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Waste-free synthesis and production all across chemistry with the benefit of self-assembled crystal packings

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A systematic mechanistic discussion of solid-state reactions (intracrystalline, intercrystalline, gas–solid thermal, or photochemical) at local molecular resolution is the basis for industrial sustainable production with waste-free solid–gas and stoichiometric solid–solid reactions at low energy requirement. These profit from the bargain of the self-assembled crystal packing. They rapidly complete to give 100% yield and require no solvent for workup. The basic requirements are thermodynamic feasibility and anisotropic molecular migrations at local pressure or suction in opposition to claims of 'minimal atomic and molecular movements' that do not know gas–solid and solid–solid reactions. Topochemical failures are settled on that experimental basis by atomic force microscopy (AFM), correlation with the crystal packing, scanning near field optical microscopy (SNOM), and nanoscratching. A general three-step phase rebuilding mechanism is derived that provides directions for all experimental situations including stereoregular polymerizations. Heat control in gas–solid equipment and solid–solid small-scale vibration or large-scale rotation ball-mills is essential. If AFM identifies (nano)liquids cooling is required. Also rare cases of surface passivation are detected by AFM. Molecular solid-state chemistry and mechanochemistry are differentiated. Solid-state techniques easily exclude moisture and are able to synthesize hitherto inaccessible compounds. Some of the latter are selected for discussion out of more than 1000 waste-free solid-state reactions in addition to already executed kg-scale productions using reasonably inexpensive starting materials with promise for industrial applications and extensions. They cover salt formations, complexations, additions, eliminations, substitutions, esterifications, carboxylations, rearrangements, linear dimerizations, cycloreversions, cyclizations, ring openings, cascade reactions, and C—C-couplings (Knoevenagel, Michael, aminomethylation). Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: AFM; ball-mills; environmental protection; gas–solid reactions; mechanochemistry; phase transitions; responsible care; solid–solid reactions; sustainability; topochemistry; upscaling

INTRODUCTION

Solid-state reactions have matured and deserve appreciation. Hundred per cent yield are obtained in already more than 1000 waste-free reactions all across chemistry in more than 25 reaction types with gas–solid and solid–solid techniques. They can be upscaled and they do not require purifying workup. Therefore, neglecting the benefit of well done solid-state reactions is severely violating the concept of sustainable responsible care to the environment. Well done solid-state reactions are highly superior to 'solvent-free' reactions that produce wastes because of chromatography and recrystallization requirements. In fact, the latter should not be called 'solvent free', but unfortunately there is widespread undue endowment with this bewildering label at present. The mechanism and application of the solid-state chemistry are well known. Hundred per cent melt reactions are rare but also useful. Comprehensive literature is available that covers the achievements,[1] the scale up,[2] and the prediction.[3] If crystals are available these should not be dissolved. The bargain of self-assembled alignment might be wasted, and the molecules deactivated by solvation. The maturation of the new solid-state techniques required the application of local investigations with molecular precision of rough and reacting molecular crystals from 1989 when atomic force microscopy (AFM) became commercially available. Suitable scanning near field optical microscopy (SNOM) and nanoscratching techniques followed and verified the conclusions together with depth sensitive grazing incidence diffraction (GID).[4] Contrary to textbooks of chemistry relying on topochemistry with minimal atomic and molecular movements (<3 Å range) the ingenious three-step 'phase rebuilding mechanism' with far-reaching anisotropic molecular migrations by (1) phase rebuilding, (2) phase transformation, and (3) crystal disintegration was proven to apply for all types of solid-state reactions with geometric change.[3] The first step involves anisotropic molecular migrations within polar (including salts) and nonpolar molecular crystals.

These are well documented by unequivocal physical measurements, but they are still not duly acknowledged, because topochemical thinking still prevails. This is unfortunate, because acceptance of experimental results with molecular precision easily removes all of the common pseudo-problems as created by topochemistry and it would save research funds for environmen-

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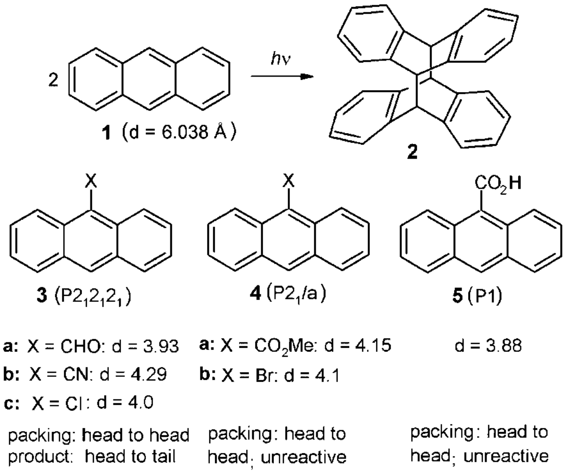
tally benign intercrystal and gas–solid syntheses.[1–3] These new techniques are even superior to contemporary 'green chemistry' on the basis of its 12 commandments.[5] General claims for protection of the environment by solid-state chemistry perpetuate in the wider field (e.g., incomplete photoreactions or reaction stop by melting), but they usually suffer from lack of realization. They would be more realistic if they were substantiated by waste-free performance using the benefit of favorable crystal packing, and if large-scale execution could be demonstrated. Only the latter quality is a basis for industrial production capability.[1–4]

The anisotropic molecular migrations within crystals are not only important for explosives by initiation with mechanical shock, which is genuine mechanochemistry, but also with molecular solid state photochemistry, intra- and intermolecular crystal reactions, gas–solid and solid–solid reactions. Solid–solid reactions do not belong to 'mechanochemistry' despite grinding or milling.

RESULTS AND DISCUSSION

Topochemistry considerations

As we deal with a change in paradigm a brief reminder of the term 'topochemistry' is in order. Textbooks still rely on 'topochemistry' that denies molecular migrations within crystals and thus severely hampered the development of gas–solid and intercrystalline syntheses and production. The term 'topochemistry' was coined by Kohlschütter in 1919 when he produced colloidal alumina inside the boundaries of the original $KAl(SO_4)_2$ crystal by aqueous alkaline hydrolysis.[6] That meaning of 'topochemistry' was totally changed by Schmidt in 1964, when he speculated that molecules in crystals might experience 'only minimal atomic and molecular movements' upon chemical reaction with a limit from 4.2 to 1.5 Å.[7] This assertion assumed the formation of solid solutions in so called 'reaction cavities'[8] with product crystallization when the solubility limit is exceeded. Such speculations found immediate inclusion into textbooks. They promised reactivity and prediction of product stereochemistry from the orientation of reactants not requiring crystal packing analysis if the distance between reacting centers was smaller than 4.2 Å. This is very strange, because the assertions forgot to consider the enormous local pressure that would be imposed to a crystal lattice when there is geometric change incompatible with the crystal lattice in the absence of immediate release. Furthermore, there were numerous failures of the claims from the beginning (see Reference [9]). Even the origin of the speculation with α- and ß-*trans*-cinnamic acid providing predominantly α-truxillic and ß-truxinic acid upon solid-state photodimerization[7] involves long-range anisotropic molecular migrations rather than minimal atomic movements. This can be seen by microscopic inspection and more detailed with the molecular precision of AFM (cracks and features along cleavage plane directions) on regular selective and 'tail-irradiation' at (very) low intensities (see References [3,9,10], there references to earlier work since 1992), it did however not appear to impress contemporary topochemists who are engaged in crystallography. They still continue to stay with 'minimal atomic movements' even though they are apparently not able to present microscopic images of 'tail-irradiated' crystals of α-cinnamic acid without such lattice controlled changes (but only of crystals before irradiation), or to challenge the striking anisotropic events with molecular precision up to now. The clear-cut failures of 'topochemistry' concern reactivity at much larger distances or unreactivity at lower distances of the reacting centers and wrong prediction of the stereochemical outcome. This is exemplified with some examples from the photodimerization of anthracenes **1**–**5**. The solid-state photodimerization of anthracene **1** to give **2** is known since 1904.[11,12] The distance *d* of reacting centers is 6.038 Å, much larger than 4.2 Å.



a: X = CHO: d = 3.93
b: X = CN: d = 4.29
c: X = Cl: d = 4.0
packing: head to head
product: head to tail

a: X = CO_2Me: d = 4.15
b: X = Br: d = 4.1
packing: head to head; unreactive

d = 3.88
packing: head to head; unreactive

The total predictive failure of topochemistry has been demonstrated with the 9-substituted anthracene derivatives **3**–**5**.[13] The crystals of **3a**–**c** with $P2_12_12_1$ space group give a product orientation in the corresponding photodimer that is opposite to the monomer orientation in the crystal. Furthermore, the crystals of **4a,b** with $P2_1/a$ and **5** with P1 space group (four more cases) are unreactive despite short and very short distances. This was termed a 'topochemical abnormality' lacking any idea or guideline for an experimental approach to solve the inconsistencies (the obvious solution is convincingly described in Reference [3]).

Surprisingly, all of these and the other examples that contradicted the topochemical assumption were being eliminated without hesitation from the scope of topochemistry and said to be 'crystal defect reactions', because the formally 'topochemically allowed' processes were taken as support for topochemistry without further proof for decades. This is far from being convincing. All of the topochemical failures are pseudo-problems. Nothing is special with these reactions. They all depend on whether the molecules can migrate within the crystal packing or not (due to availability of suitable cleavage planes, channels, or voids).[3] Also the assertion of exclusive 'defect reactivity' has been disproved with SNOM at molecular defect sites, as identified by AFM, that did not exclude the bulk reactions.[4,14]

Face selectivity with the nanoscopic local resolution of AFM

The first reports on the application of AFM to rough reacting molecular crystals were in 1991,[15,16] the first publications in 1992.[17] They presented molecular steps on rough surfaces and anisotropic molecular migrations upon photodimerizations of α- and ß-*trans*-cinnamic acid and several anthracenes in striking opposition to the topochemical speculation. The anisotropy of the far-reaching migrations is face selective and strictly correlates

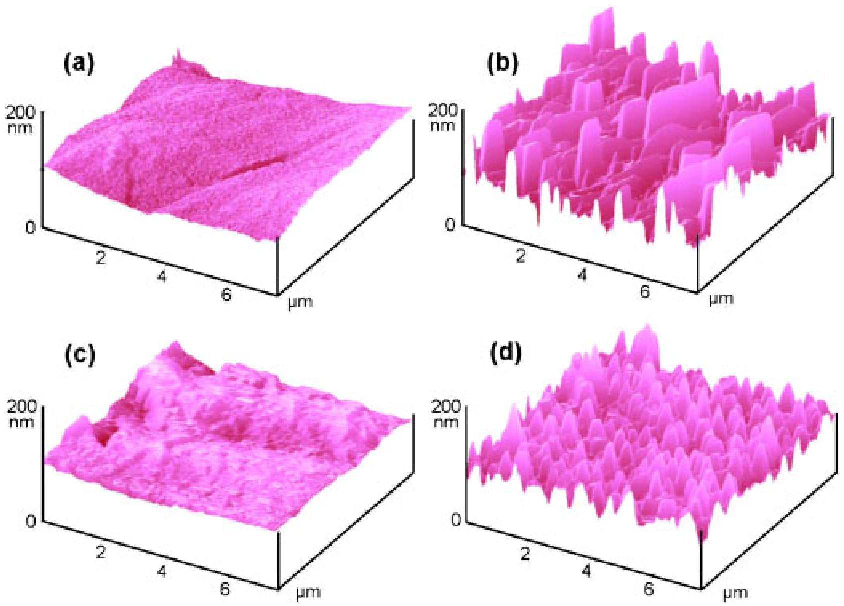


Figure 1. AFM topologies on 9-chloroanthracene **3c**. (a) Fresh main face; (b) main face after irradiation; (c) fresh long side face; (d) long side face after irradiation, these features start with hilly islands that extend to fill the whole surface as expected. This figure is available in colour online at www.interscience.wiley.com/journal/poc

with the crystal packing.[3,4] Figure 1 represents a typical example. 9-Chloroanthracene (**3c**) consistently forms oriented prismatic floes upon selective photodimerization ($\lambda > 290$ nm from 6 cm) on the main face (indicating that a cleavage plane cuts there) and volcano-like cones on the perpendicular longer side face (indicating migration penetrating flat monolayers).[18,19] The face-selective anisotropic far-reaching migrations can be clearly seen despite the roughness of the original surfaces. Face selectivity is a very clear indication that the crystal packing is decisive and that the migrations choose cleavage planes or similarly channels. Similar face-selective anisotropic migrations are found for gas–solid and solid–solid reactions, for example, with α- (on (010)) and *ß-trans*-cinnamic acid (on (100) and (010)) upon addition of gaseous bromine.[14,20] Twelve basic feature types are known, depending on the orientation and the shape of the molecules (10 in Reference [9], new are 'fissures' and 'bricks' in Reference [4] that also shows variability within the types).

It is also possible to distinguish reactive and unreactive crystallographic faces with the molecular local resolution of AFM and correlate it with the crystal packing features.[21] For example, the acid catalyzed solid–solid rearrangement of benzopinacol occurs on the (100) face but not on (001) as judged from the development or non-development of features. This is explained with the crystal packing.[22] Furthermore, molecular steps on an unreactive face exhibit a different crystallographic step face and will therefore be reactive there if the molecules are in the same orientation as on the corresponding extended reactive face of the crystal. For example, crystalline thiohydantoin undergoes ring opening addition of gaseous methylamine with remarkable rate differences between the natural (110) and the cleaved (10$-$2) face that is 66.07° inclined. The ridges and valleys that form rapidly on (110) are, of course, different from the lower height flat volcanoes on (10$-$2). Such ridges and valleys were also recorded by AFM at a 9 nm step on (10$-$2) (27 molecular layers according to the interlayer separation of 3.34 Å) in a necessarily flat orientation, as the step is a genuine (110) face. This is imaged and correlated with the crystal packing in Reference. [23] Similar step selectivity has been reported with benzimidazole **6** exhibiting channels along the [010] direction (Fig. 2).

Crystals of benzimidazole **6** react quantitatively with gaseous ClCN to give *N*-cyanobenzimidazole and HCl. However, ClCN does not attack the plain (100) face, because the functional groups are hidden under the shielding benzo-groups. However, the reagent enters along [010] through the channels for reaction and migrations upon reaction. This nanoscopic effect is shown in Fig. 3. The channels under (010) are available at the steps on (100) and reaction is only there as indicated by the enormous feature heights up to >300 nm.[3,25]

Even better and more sensitive proof is provided if AFM is combined with SNOM, which provides identification of products by chemical contrast. Air autoxidation at slopes on unreactive (110) of anthracene or around a nucleation site on the unreactive (001) face of 2-mercaptobenzothiazole have been imaged in Reference [26]. Another example there is the diazotization of sulfanilic acid with NO_2 gas only at a slope on the unreactive (010) face.

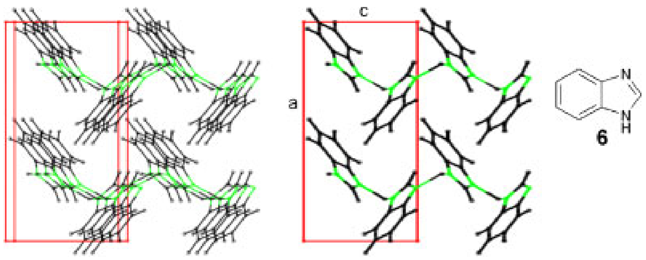


Figure 2. Stereoscopic representation of the crystal packing of benzimidazole **6** ($Pna2_1$)[24] along [010] turned around *y* by 2° for a better view, showing vertical stacks linked by hydrogen bonds forming heavily interlocked horizontal 'bilayers' and almost square channels along [010]. This figure is available in colour online at www.interscience.wiley.com/journal/poc

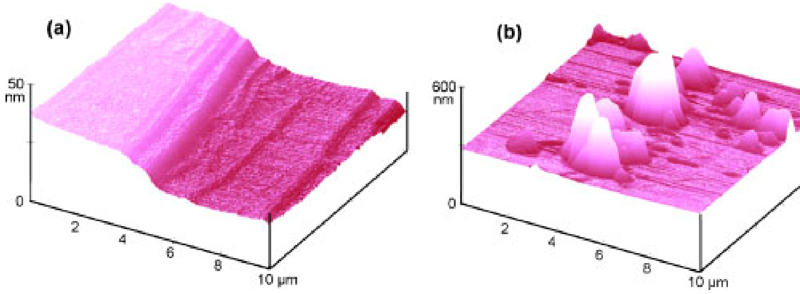


Figure 3. AFM topographies of benzimidazole **6** on the (100) face at a step site corresponding to the (010) face where the channels and the functional groups are available. (a) Before reaction; (b) same site after application of diluted ClCN gas, showing formation of high features at the step sites. This figure is available in colour online at www.interscience.wiley.com/journal/poc

These and many further results that are found in the comprehensive reviews[1–4] clearly prove that unlike the speculations of topochemistry[7] and reaction cavity[8] molecules in reacting crystals migrate anisotropically and strictly guided by the crystal packing along cleavage planes or channels. The reason is release of local pressure.

The local pressure in reacting crystals

The local pressure that would be created within the crystal upon molecular change that cannot be accommodated by conformational flexibility within the lattice in the absence of molecular migration can be judged from mechanical results of nanoindentation. Typical nanohardness values of organic molecular crystals are in the range of $H = 0.1$–1 GPa, whereas the elasticity moduli cover the range of 5–20 GPa.[4] On the physical basis of plastic and elastic theory it becomes clear that the average pressure imposed is the H-value in all of these cases, as an elasticity derived value based on the moduli[27] would give higher values, irrespective of the cone shape or sphere radius of the diamond indenter tip. It is quite clear that the enormous local pressures of 0.1–1 GPa within a crystal lattice are out of reach for molecular reactions unless we deal with the initiation of explosives, when genuine mechanochemistry by local bond-breaking is followed by extreme release of chemical energy (increasing heat and pressure) so that explosion of the whole crystal can occur with uncontrolled extreme migration of material.

It is highly gratifying that anisotropic molecular migrations can be mechanically induced by nanoindentation and nanoscratching in various distinct directions in relation to skew and straight cleavage planes.[4,28–30] The different behavior of skew (left or right migrations) and vertical cleavage planes has been exhaustively imaged for thiohydantoin, anthracene, tetraphenylethene, thiourea, and α-*trans*-cinnamic acid.[4] All directionally different scratching results are convincingly analyzed in terms of geometry. The simplest case of thiourea **7** is exemplified in Fig. 4. It also images the crystal packing of **7** on (100) exhibiting slightly zigzagged monolayer sheets in alternating stacks vertically under (100).

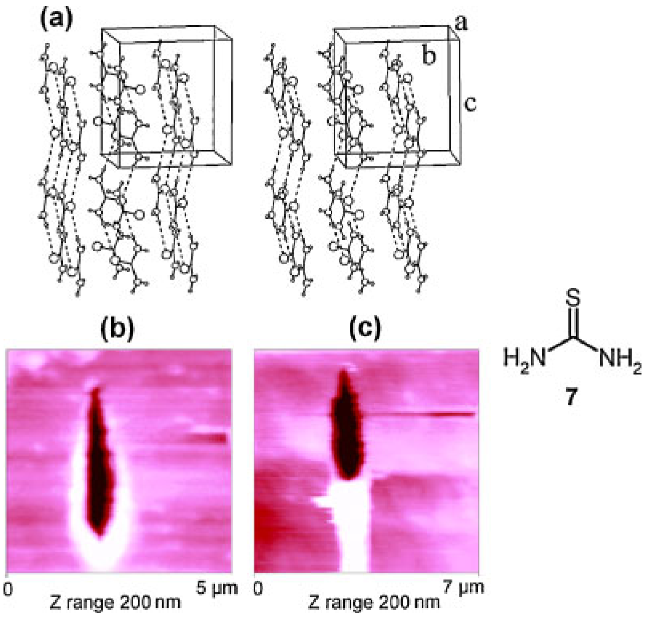


Figure 4. Thiourea **7** on (100) (Pbnm).[31] (a) Stereoscopic representation of the crystal packing rotated around x and y by 10° each, showing vertical monolayer sheets separated by cleavage planes under (100) and (001); (b, c) AFM images after 4 µm cube corner nanoscratching from 0–150 µN normal force in 30 s; (b) along the b-direction with the cleavage planes guiding the migrations to both sides and in front; (c) along the c-direction when the vertical layers are shifted in front of the tip, as molecules cannot migrate to both sides. This figure is available in colour online at www. interscience.wiley.com/journal/poc

Systematics of molecular migrations

Molecular migrations within crystals have been amply shown with molecular precision using AFM and the interpretation has been secured with SNOM and GID. Additional support for anisotropic molecular migrations has been obtained by local pressure as applied to molecular crystals by nanoindentation and nanoscratching.[4] The reason for anisotropic molecular migrations is release of local pressure if molecules change their shapes or volumes upon chemical reaction. Three different situations have to be differentiated: (1) the volume may decrease creating voids by negative local pressure with migration, (2) there may be no significant change and it can be accommodated by the crystal structure without creating pressure or migration, and (3) geometric or volume change would produce enormous local pressure to the crystal structure so that reaction can only occur if the crystal packing allows for molecular migrations along cleavage planes, channels, or to already available voids. Cleavage planes and/or channels are also used for the entry of reagents in intercrystalline or gas–solid reactions. This is amply proven with molecular precision by AFM. The differences are summarized in Table 1. Shrinking is typical for linear dimerizations or removal of molecules and leads to voids in the crystal, for example, craters

Table 1. Systematics of anisotropic migrations within reacting crystals

Negative local pressure (suction)	No local pressure	Positive local pressure
Shrinkage	No geometric change	Expansion
Migration	No migration	Migration
Surface features	No surface features	Surface features
Not very frequent	Extremely few approved cases	Very frequent or common

(Fig. 7), or deep valleys into flat surfaces are formed (Fig. 9). No surface features are observed with genuine topotactic (single-crystal-to-single-crystal) reactions.[19] In the 'normal' and most important case of positive pressure various kinds of characteristic face specific surface features are detected by AFM analysis. It should also be mentioned here that thermal expansion, piezoelectric effects, or pressurizing without reaching the threshold of phase transitions change the shape of the crystal by cooperative movements but not by local anisotropic migrations, whereas phase transitions between polymorphs may occur with conservation or destruction of the crystal. Pure surface reactions that do not reach the bulk do not change the crystal shape, but are very important for protective surface passivation, both in molecular crystals (e.g., Fig. 11) and metals or inorganic oxides (e.g., hydroxides with water layers).

The initial introduction of the term 'topochemistry' of Kohlschütter[6] described the conservation of the macroscopic shape of a $KAl(SO_4)_2$ crystal that was transformed into colloidal alumina. But the redefinition of the term since 1964 claims 'minimal atomic and molecular movements' (from <4.2 Å to about 1.5 Å), which has been disproved for the 'testimonies' of the 'crown witnesses' α- and ß-cinnamic acid, which actually photodimerize with very pronounced anisotropic molecular migrations followed by crystal disintegration. On the other hand only the present author proved the topotaxy of two photoreactions with the molecular precision of AFM and disproved several unjustified claims of topotaxy.[19,28] The now general availability of AFM will certainly help to proceed from topochemical speculation to experimental evaluation.

Positive pressure, phase rebuilding mechanism

By far the most molecular solid-state reactions proceed with positive local pressure. So this is the general case. AFM is very helpful in following the course of solid-state reactions on crystal surfaces with molecular precision. Irrespective of the reaction type (thermal or photochemical, intra or intercrystalline, or gas–solid) it is consistently found that distinct steps of solid-state change can be differentiated. These were comprehensively termed (1) phase rebuilding (it proceeds gradually, molecules migrate anisotropically forming a distorted lattice), (2) phase transformation (typically a sudden process, formation of the product phase frequently with huge changes), and (3) disintegration (the product phase separates from the starting phase forming new surface). These processes are easily distinguished and it is this phase rebuilding mechanism that also allows for intercrystal and gas–solid reactions. It also explains why transparent crystals become dull upon short reaction. Figure 5

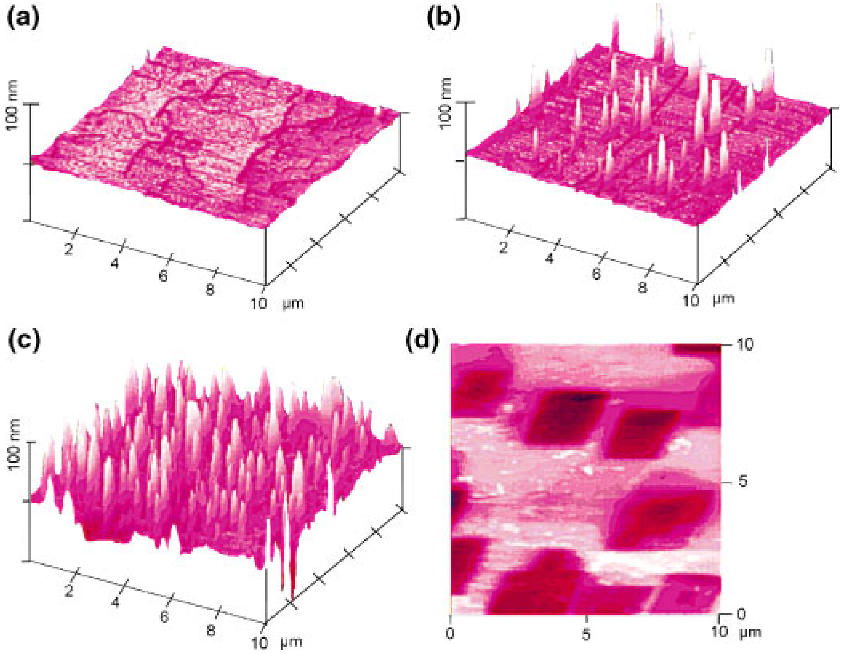


Figure 5. AFM topologies of benzohydrazide on the (100) face. (a) The fresh surface is flat with molecular terraces; (b) the phase rebuilt surface with islands after application of 0.2 ml gaseous BrCN; (c) the more phase rebuilt surface with more islands after application of 0.4 ml BrCN; (d) the phase transformed surface after application of 1 ml BrCN gas with a Z-range of 400 nm. This figure is available in colour online at www.interscience.wiley.com/journal/poc

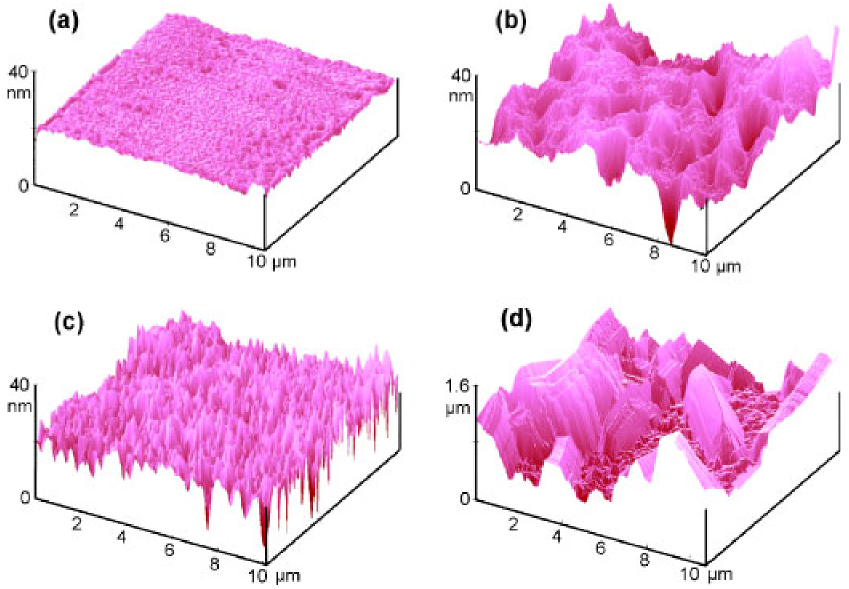


Figure 6. AFM topologies on (010) of (*Z*)-α-benzylidenebutyrolactone. (a) Starting surface; (b) after 10 min irradiation (365 nm, 6.0 mW cm^{-2}, bandpass 6.4 nm); (c) after 15 min irradiation; (d) after 60 min irradiation. This figure is available in colour online at www.interscience.wiley.com/journal/poc

provides an example out of hundreds for a demonstration. Solid benzohydrazide is exposed to BrCN vapor in air from a syringe at the AFM stage and forms (in preparative runs with 100% yield) 2-amino-5-phenyl-1,3,4-oxadiazole hydrobromide.[25] The fresh surface with molecular steps forms characteristic islands upon reaction with the reactive gas. These grow and augment gradually while the original phase rebuilds and that is followed by a sudden event that makes everything different if the product phase is formed, which is called phase transformation. Shortly thereafter the product phase disintegrates and fresh surface is obtained for further reaction, which is very important for complete reaction in synthetic runs. The feature type during the phase rebuilding stage correlates strictly with the crystal packing[3,4,9] that gives in this example a slow start as a flat double layer has to be penetrated (the shape of the fresh surface had not significantly changed after application of 0.1 ml BrCN gas). Conversely, the features from the phase transformation must, of course, not necessarily correlate. Further examples are depicted in References [3,9,21]. The conclusions from the AFM results have been fully verified by depth dependent GID measurements for the diazotization of sulfanilic acid with gaseous NO_2.[32]

Correspondingly, the three-step 'phase rebuilding mechanism' is also found in intracrystalline solid-state photochemistry, as repeatedly imaged for α- and *ß*-cinnamic acid dimerizations.[3,4,17,19] However, due to the deep penetration of light the product molecules are further apart in the phase rebuilding stage, which usually makes the phase transformation a less sudden event (with some intermediate features), than in intercrystalline and gas–solid reactions. This is demonstrated with the solid-state $Z \rightarrow E$ photoisomerization of (*Z*)-α-benzylidenebutyrolactone upon selective irradiation in the absorption tail (Fig. 6).[19,33] After initial phase rebuilding to give large craters and hills these become smaller and more numerous in an intermediate stage (c). Totally different and more than 40-fold higher are the solid structures of the phase transformation (d). Shortly thereafter there is disintegration. It should be noted here that previous claims of a 'topotactic' $E \rightarrow Z$ photoisomerization of 1,2-dibenzoylethene[34] could not be substantiated by AFM that proved phase rebuilding (anisotropic migrations) followed by phase transformation and disintegration.[35] The unidirectional behavior could be explained by an unsuitable interlocked packing of the *Z*-isomer impeding molecular migrations.[35] Turbidity and disintegration of the crystals cannot be overlooked, but the previous authors[34] might have partially melted their crystals by heating them with their irradiation equipment. AFM would easily detect such feature (see below). The molecular migrations are long-range indeed.

Only in topotactic reactions (no pressure), or in exceptional rare cases with migration to crystallographic void cages, no

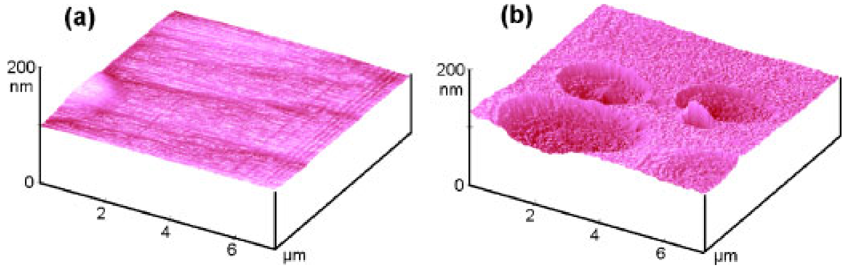
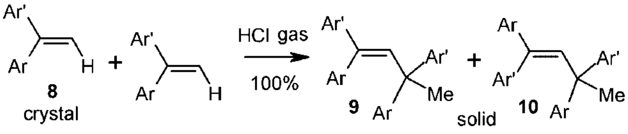


Figure 7. AFM topologies on (100) of 1,1-bis(4-tolyl)ethene **8c**. (a) Fresh surface; (b) after application of gaseous HCl catalyzing linear dimerization with hydrogen transfer and shrinking. This figure is available in colour online at www.interscience.wiley.com/journal/poc

surface changes occur at the molecular precision of AFM.[19] An example is given in Reference [36]. There the Z-3,3′-bis(diphenylhydroxymethyl)stilbene/acetone complex (m.p. 77–82 °C) photoisomerizes to a transparent crystal of the E-isomer while the more extended product molecules migrate to crystallographic void cages. The molecular mechanism should choose the hula-twist, or bicycle pedal motions as one-bond-rotation appears impossible here, but it could not be elucidated by X-ray crystallography: an amorphous phase was forming on irradiation at 250 K. This is a further example of Kohlschütter type topochemistry not to be confused with Schmidt type 'topochemistry'. Furthermore, AFM revealed surface melting upon high intensity irradiation at room temperature and 15 cm distance (700 W water cooled mercury arc), but not at −17 to −15 °C when no surface corrugation occurred except on (100) where very minor efflorescence was detected. Also this feature correlates with the crystal packing.

Negative and no pressure, shrinking, and topotaxy in solid-state reactions

This section deals with shrinking transformations that are accommodated by the lattice[21] and with exit of molecules for reaction in a contacting different crystal. Table 1 indicates important applications for these[3,9,37,38], and there is a continuing run for topotactic reactions.



catalysis also with HBr, BF_3, XeF_2

	Ar	Ar'	T(°C)	9 : 10
a:	Ph	Ph	-50	
b:	Ph	*p*-Tol	-25	33 : 67
c:	*p*-Tol	*p*-Tol	-25	
d:	Ph	*p*-An	-25	15 : 85
e:	*p*-Tol	*p*-An	25	52 : 48
f:	*p*-An	*p*-An	25	

Most rather bulky 1,1-diarylethenes **8** do not exhibit favorable cleavage planes or channels. These are therefore not able to add HCl gas to their double bonds in crystals, because the more voluminous product molecules could not migrate. However, they use the possibility of acid catalyzed linear head/tail dimerization with hydrogen transfer after protonation with low but distinct stereoselectivity to give **9** and **10**, because that shrinks the volume. Huge craters form without concomitant rims in the AFM image by migration at negative local pressure (Fig. 7). These reactions are not accompanied by polymerization. These are acid catalyzed intracrystalline intermolecular reactions.

The structures of some of the 1,1-diarylethenes have been reported: **8c** ($P2_1/c$),[39] **8d** (Cc), and **8f** (Aaba2).[40] A detailed reactivity discussion is given on the basis of Fig. 8.

It shows a view of the packing that explains the situation of crystals out of 8**c**. The interlocked bilayers arrange the double bonds to point into the poor horizontal (010) cleavage plane. Migration along such cleavage plane appears impossible after linear dimerization of the skew opposing double bonds. Therefore the shorter (4.402 Å) head–head interaction is not used at the expense of the head–tail combination (4.566 Å) in the acid catalyzed dimerization with completing hydrogen transfer (tail–tail distance is 5.826 Å and the parallel molecules behind are 7.718 Å away). The extended dimer molecule so formed has shortened with respect to the original lattice and can be accommodated along its previous direction as the final methyl group is generated in the cleavage plane environment. Therefore, the shrinking with crater formation can proceed in the next neighbor's rows etc. The crystals formed by **8d** and by **8f** pack in monolayers with the double bonds inside. They have parallel and almost parallel displaced double bonds with shorter head–tail distances (4.417 and 4.380 Å, two pair types for **8d**, and 4.334 Å for **8f**), respectively, and exhibit interpenetrating cleavage planes. A more detailed analysis of the crystals formed by **8d** and of E/Z ratios **9**/**10** is given in References [3,37,38].

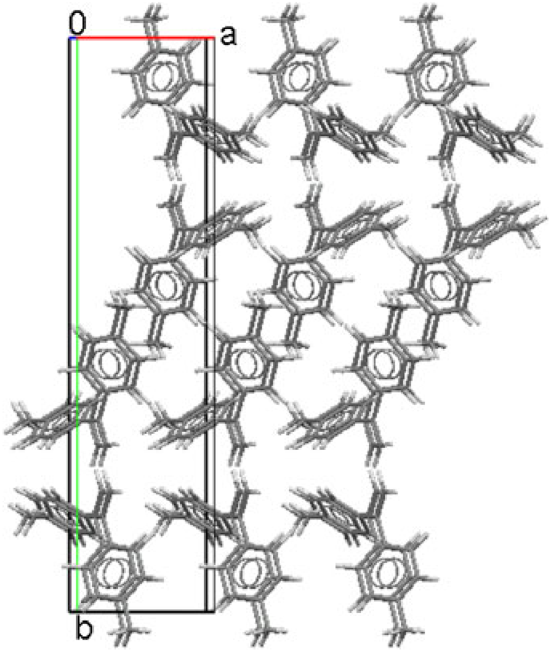


Figure 8. Crystal packing along [001] (slight rotation around y) of 1,1-bis(4-tolyl)ethene **8c**. This figure is available in colour online at www.interscience.wiley.com/journal/poc

Removal of molecules from crystals is encountered in solid–solid reactions if the fate of the crystal is studied that provides the reagent. Figure 9(a) shows the flat initial surface and Figure 9(b) the removal of migrating 4-hydroxybenzaldehyde molecules along the plane of the hydrogen bonded strings for reaction with an anisidine polycrystal that has been deposited on it. The yellow color of the imine product is only seen at the initial anisidine crystal. Clearly, deep valleys between residual hills are formed by 'suction' of the nearby anisidine in which the migrating molecules are consumed by condensation reaction. The also formed connecting side valleys isolate the remaining heights from being sucked. All features are in the directions of the two cleavage planes under (010) – that intersect at 32° – with deep and steep (up to >55°) valleys where the material was removed (further images in Reference[41,42]).

The applications of Table 1 to the field of thermal and photochemical stereoregular polymerizations are particularly fertile as the long known structural facts can now be successfully used for the prediction of reactivity along columnar stacks. The topochemical assumptions fail in the cases of 'topochemical distances' (<4.2 Å) between the reacting centers, at nonreactivity or when the stack is reactive at much larger distances.[3,38,43] It is well known that crystalline Z,Z-muconic esters **11** can be reactive at distances of the centers from 3.30 up to 5.69 Å (six of them

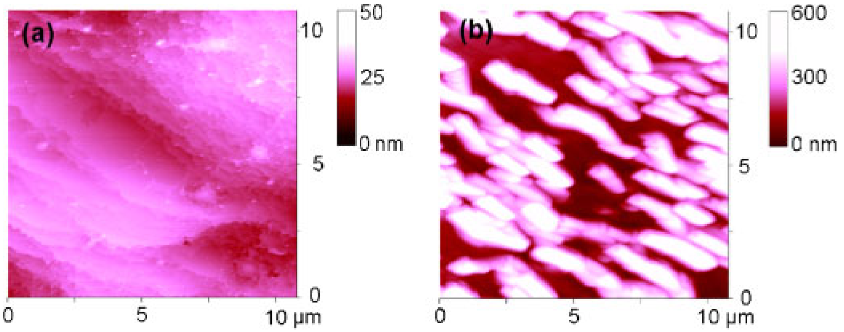
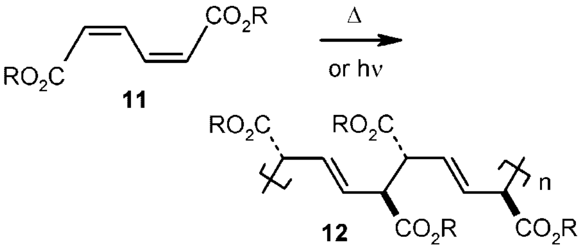


Figure 9. AFM topology on (010) of a 4-hydroxybenzaldehyde single crystal at 0.2 mm from the edge of a small polycrystal of anisidine. (a) Shortly after the laying down and positioning; (b) 90 min after the laying down when the anisidine crystal had become yellow by the condensation reaction. This figure is available in colour online at www.interscience.wiley.com/journal/poc

above 5.3 Å), whereas 10 examples with distances <4.2 Å do not polymerize. Surprisingly, this was not interpreted beyond topochemistry.[44] More important is the stacking spacing of the monomers. For example, the high temperature



polymorph of *Z*,*Z*-diethylmuconate **11** (R = Et) has a monomer spacing of 4.931 Å and polymerizes upon UV or X-ray irradiation to give **12**. On the other hand the low temperature polymorph with a spacing of 4.25 Å does not react. It was stated that such diminution of the spacing by 14% be 'minor' but that 'it deviates from the empirically found favorable 4.7–5.2 Å' spacing.[44] An obvious predictive reason can only be given if the mechanism is not termed 'topochemical' (denying molecular migrations) but if molecular migrations are accepted. One has to also consider the polymer period of 4.841 Å (**12**, R = Et). In the high temperature case the situation of negative pressure occurs as the polymer becomes shorter. Clearly, the growing polymer cannot migrate. Therefore, after 100 polymerization steps the 101st monomer molecule must migrate along the undisturbed stack by 9 Å under negative pressure, which looks very favorable. Regular polymerization was verified when a qualified single crystal of **11** (R = Et) was exposed to slow X-ray irradiation and a single crystal of the polymer with *meso*-diisotactic *trans*-2,5-repeating unit **12** was obtained almost free of monomer impurities.[45] A totally different situation obtains with the low temperature polymorph, from which no polymer is obtained: after 100 periods the polymer would be 59 Å larger than the monomer stack. The positive pressure by such an expansion inside the crystal bulk is totally impossible to be created. Therefore, there can be no stereoregular polymerization within the stack, as the polymer cannot move out, a fact that has been totally overlooked. Generally, coincidence or shrinking is the prerequisites of reactivity. But there are also limitations, as the molecular migrations within a stack under negative pressure (Table 1) cannot proceed indefinitely. Still reactive is the *Z*,*Z*-di-(*p*-chlorobenzyl)-muconate **11**. Its monomer stacking is 5.122 Å; the polymer period is 4.8631 Å. It has been found to provide regular polymerization (**12** with *meso*-diisotactic-*trans*-2,5-repeating unit),[46] while the migration distance for 100 polymerization steps calculates to 26 Å. That is still not bad but far away from being 'topochemical'[7,8] as claimed in Reference[46]. The limit for migrations of *Z*,*Z*-, *E*,*Z*- or *E*,*E*-muconates (different tacticities in Reference[47]) and *E*,*E*-sorbates within simple columnar stacks appears to be at about 60 Å of the necessary migration for 100 polymerization steps.

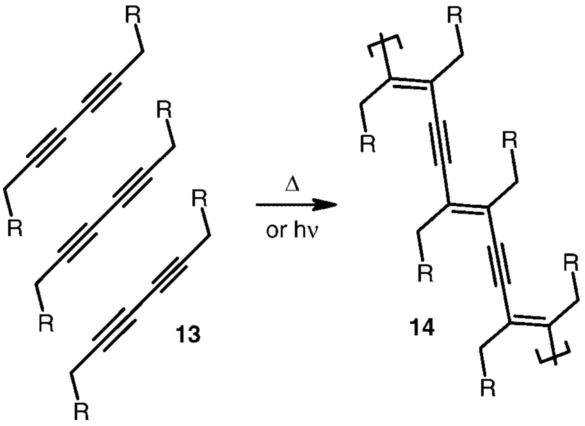
The successful analysis of more than 40 non-polymerizing monomers of that type with known structure equally supports our straightforward arithmetic on the basis of Table 1, which should replace the claims of 'topochemistry' that must admit[44] not being able to 'predict any reactivity of molecules in the crystalline state from chemical structure information'. The overwhelming success of our self-evident treatment secures that no reaction induced phase transformations of the monomer lattice had occurred and that the stacking did not collapse upon reaction in these systems. Such events would, of course, complicate predictions but they would have to be looked for if future deviations might emerge. Now the new clear-cut interpretation of reactivity on the basis of molecular migrations within crystals makes easy and reliable predictions, as extended polymer geometries can also be calculated with reasonable reliability if structural data are not available.

In the case of solid-state styryl polymerizations a reconsideration of the possibility for stereoselectivity on the basis of 'topochemistry' met with very limited success,[48] because the migration requirements and accommodation of the polymer with the monomer lattice were disregarded. The application of the experimentally secured molecular migrations will avoid the present pseudo-problems of topochemistry that are actually expensive non-problems.

Furthermore, columnar diacetylene stacks exhibit always distances between reaction centers smaller than 4.2 Å, but the overwhelming number of studied examples is unreactive with respect to stereoselective polymerization. Again these striking failures of 'topochemistry' could not convincingly be explained despite very complicated efforts for decades. Importantly, decreasing the spacing of the stacks resulted in less success (the smaller the worse), but no answer has emerged on the basis of topochemistry ('smallest atom displacements'; 'limiting distance of approximately 4 Å') that is constantly being invoked.[49] Empirically a 5 Å rule (stacking close to 45°) has been found but not discussed beyond topochemistry.[49] As X-ray crystal analyses are available for most crystals of monomer **13** and polymer **14** it was known that the lattice parameters change upon polymerization. This provoked the development of the crystal strain theory of Baughman with four assumptions,[50] but it was not accepted in the field as it was only successful with the diacetylene **13** ($R=OSO_2$-*p*-Tol).

Most disturbing are the kinetics reports of the thermal polymerization of the diacetylene **13** ($R=OSO_2$-*p*-Tol). Always after induction periods a zero order reaction was reported (linear plot) in Reference [51] and also in Reference [52], first order claims (linear log plot) followed in Reference [53] and also in Reference [54], but it was switched back again to zero order (although the linear plot was erroneously termed 'first order') in Reference [49]. Such unsettled inconsistencies detract from confidence in the data.

As in the case of the muconates **11** above, the necessity of molecular migrations is so stringent that they should be applied to the prediction of reactivity and overwhelming non-reactivity. Coincidence or moderate decrease of the polymer period with respect to the monomer spacing will grant reactivity but the difference must not be too large to avoid excessive migration distances in the delicate stacks so that the oligomerization will stop or continue unspecifically with molecules of neighboring stacks and destruction of the columnar structure.

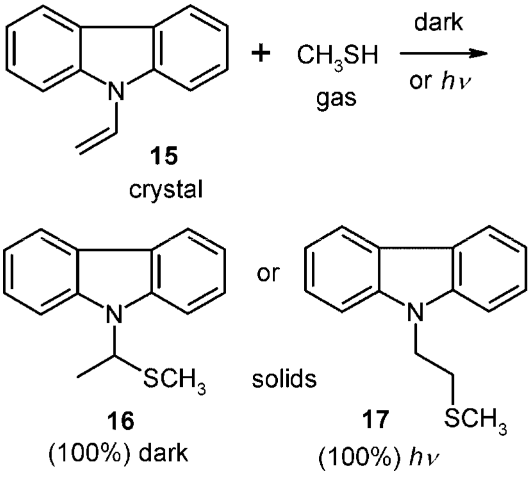


Conversely, larger polymer periods than the monomer spacings will impede polymerization, as a growing polymer cannot migrate out of a crystal bulk and too much local pressure would be created. However, a difficulty may arise in the diacetylene field that can enforce further investigations: some structural phase transitions have been discussed or found in these systems in addition to polymerization.[49] Therefore, if a particular polymorph with a shorter monomer spacing than the polymer period nevertheless polymerizes one has to consider a structural phase transition to a reactive polymorph with larger monomer spacing and try to identify it. The 1,6-di-(*N*-carbazolyl)-2,4-hexadiyne (DCH) system **13** ($R=$ *N*-carbazolyl) represents such a case. The monomer has a spacing of 4.55 Å (caused by an unusual stacking angle of 61°), whereas the measured polymer period **14** ($R=$ *N*-carbazolyl) is 4.91 Å, which clearly excludes such reaction without previous phase transition of the monomer. It turned out that DCH provided the polymer, but as expected now only after previous phase transition by a sudden change of the monomer spacing to 4.9 Å (with concomitant changes of the other crystal parameters). After reaching the coincidence in the induction period the polymerization proceeded rapidly,[49] and that is almost certainly topotactic behavior.

The arithmetic predictions are very valuable for the understanding why the overwhelming number of the studied examples is unreactive, because structural phase transitions do not seem to be very frequent. As the known periods of the 2,4-hexadiyne polymers **14** are very stable at a length of 4.91 Å the prediction is very simple on the basis of this value. A simple geometric analysis of the stiff molecules indicates that the stack volume is best accommodated for both the substituted 2,4-hexadiyne and its polymer at a stacking angle close to 45°, which is a reasonable additional requirement. We then understand that the 2,4-hexadiynes **13** with $R=OSO_2$-*p*-Tol (44°, 5.11 Å), or OSO_2-2-naphthyl (44.8°, 5.07 Å) are well suited for *trans*-tactic polymerization, as the migration distances along the stacking axis under negative pressure for 100 polymerization steps are only 20 or 16 Å. On the other hand **13** with $R=OSO_2$-*p*-fluorophenyl (62.7°, 5.80 Å) starts with a too wide stack and too far distances for local migration (89 Å after 100 steps), with $R=OSO_2$-*p*-Cl-phenyl (67°, 5.03 Å) it suffers only from the too wide stack and with $R=$ *N*-carbazolyl (60.8°, 4.36 Å) it must also be unreactive as must all other systems with spacings below 4.9 Å for the columnar polymerization. The length increase of the polymer cannot be tolerated. This experimentally based analysis (molecular migrations within crystals) is so simple and successful that it provides a unique understanding of the empiric findings that cannot be explained on the basis of topochemistry (the distance between reacting centers is always <4.2 Å here). Much effort and costs could have been avoided for decades. An AFM investigation on the (100) face of the thermolyzed diacetylene **13** ($R=OSO_2$-*p*-Tol) exhibits ridges along the polymerization axis[55] however, the surface changes on the front face (010) would be much more interesting but AFM on that face was not reported.

Detection of liquids with AFM

There might be concern whether liquids are involved on the surface in solid-state reactions, but liquids can be very sensibly differentiated from solids by AFM. The spreading of the liquid along scan-direction or immediate stable features (>5 frames) on the surface can be distinguished at the molecular scale. An example is the addition of methylthiol gas to *N*-vinylcarbazole crystals (**15**) thermally at 20 °C in the dark or with 500 W tungsten lamp irradiation at 0 °C. Interestingly, there is full regiospecificity in both cases: only Markovnikov orientation in the dark to give **16** or only *anti*-Markovnikov orientation under illumination to give **17** is quantitatively obtained.[56] AFM investigation at 20 ± 1 °C clearly indicated that the difference is also caused by the phase



difference.[57] Figure 10 indicates that the thermal reaction is more susceptible to liquefaction than the photochemical one. In Figure 10(a) there is spreading of the liquid along the scan direction, whereas Figure 10(b) shows stable high hills that formed on a previously flat surface. Clearly, the dark reaction runs via partial intermediate melting at 20 °C and is therefore not a solid-state reaction, whereas the photoreaction is a genuine solid-state reaction – inasmuch as the temperature in the synthesis had been lowered to 0 °C – while any liquid formation would have detracted from the complete stereospecificity that is observed.

Further detections of liquids by AFM have been reported. The test of spreading can be further secured by changing the scan direction. In other cases nano-recrystallization has been obtained by continued scanning.[4,9,20]

It should be mentioned here that only reactions with low activation energy might continue upon partial intermediate melting at room temperature. But solid-state reactions profit from the bargain of self-assembled crystal packing. Melt reactions typically require more than 100 or up to 150 °C higher temperatures than solid-state reactions with the consequence that the intended solid-state reaction stops if a (nano)liquid forms. Such reaction must be performed at lower temperatures well below any eutectics (some comparisons of solid-state and melt reactions are found in References [58–60]). Needless to say that large-scale mills do not work as kneading devices under conditions of a viscous melt but stall. The lower activation energy for solid-state reactions due to lack of deactivating solvation allows to avoid catalysts or to synthesize new delicate products at low temperatures that are not available by any other means.[1] If cooling is not possible in self-made mills for intercrystal reactions and if liquid phases occur, the mill is misused as a heating device for liquids. The resulting melt reactions should rather be performed in a flask at the higher temperature that was reached in the mill without temperature control (it can be useful to pre-mill solids of low solubility to micrometer size). Such uncontrolled temperatures might reach 80 or 100 °C and more. Therefore so-called 'high-speed milling' without temperature control (e.g., References [61–64]) accelerates melt reactions by heating. Use of such mills, which actually are not running at higher 'speed' than the mills with cooling/heating mantle, are a severe step backward. Such reports must state that they do not know the temperature and their claims of having increased the rate of reaction by milling impacts are totally unsupported. All reliable waste-free lab-scale and large-scale solid–solid syntheses or productions were performed in temperature controlled vibration mills or industrial rotor mills at the necessary but not at excessive energy consumption.[1–3,65,66] We need only the creation of multiply repeated contacts of micronized reacting crystals and profit thereby from the bargain of self-assembled crystal packing of the reaction partners. The thermodynamically possible solid–solid reaction is chemically driven (see Figs 9 and 12). This should not be confused with mechanochemical (that is also called tribochemical) grinding/milling (explosives, polymers, flint, and other infinitely covalent solids) where the mechanical impact plays an important role (see below).[65–69]

If 'a little' solvent or liquid catalyst or a liquid reagent is added the alternative to solid-state may be kneading,[70,71] but that does not profit from the crystal packing of the reagents. If for an unsuitable crystal structure (not permitting molecular migrations in the bulk) no solid-state reaction can occur and the kneading equipment is not available, the melt reaction should be tried rather in a heated vessel but not in a mill. The only useful technical milling of solids with large amounts of low viscosity liquids is the leaching technique, that must not be restricted to applications in metallurgy.[72] Importantly, the same ball-mills are most profitably used.

Surface passivation

Gas–solid reactions might not only be stopped by local liquefaction (previous section) but also by surface passivation. This happens if either the phase transformation or the disintegration steps of the phase rebuilding mechanism do not readily occur. AFM is able to identify such events of non-reactivity in the solid state. A typical example is given in Fig. 11. *DL*-penicillamine does not undergo the condensation reaction with gaseous acetone, even though the crystal packing would allow for migrations. AFM at a very flat site on the overwhelming (100) face does not exhibit any change upon application of acetone gas (there are the shielding methyl groups of the double layers). Therefore, a rough site (most faces are available there) had to be crystallized for the experiment in Fig. 11. Clearly, there is a rapid start of reaction at nanoscopic faces with access to the functional groups. The features in Fig. 11(b) reach heights of up to 100 nm after 5 minutes, however these decline upon continuation of the reaction and end with a solid cover that protects the crystal from further reaction. It appears that the phase transformation step does not proceed and that no disintegration follows. This passivation and a similar passivation with *L*-cysteine can be avoided by previous salt formation.[21,73]

Surface passivation is face selective in the gas–solid neutralization of dicarboxylic acids. For example, solid adipic

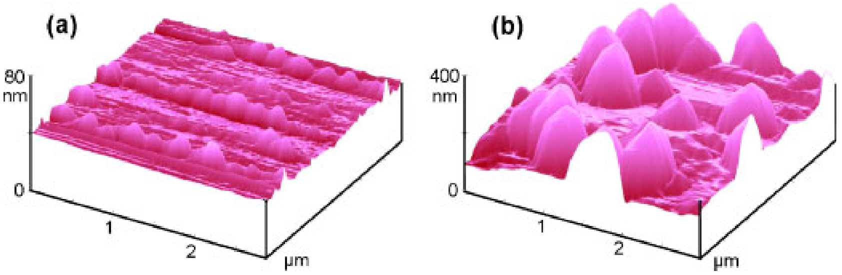


Figure 10. AFM topology of crystalline *N*-vinylcarbazole **15** at 20 ± 1 °C. (a) After application of methylthiol, indicating a liquid that is transported by the tip; (b) after application of light and methylthiol gas for 5 min producing stable solid features. This figure is available in colour online at www.interscience.wiley.com/journal/poc

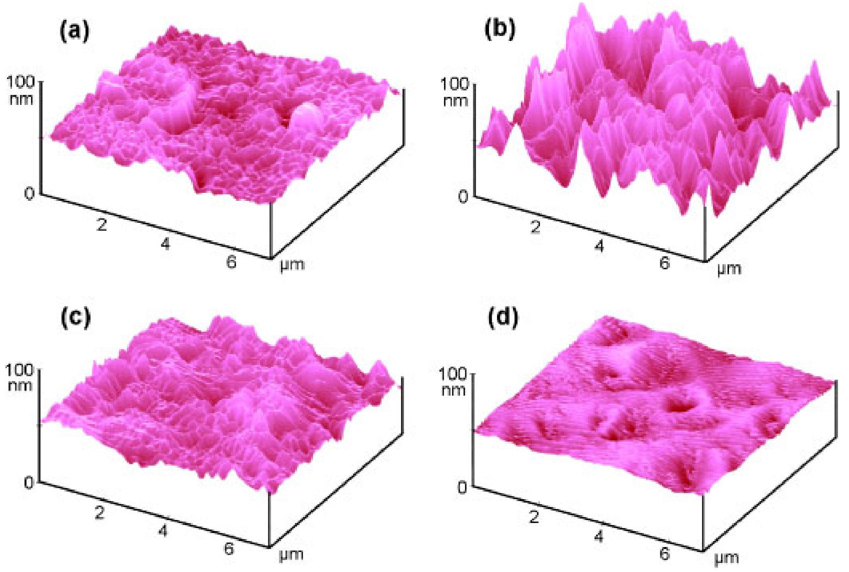


Figure 11. AFM topologies of *DL*-penicillamine on the (100) face at a site of some roughness. (a) Fresh surface; (b) after 5 min; (c) after 10 min; (d) after 30 min exposure to acetone vapor in air. This figure is available in colour online at www.interscience.wiley.com/journal/poc

acid reacts with ammonia on its (010) face with great ease. However, the reaction comes to an immediate stop on (100), because the H-bonded infinite strings of adipic acid molecules under that face will not release their front molecules.[9,74,75] The stable volcano features are less than 50 nm high and do not disintegrate in this case and do not increase further. This reaction was investigated before by Curtin, Paul, and Miller with respect to its anisotropy but it was termed 'extraordinary behavior', the explanation of which had to be postponed.[76] Clearly, they could not see the passivating layer under a light microscope and argued on the topochemical basis rather than considering molecular migrations.

Surface passivation by problems with the detachment of the product phase initially impeded a quantitative yield in the gas–solid halogen additions to *trans*-stilbene. That problem could be solved by milling and very careful slow addition of stoichiometric amounts of Cl_2 or Br_2 gas at low temperature to keep the reaction rate down.[37,38] A similar problem was solved by milling of sodium nitrite in NO_2 gas to produce NO gas and sodium nitrate, that did not readily detach by itself.[1,2,66]

Molecular solid-state chemistry versus mechanochemistry

After the systematic discussion of the experimental mechanisms of solid-state molecular reactions under various conditions at the molecular level it is easily recognized: grinding or milling activates none of these mechanically. In particular, it is not possible to enforce counter-thermodynamic reactions of molecular crystals with the help of mechanical impact unless a Bridgeman's anvil was applied. Conversely, in mechanochemistry mechanical energy is used to initiate decomposition reactions to highly energetic species that induce follow-up reactions of various kinds. Unfortunately, various authors uncritically used the expression 'mechanochemistry' or 'mechanochemical reaction' if they grinded or milled or kneaded molecular solids and they appear to speculate that molecular reactions might be driven by mechanical impact for activation rather than by chemical potential. Clearly, one has to differentiate between chemically driven and mechanically initiated reactions. But such distinction is also not strictly followed in reviews on 'mechanochemistry' (Reference [77] and even worse in Reference [78], to name the most recent ones). These included also reactions of molecular crystals where no bonds are broken with formation of radicals, but that were erroneously termed 'mechanochemical' by the cited authors. However, the differences are very clear and important: here destruction (nevertheless sometimes useful chemistry in radical initiations), there waste-free synthesis if properly done.

Mechanochemistry produces surface plasma by breaking infinite covalent crystals (e.g., sparkling flint, sand, etc.) that can be used for igniting fires or for mineralization of any organic material.[65,66] Reference [67,68] contains a large number of organics from methane to tetrachloro-dibenzodioxine (TCDD) that were mineralized by mechanochemical milling with various infinitely covalent solids. Mechanochemistry also produces radicals by bond breaking in polymers, radical initiators, and many explosives. Covalent bonds are also broken in experiments on Bridgeman's anvil, where no escape is possible. Shocked explosives may detonate according to different mechanisms (e.g., Reference [69]) and mechanic alloying presents examples of mechanochemistry. In all of these experiments the mechanical impact is decisive and activating. On the other hand, molecular van-der-Waals and hydrogen-bonded crystals or salt crystals (with the exception of weak bond radical initiators or explosives) are not mechanically activated upon ball milling. To make it clear: if solid diazonium salts are hit with a hammer on an anvil they explode (mechanochemistry); if the same solid diazonium salts are cautiously co-ground with KI (here excess for safety reasons) solid aryliodides are quantitatively obtained (molecular solid-state chemistry).[79] The milling has to create repeated contacts between the reacting crystals, nothing else. This fact has been amply proven by AFM scans close to a contact edge of reacting crystals. Anisotropic feature formation indicates chemical reaction in the absence of grinding or milling. Figure 12 shows it for the 4-cascade reaction of ninhydrin with *o*-phenylenediamine crystals to give 11-*H*-indeno[1,2-*b*]quinoxaline-11-one (substitution, elimination, cyclization, elimination).[80] The features (island type)

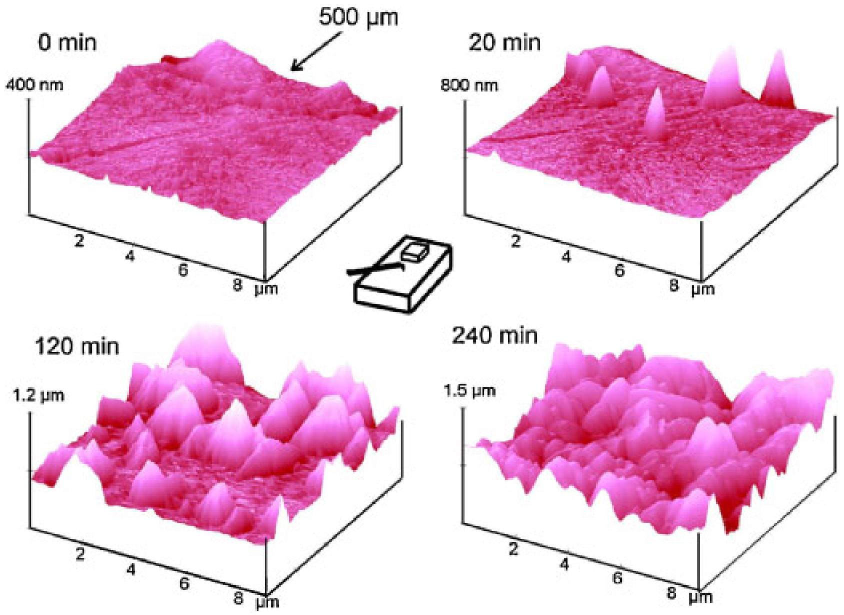


Figure 12. AFM topology on (−110) of ninhydrin with a small crystal of *o*-phenylenediamine on it at 0.5 mm from the scanned frame as measured according to the central sketch shortly after alignment (0 min) and after 20, 120, and 240 min, indicating feature formation by chemical reaction[80]. This figure is available in colour online at www.interscience.wiley.com/journal/poc

develop from the upper edge into the frame while they grow and change after growing together. The anisotropic migrations are over more than half a millimeter, which is a very long distance indeed, and all is driven chemically. The corresponding experiments on (10−1) at 0.1 mm distance and on (1−10) at 0.5 mm distance gave different features and higher rates.[80] Further systems have been studied according to the same technique and prove equally well that solid–solid reactions are driven by chemistry and that the use of milling is only necessary for creating repeated contacts of micronized crystals for a rapid completion of the reaction. Figure 9 is discussed above, further published images cover the rearrangement of benzopinacol with *p*-toluenesulfonic acid (0.1 and 0.5 mm distance),[22] hydrazine-hydroquinone complex with *p*-hydroxybenzaldehyde condensation (0.1 mm distance, both crystals measured), hydrazine-hydroquinone complex with 4-dimethylaminobenzaldehyde condensation (1 mm distance),[81] and thiourea with phenacylbromide cascade to give the 2-amino-4-phenylthiazole hydrobromide (0.5 mm distance).[82] All of these are solid–solid reactions and the features correlate with the crystal structures. If water was a stoichiometric by-product it was taken up as crystal water.

Application for sustainability in gas–solid and solid–solid syntheses

Technical remarks

Responsible care should address to wasteless chemical production whenever possible. The detailed mechanistic knowledge at the local molecular level is the basis for running 100% yield waste-free solid-state reactions on a broad scale with already more than 1000 examples in more than 25 reaction types[1] and amply executed upscaling.[2] These avoid the requirement of purifying workup, as the products arise in pure form. It was urgently necessary to get rid of the unrealistic trammels of 'minimal atomic movements'[7] that unfortunately found their uncritical way into textbooks despite numerous obvious inconsistencies. Gas–solid and solid–solid reactions are rapid, safe, quantitative, energy saving, atom economic, cheap, and they allow to obtain new otherwise unaccessible products, if properly performed. First of all, profiting from the crystal structure bargain requires absence of (partial) intermediate melting or any other liquid phases. It is often necessary to cool down below eutectics, but heating above room temperature can become necessary at reactions with higher activation energy. The ingenious three-step 'phase rebuilding mechanism' provides a constant rate (close to zero order)[9,21,83] with sharp completion, which can be easily controlled also with respect to (mostly low) heat production both in solid–solid and gas–solid reactions.

Gas in excess (to be recovered after reaction) can be applied at constant pressure, but stoichiometric gas leads also to quantitative completion (this requires really vacuum tight equipment). Static gas–solid equipment must be gas-tight in order to avoid 'air blankets'. If a product gas is liberated some agitation must mix the gases. Agitation is also required for reliable temperature control. Gas flow is essential with inert gas at strongly exothermic reactions or if highly diluted gases are applied. The small- and large-scale equipment for gas–solid and solid–solid reactions has been exhaustively imaged in Reference [2]. It is simple, versatile, and low-cost. Grinding in mortars is inefficient for solid–solid reactions. Ball-mills and industrial horizontal ball-mills with large heat capacity must be equipped with temperature control by external cooling or heating. That is state-of-the-art from the beginning in 1992 and it should not be omitted in self-built mills because it is a serious step backward not knowing the temperature range or to run a risk of stopping the reaction because of melting or of its becoming violent. Industrial rotation ball-mills with up to 400 l and larger chamber volume (convenient labsize is 2 l) with a minimum of noise and vibration are connected to a semi-continuous powder filling and collection autobatch arrangement in a closed cycle with inert gas. Milling times should be adjusted to 10, 20, 30, and rarely 60 min.[66]

The solid-state reaction will not start if the crystal packing does not provide the possibility for anisotropic molecular migrations along channels or cleavage planes. Fortunately, their occurrence is frequent and one must not perform an X-ray crystal structure analysis prior to the testing of a new reaction. If easy ways for migration within the crystal are unavailable this obstacle can only be circumvented with suitable polymorphs or salt formation or complexation (this may detract from the waste-freeness). Stoichiometric melt reactions may then be tried but these require much higher temperatures and often produce side reactions or are incomplete. Another though rare obstacle is surface passivation. It can be detected by AFM as described above. Remedy may be slight heating for facilitation of the phase transformation. Milling is only required for gas–solid reactions that experience trouble with the crystal disintegration (solid–solid reactions in the mill never have a disintegration problem). But regular gas–solid reactions must not be milled, as the crystals shall not be too small initially because they would violently react.

The already available upscaled syntheses (up to 500 g gas–solid or 200 g solid–solid organic batches in an university laboratory) cover virtually all known reaction types across chemistry.[1,2] The Supplementary Material Section contains upscaled examples and reactions giving products that cannot be obtained by any other technique are added.

CONCLUSIONS

The systematic mechanistic investigation of organic molecular solid-state chemistry at the molecular level of AFM reveals strict correlation of anisotropic molecular migrations with the crystal packing. Numerous local effects and fine details have been analyzed on that experimental basis and secured by SNOM, GID, and nanoscratching. They constitute the profound change in paradigm. The reason for the long-range migrations are in most cases release of positive local pressure, but molecules migrate also at negative pressure in the case of shrinking and suction. The general new solid-state mechanism with phase rebuilding, phase transformation, and crystal disintegration is the basis for solid-state reactivity and for the excellent performance of gas–solid and solid–solid reactions. These new sustainable possibilities rely on experimental findings. It is for important practical and scientific reasons that these must remove the 'topochemistry' speculations of 1964, which unfortunately entered into textbooks with the strange claim of 'minimal atomic and molecular movements' within crystals.[7] Clearly, the pressure issues had not been considered. Fortunately, the experimental facts now convincingly and easily remove all pseudo-problems that are inherent to Schmidt's topochemistry with numerous wrong 'predictions' and other failures, which were, of course, restricted to intracrystalline reactions. Strangely enough, topochemists have also been running into severe difficulties with so called 'topochemical distance' polymerizations (<4.2 Å) that did not proceed in the overwhelming number of cases, and they still deny the obvious requirement for monomer migrations within stacks if the polymer becomes shorter than the monomer stack. The more important intercrystalline and solid–gas reactions could not be foreseen by the minimal movement speculation. Therefore, topochemical thinking strongly hampered the development of waste-free gas–solid and solid–solid reactions that are most sustainable. This detracted from responsible care for the environment of anonymous referees who disapproved research proposals and stopped publications, as the experimental facts could not be correlated with the invalid topochemistry speculations. Fortunately, the field has now matured and includes industrial applications, as properly executed gas–solid and solid–solid reactions really avoid solvents and further auxiliaries or high pressure or excessive energy, time, and labor. They enable previously inaccessible products, do not require activated reagents (no solvation is decreasing the reactivity), are of highest atom economy (e.g., no solvents and silica or alumina for purification) and provide the highest standard of environmentally benign sustainability. The proper execution of waste-free 100% yield reactions is therefore systematically detailed in this work. The basis for its scholarly teaching and for first steps for newcomers in research laboratories has already been provided with a case study for OECD with IUPAC in 2001, which presents a full students course in waste-free organic synthesis with 35 100% yield syntheses not using solvents and not requiring solvent consuming purifying workup, if the starting materials were pure crystals. It is freely available from Reference [84] and strongly recommended for use, as readily available materials and equipment have been taken care of. The execution of gas–solid and solid–solid production will improve the global environment.

Supplementary material

Fourteen different types of experimentation covering various encountered conditions for reaching 100% yield without wastes include condensation reactions with formation of the couple product water (which is taken up into the product crystals as crystal water or may require drying agent to bind liquid water) and substitutions with alkali salt formation (producing minimal stoichiometric waste that is removed by product sublimation or by salt extraction with water). They serve as guideline for successful waste-free performance of solid-state syntheses and production. The materials that are discussed here are available at the epoc website in Wiley Interscience.

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