid-state reactions, dynamics in molecular crystals; *Curr. Opinion in Solid State & Materials Science* **2002**, *6*, 131-138.

Kaupp G., Naimi-Jamal M. R., Quantitative Cascade Condensations of *o*-Phenylenediamines and 1,2-Dicarbonyl Compounds without Producing Wastes, *Eur. J. Org. Chem.* **2002**, 1368-1373.

Kaupp G., Naimi-Jamal M. R., Schmeyers J., Quantitative Reaction Cascades of Ninhydrin in the Solid State, *Chem. Eur. J.* **2002**, *8*, 594-600.

Kaupp G., Schmeyers J., Naimi-Jamal M. R., Zoz H., Ren H., Reactive milling with the SimoloyerR: environmentally benign quantitative reactions without solvents and wastes, *Chem. Engin. Sci.* **2002**, *57*, 763-765.

Kaupp G., Solid-state molecular syntheses: complete reactions without auxiliaries based on the new solid-state mechanism, *CrystEngComm* **2003**, *5*, 117-133.

Kaupp G., Naimi-Jamal M. R., Ren H., Zoz H., Dry and reactive: Reactive dry-milling for environmental protection, *PROCESS-Worldwide*, **2003**, *4*, 24-27; for long version see www.process-worldwide.com/fachartikel/pw_fachartikel_541233.html
<http://vmg01.dnsalias.net/vmg/process-worldwide/download/102327/Long-Version.doc>

Kaupp G., Naimi-Jamal M. R., Schmeyers J., Solvent-free Knoevenagel condensations and Michael additions in the solid state and in the melt with quantitative yield, *Tetrahedron*, **2003**, *59*, 3753-3760.

Kaupp G., Naimi-Jamal M. R., Nanoscratching on surfaces: the relationships of lateral force, normal force and normal displacement, *Z. Metallkd.* **2004**, *5*, 295-305.

Kaupp G., Organic solid-state reactions with 100% yield, *Top. Curr. Chem.* **2005**, *254*, 95-183.

Schmitt G. M. J., Topochemistry . Part III. The crystal chemistry of some *trans*-cinnamic acids, *J. Chem. Soc.* **1964**, 2014-2021.

Tanaka K., *Solvent-free Organic Synthesis*, Wiley-VCH, 2003.

الكيمياء العضوية التخليقية نون استخدام المذيبات

M. R. Naimi-Jamal* and G. Kaupp**

* كلية الكيمياء - جامعة ايران للعلوم و التكنولوجيا - طهران - ايران

** كلية العلوم - الكيمياء العضوية - جامعة أولدنبورج - أولدنبورج - ألمانيا

أحدثت كيمياء التفاعلات غاز-صلب و صلب-صلب خالية العوادم التي تعطى ناتج كمي ١٠٠% من الناتج ثورة في عالم الكيمياء نظرا للأهمية الاقتصادية التي تتميز بها حيث يتم الحصول على الناتج بنسبة كمية ١٠٠% دون استخدام المذيبات العضوية المعروفة. تفاعلات الحالة الصلبة تكون أسرع تبعا لخطوات الميكانيكية الثلاثة (إعادة البناء - تغيير الحالة - التكسير). خطوات هذه التقنية الجديدة تتم دون استخدام المذيبات و لا تحتاج الى استخدام المحفزات و المساعدات بالإضافة الى الحصول على الناتج بصورة نقية دون اللجوء الى عمليات التنقية المعتادة مثل إعادة التبلور.

البحث يحتوي على شرح وافى لهذه التقنية الحديثة والتي تغطي أنواع التفاعلات المختلفة (حوالي ٢٥ نوع من التفاعلات) بالإضافة الى العديد من الأجهزة المستخدمة في هذه التقنية صلب-صلب او غاز-صلب. يشتمل البحث أيضا على العديد من التفاعلات الكيميائية التي تم اجزؤها بتقنية صلب-صلب او غاز-صلب مثل تفاعل غاز ثاني أكسيد النيتروجين مع مركب ٤-برومو أنيلين للحصول على ملح الديازونيوم الصلب المقابل بنسبة ١٠٠% بالإضافة الى فحص التفاعل باستخدام تقنية القوة الذرية المجهرية AFM.