Understanding Solid/Solid Organic Reactions

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Abstract: The concept of an organic reaction between two macroscopic solid particles is investigated. Thus, we study several reactions that have been recently reported to proceed "in the solid phase" and clearly show that, in most cases, grinding the two solid reactants together results in the formation of a liquid phase. This is true both for catalytic transformations (e.g., aldol condensations and oligomerization of benzylic compounds) and for noncatalytic reactions (Baeyer−Villiger oxidations, oxidative coupling of naphthols using iron chloride, condensation of amines and aldehydes to form azomethines, homo-etherification of benzylic alcohols using *p*-toluenesulfonic acid, and nuclear aromatic bromination with NBS). This liquefaction implies the existence of a eutectic mixture with T_{fusion} below ambient temperature (although both reagents have higher than ambient melting points). In cases where heating is required, it is again clear that a phase change (from solid to liquid) occurs, explaining the observed reaction kinetics. On the basis of 19 experimental examples, we discuss the possibility of solid-phase organic reactions and the implications of these findings to the reaction between two solid reagents. A general description of such reactive systems is proposed, based on a consideration of the potential for eutectic (or peritectic) formation between the constituents of the liquid phases that arise during the process of mechanical mixing of the solid reagents and products.

Introduction

Solid-state chemistry is a fast-developing science, enhanced by its numerous applications in the high-technology industries.[1] Often depending on specific crystal modifications and high-temperature interactions, it is associated primarily with inorganic crystalline compounds, where reactions are thought to occur via ion displacement and crystal deformation mechanisms.[2] It seems unreasonable that a physical class of reactions should be confined solely to "inorganic" materials, so it is not surprising that several studies on organic reactions in the solid phase have also been published.[3,4] What is surprising is the fact that many of these organic transformations were reported to afford high conversions and yields after short reaction times, at moderate and even ambient temperatures, yet were reported to occur between two macroscopic solids.

The concept of a chemical reaction between two solids is a difficult one. Moreover, various name tags are frequently employed in this context. In the interests of clarity, we distinguish here between *solid-phase synthesis* (the reaction of molecules from a fluid phase with a solid substrate, e.g., the polymer-supported peptide syntheses), *solvent-free synthesis* (any system in which neat reagents react together, in the absence of a solvent), and *solid-state synthesis* or *solid−solid reactions*, in which two macroscopic solids interact directly and form a third, solid, product without intervention of a liquid or vapor phase. A cartoon of these three processes is shown in Figure 1.

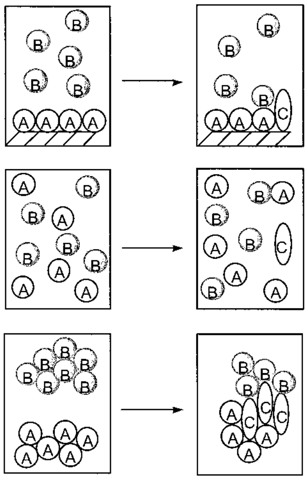

Figure 1. Cartoon of solid-phase reaction (top), solvent-free reaction (middle), and solid-state reaction (bottom).

In several studies, it has been proposed that when two solid organic compounds capable of a chemical reaction are ground in the absence of a solvent (therefore, "solvent-free"), a chemical reaction occurs in the solid phase. Such solvent-free systems have been recently reviewed[5] and variously termed solid−solid[6]

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(1) Smart, L.; Moore, E. *Solid State Chemistry, an Introduction,* 2nd. ed.; Chapman and Hall: London, 1996.

(2) For a discussion, see: Corbett, J. D. In *Solid State Chemistry Techniques*; Cheetham, A. K., Day, P., Eds.; Oxford University Press: Oxford, 1987; pp 1−35.

(3) For reviews, see: (a) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480−486. (b) Toda, F. *Synlett* **1993**, 303−312.

(4) Rastogi, R. P.; Singh, N. B.; Singh, R. P. *J. Solid State Chem.* **1977**, *20*, 191−200.

(5) Toda, F.; Tanaka, K. *Chem. Rev.* **2000**, *100*, 1025−1074.

(6) (a) Schmeyers, J.; Toda, F.; Boy, J.; Kaupp, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 989−993. (b) Toda, F.; Yagi, M.; Kiyoshige, K. *J. Chem. Soc., Chem. Commun.* **1988**, 958−959.

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or solid-state reactions.[7] However, in many cases, this description is oversimplified, as will be demonstrated herewith. It should be emphasized, though, that our study pertains to the reaction between discrete solid compounds to produce a chemically different product by the formation of new covalent bonds. It does not pertain to reactions resulting in the formation of complex structures such as a charge-transfer or molecular[8] complex or to reactions in a single crystalline phase such as photochemically induced solid-state transformations (e.g., 2 + 2 dimerizations) which can, and do, occur within the organic crystal itself.[9] In addition, the reaction of two components that crystallize together to form a discrete stoichiometric cocrystal, or inclusion compound, may be considered to occur in the solid phase,[10] although this is clearly not an interaction between two discrete solids but rather a reaction between two components of a single crystalline phase.

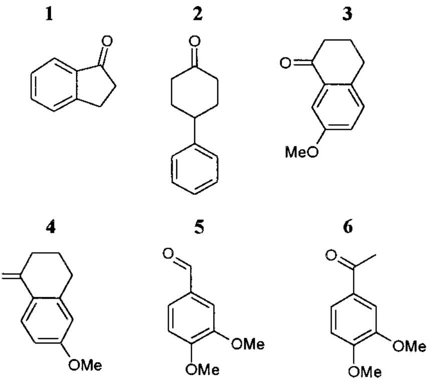
In this paper, we examine some of these so-called "solid–solid" organic transformations and produce clear evidence that many are actually reactions in a liquid melt. On the basis of the experimental evidence of 19 examples, we discuss the implications of the phase change to a melt as a precondition for a rapid chemical reaction between solid organic compounds under solvent-free conditions.

Results

It is important to emphasize that the following results represent a random selection of both previously reported and new reactions and *not a post-experimental selection* of systems that exhibit solid to liquid phase changes. The systems described herewith encompass a diverse range of reagents and products and are entirely representative of the reactions tested.

Aldol Condensation. The Aldol condensation in its simplest form involves the synthesis of α,*β*-unsaturated ketones from two carbonyl compounds (aldehyde and ketone, or ketone and ketone) in the presence of a strong base.[11] A common carbon–carbon homologation protocol, the Aldol reaction has been reported to proceed with alacrity under solvent-free conditions by grinding the reagents together with a solid base in either stoichiometric or catalytic amounts.[12]

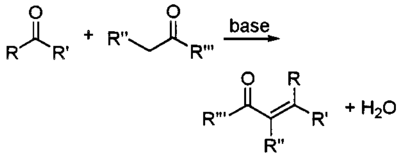
Table 1. Binary Mixtures of Ketones and Aldehydes Used in Aldol Condensation Reactions. Shaded Cells Indicate Reactive Systems (on Addition of NaOH)


1 2 3

4 5 6

	6	5	4	3	2
1	melt	melt	partial melt[a]	melt	melt
2		melt			
3	melt	melt			
4		partial melt[a]			
5	melt				

[a] "Sticky" powders: xrd analysis reveals peaks due to one component only, i.e., melt incomplete.


(1)

Grinding together the solid aldehydes or ketones without addition of the base catalyst reveals an interesting phenomenon: in some cases a liquid melt is observed while in others the solid reagents remain present as discrete crystalline phases (as evidenced by powder X-ray diffraction analysis). More importantly, upon addition of the solid base catalyst, reaction is *only* observed in those systems that exhibit a phase change to a melt. Thus, *the existence of a liquid phase is a prerequisite for reaction in these systems.* Correlation between appearance of a liquid phase and reactivity for the aldehydes and ketones **1**–**6** is illustrated in Table 1 (note that the converse is not true, viz. that the existence of a liquid phase does not necessarily augur reactivity at ambient temperature).

In all of the cases where reaction is observed, the mixture solidifies as the solid dehydration product separates from the melt. This removal of the dehydration product from the (melt) reaction mixture as it is formed means that, unlike similar reactions in solution, the Aldol condensation is inherently irreversible under these conditions.

The phase diagram for the mixture of 1-indanone **1** and 4-phenylcyclohexanone **2** has been constructed from measurements of thaw and melt points and is presented in Figure 2. The eutectic temperature of 19 °C is below the ambient temperature at which the experiments were conducted. However, it is interesting to note that at a 1:1 molar ratio of **1**:**2** the liquidus temperature is above ambient temperature, implying that some unmelted solid **2** should be present. This is not observed in the

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(7) (a) Goud, B. S.; Desiraju, G. R. *J. Chem. Res., Synop.* **1995**, 244–245. (b) Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007–3009. (c) Toda, F.; Takumi, H.; Masafumi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1270–1271. (d) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2896–2899. (e) Toda, F.; Tatsuya, S.; *J. Chem. Soc., Perkin Trans. 1* **1989**, 209–211. (f) Im, J.; Kim, J.; Kim, S.; Hahn, B.; Toda, F. *Tetrahedron Lett.* **1996**, *38*, 451–452.

(8) (a) Rastogi, R. P.; Singh, N. B.; Singh, R. P. *J. Solid State Chem.* **1977**, *20*, 191–200. (b) Rastogi, R. P.; Singh, N. B.; Singh, R. P. *Indian J. Chem., Sect. A* **1977**, *15A*, 941–946. (c) Rastogi, R. P.; Singh, N. B.; Singh, R. P. *Indian J. Chem., Sect. B* **1995**, *34B*, 764–767.

(9) For a very readable treatment of these reactions, see: (a) West, A. R. *Solid State Chemistry and it's Applications*; Wiley: Chichester, 1987; pp 666–679. See also: (b) Tanaka, K.; Toda, F.; Mochizuki, E.; Yasui, N.; Kai, Y.; Miyahara, I.; Hirotsu, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 3523–3525. This reactivity in the solid phase pertains chiefly to photochemical processes (e.g., dimerizations, polymerizations) but also for some thermochemical rearrangements and isomerizations and should not be confused with the subject of the present study. For examples, see: (c) Cohen, M. D. In *Reactivity of Solids*; Anderson, J. S., Roberts, M. W., Stone, F. S., Eds.; Chapman and Hall: London, 1972; pp 456–471. (d) Alder, G. *Organic Solid State Chemistry*; Gordon and Breach: New York, 1969. For X-ray diffraction studies of such solid-state photochemical transformations, see: (e) Gougoutas, J. Z. *Pure Appl. Chem.* **1971**, *27*, 305–325.

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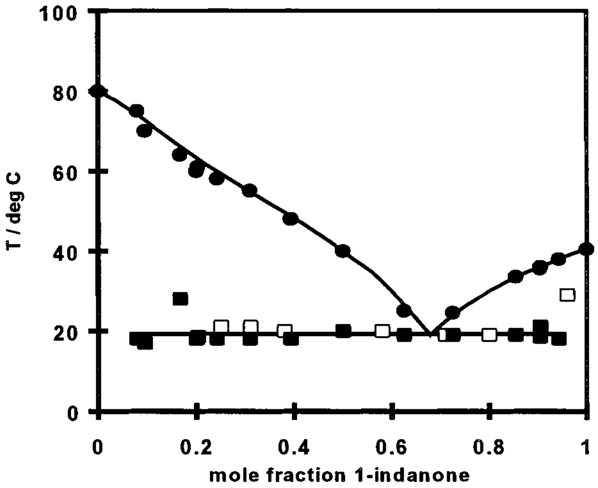
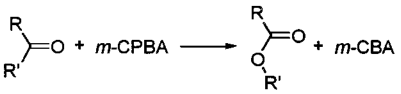


Figure 2. Phase diagram of 1-indanone **1** and 4-phenylcyclohexanone **2** at constant (ambient) pressure. Filled circles represent liquidus temperatures, filled squares thaw points, and open squares the onset temperature of the first endotherm measured by DSC analysis.

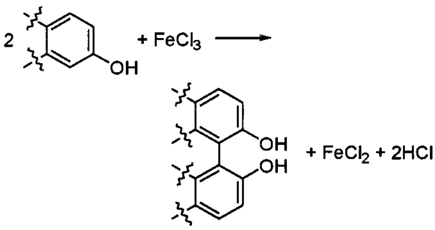
bulk samples and may indicate the tendency of the system to supercool.[13] In addition, this implies that some heat is released upon the grinding of the two components which leads to complete melting of the mixture. Such heat may be generated by the occurrence of "hot spots" [14] during initial grinding of the solids, and this phenomenon should be carefully considered when high-intensity grinding techniques, such as ball milling, are employed (even in cases where temperature-controlled apparatus is used). Coexistent solid and liquid phases are also evidenced in other systems. For example, gentle grinding of 6-methoxytetralone **4** and veratraldehyde **5** in the absence of a base yields a sticky paste which contains solid **4** dispersed in a viscous liquid phase. The presence of unmelted/undissolved **4** is verified by powder X-ray diffraction. Note that the powder pattern due to crystalline **5** is not detected.

Baeyer−Villiger Oxidation. The reaction between various ketones and *m*-chloroperbenzoic acid (*m*-CPBA) is a well-known general method for lactone production.[15] It has been recently reported to occur more rapidly at ambient temperature "in the solid state" than in solution.[6b] However, upon repeating the reaction between 4-*tert*-butylcyclohexanone and *m*-CPBA (eq 2), we observe that when each reagent is ground separately no changes occur, yet when the powders are ground together a liquid melt forms. This melt rapidly solidifies to afford the product as a glassy material. Previously, the reaction was reported to be complete in 30 min, but we have observed that the bulk of the reaction is over in a matter of seconds.



(2)

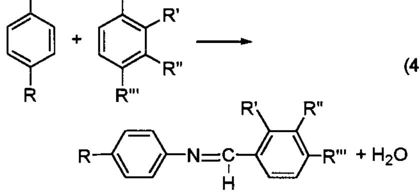
Oxidative Coupling of Naphthols. Simple thermal oxidative coupling of naphthols to binaphthols is of paramount interest to the agrochemical and pharmaceutical industries, as biaryls are key building blocks for pesticides, pharmaceuticals, and natural products.[16] The synthesis of 2,2′-dihydroxybinaphthalene (BINOL) is especially important in the production of various chiral ligands.[17] This reaction was reported to occur "in the solid phase" at 50 °C in the presence of 2:1 stoichiometric amounts of $FeCl_3 \cdot 6H_2O$ (eq 3).[7b] We have studied this process and found that no reaction occurs when 2-naphthol (white-cream powder) and $FeCl_3 \cdot 6H_2O$ (yellow-orange powder) are ground separately, nor is any reaction or phase change observed when the two powders are ground together (strong, light yellow powder) at 25 °C. However, when the combined powdered mixture is heated to 50 °C, the sample begins to melt after ca. 1 min, producing a bright yellow liquid. Reaction progress in the melt is easily observable, starting from the edge of the Pyrex tube and proceeding inward. The product solidifies and the reaction is nearly complete after 45 min. Significantly, no reaction is observed for an identical sample kept at 25 °C for 24 h.



(3)

The previous report states that at 50 °C the reaction took 2 h to complete, while at room temperature (no value is given but it is reasonable to assume that room temperature is somewhere between 20 and 30 °C) the reaction took 144 h. This enormous difference is significant, as both samples are claimed to react "in the solid state". However, if both samples were to react in the solid state, it is difficult to explain the large differences in reaction rates ($k_{50\,^\circ C}/k_{25\,^\circ C} \sim 80$). Temperature sensitivity is clearly not enough to account for this.[18] In fact, the reaction proceeds much faster at 50 °C simply because it is not in the solid phase but rather in a liquid or melt phase.

Condensation of Amines and Aldehydes to Azomethines. Interest in azomethines relates to their function as primary reagents for cycloadditions, cyclizations, and enantioselective oxidations. Their production via the condensation of various anilines with aromatic aldehydes was recently reported to proceed efficiently in the solid state.[6a] We reexamined a number of such examples and note the formation of a distinctly liquid or molten phase in a majority of cases. For example, in the reaction of 4-aminotoluene with 4-bromobenzaldehyde, grinding each reactant separately does not lead to any changes in bulk physical characteristics except particle size (both are white powders). However, grinding equivalent molar quantities of the



(4)

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(13) Sangster, J. *J. Phys. Chem. Ref. Data* **1997**, *26*, 351−502.

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(16) For reviews on biaryl preparation methods and applications, see: (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327−3359.

(17) For a review, see: Rosini, C.; Franzini, L.; Rafaelli, A.; Salvadori, P. *Synthesis* **1992**, 503−517.

(18) If at both temperatures the reactants and the products are solid (i.e., there is no other phase present during the reaction), it is to be expected that $\Delta S^{\ddagger}_{25\,^\circ C} \sim \Delta S^{\ddagger}_{50\,^\circ C}$. Assuming that $\Delta H^{\ddagger}$ is independent of temperature at this range, the ratio $k_{50\,^\circ C}:k_{25\,^\circ C}$ would be roughly 6:1. Since this is obviously not the case here, additional activation must be taking place at 50 °C. See: Isaacs, N. *Physical Organic Chemistry*, 2nd ed.; Longman: Essex, 1995; pp 105−118.

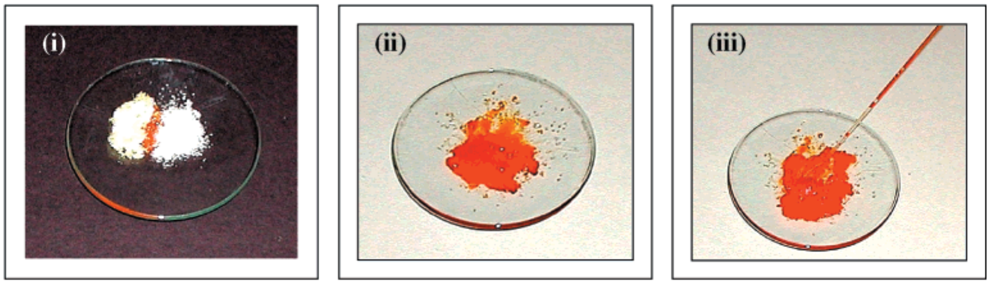

Figure 3. 4-Aminotoluene and 2-hydroxy-3-methoxybenzaldehyde ground independently and mixed at room temperature. (i) Immediately after the powders contact one other an orange, liquid phase forms. (ii) After merely mixing with a glass rod the entire mass is a homogeneous liquid. Time elapsed is approximately 2 min and the Petri dish has been shifted from a dark to a light background immediately post mixing of the powders. (iii) The orange, liquid phase is so fluid that it may be drawn into a pasteur pipet. Solid, orange azomethine product rapidly crystallizes from the liquid phase as the reaction proceeds and the entire mass is a wet crystalline solid in less than 10 min.

Table 2. Phase Changes and Reactivity in the Reaction between an Aromatic Amine and a Benzaldehyde Derivative To Form an Azomethine

Ar-NH$_2$	Ar-CHO		product
4-$CH_3C_6H_4$	2-OH-3-MeOC_6H_3	melt	orange solid
	2-$NO_2C_6H_4$	melt	yellow solid
	3-$NO_2C_6H_4$	melt	yellow solid
	4-$NO_2C_6H_4$	no melt[a]	yellow solid[b]
	4-BrC_6H_4	melt	white solid
	4-OHC_6H_4	no melt[c]	*d*
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	melts at 83−85 °C	yellow solid[e]

[a] Ground mixture changes to bright yellow powder with time. [b] Incomplete reaction after 7 days. [c] No change in ground mixture after 48 h at ambient temperature (minimal product detectable). [d] Reaction incomplete after 20 days! [e] Product formed post melt.

two powders together results in the formation of a liquid melt, of yellow color, which transforms in a matter of seconds into a white solid product. Similar behavior was noted for a number of analogous substrates (Table 2) and is particularly striking in the reaction between 4-aminotoluene and 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) pictured in Figure 3. The solid, powdered reagents liquefy almost immediately upon contacting each other without intervention of grinding or even extensive mixing. The liquefaction is rapid and complete and yields a liquid phase so fluid that it is easily drawn into a pasteur pipet. The solid azomethine product begins to separate in a matter of minutes, and the entire reaction mixture solidifies to a wet crystalline mass within 10 min. Note that similar behavior was hinted at in a previous report of the analogous reaction of aromatic amines with vanillin and 4-chlorobenzaldehyde with 4-aminotoluene.[6a,19]

Remarkably, 4-aminotoluene and 4-hydroxybenzaldehyde do not yield more than traces of azomethine product post grinding of a 1:1 mixture, even after storage at 22 °C for 5 days. The reaction mixture remains solid upon grinding, and X-ray powder diffraction analysis of this mixture after storage at 22 °C for 11 days indicates that solid unreacted starting material is still present in the reaction mixture as is illustrated in Figure 4.

These results differ from previous reports where the reaction was claimed to be complete after 6 h.[6a] Closer examination of the data presented by Schmeyers et al. gives an indication of the reduced reactivity of this system as, upon DSC analysis, endotherms due to fusion of each reagent are measured followed by an endotherm corresponding to product melt. This may imply reaction post melting of the reagents (or reaction at an elevated temperature). Indeed, heating the reagents together at 100 °C for 2 min, followed by cooling to ambient temperature and DSC analysis, leads to observation of only one significant endotherm due to product melt, as would be expected after 100% substrate conversion. This is further borne out by the fact that this system loses 1 mol of water at elevated temperature in thermal gravimetric analysis (TGA). The crystal structure of the product compound, in the polymorphic modification crystallized from wet dichloromethane, is not a hydrate as evidenced by single-crystal structure analysis (see Figure 5).[20] It is probable that the water loss measured on TGA analysis arises from a reaction occurring at a temperature significantly above ambient and post reagent fusion.

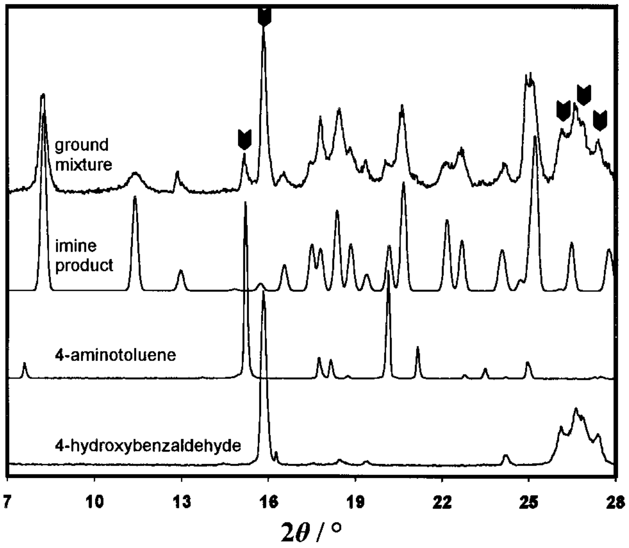

Figure 4. Comparison of powder X-ray diffraction traces for the solid reagents (bottom traces), the product (as calculated from single-crystal structure data − middle), and the ground mixture post grinding and storage at 22 °C for 11 days (top). Peaks due to unreacted starting materials are highlighted with arrows.

As noted in the Aldol reaction examples, a phase change to a binary melt appears to precede reaction in all systems tested except that comprising 4-nitrobenzaldehyde and 4-aminotoluene.

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(19) "Softening" was reported in the reactions with vanillin. SNOM measurements show that, in the reaction of single crystals of 4-nitroaniline and 4-chlorobenzaldehyde, the entire surface of the crystal is of a single chemical type and that there is no differentiation between the chemical identity of the surface features ascribed to product formation and the substrate (reagent) between these. The authors ascribe this to "short distance sublimation" of the aldehyde (ref 6).

(20) Crystal data for the azomethine product formed from 4-aminotoluene and 4-hydroxybenzaldehyde: $C_{14}H_{13}NO$, $M_r = 211.25$, orthorhombic, space group *Pbca*, $a = 11.1939(3)$ Å, $b = 9.2537(3)$ Å, $c = 21.1621(8)$ Å, $V = 2192.1(1)$ Å^3, $Z = 8$, μ(Mo Kα) = 0.081 mm^{-1}. Of 7773 reflections measured, 2588 were unique with 1415 $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] $R_1 = 0.0496$, w$R_2 = 0.0923$, GOF on $F^2 = 0.959$ for 146 refined parameters and 1 restraint (OH bond length). O−H···N hydrogen bonds yield helical chains of molecules. Double helices composed of chains of opposite handedness propagate down [010].

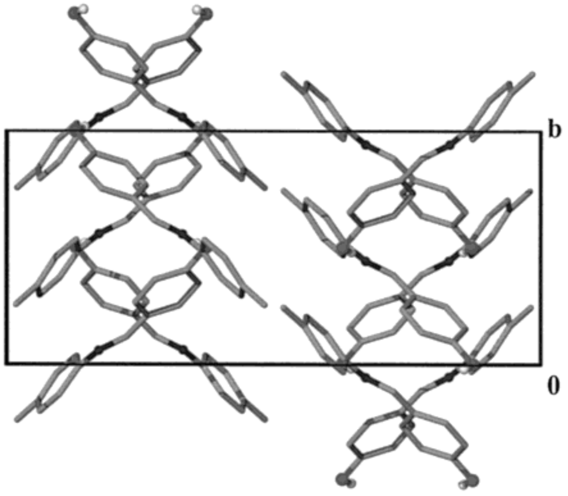
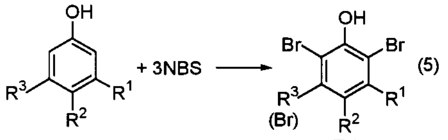


Figure 5. Packing diagram of (4-hydroxybenzylidene)-*p*-tolylamine viewed down *a*. Oxygen and nitrogen atoms are depicted as filled circles, and only the OH atom is included for clarity. No water of crystallization occurs in the structure.

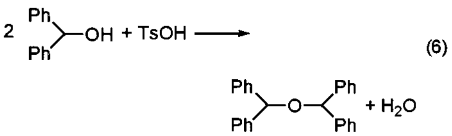
We are currently investigating this specific system further, but, in general, it appears that solid−solid reactions are not the norm in azomethine formation.

Nuclear Bromination of Aromatics. Ring bromination of aromatic compounds with *N*-bromosuccinimide (NBS) has been described as a “genuine solid-state reaction” that has “preparative and industrial value”.[7a] However, these compounds will undergo electrophilic aromatic bromination regardless of the bromine source used,[21] and it is unlikely that protocols employing NBS could compete with syntheses based on molecular bromine.[22] More importantly, upon repeating this reaction we note that it is not a solid-state reaction at all, but rather occurs in (again) a liquid melt of the two reagents. Thus, when a 1:3 molar ratio of either 3,5- or 3,4-dimethylphenol (reddish-transparent crystals and white powder, respectively) and NBS (white powder) are ground together (eq 5), a yellow liquid melt is observed which solidifies to give the brominated product as a mixture of di- and tribrominated products, as reported previously.

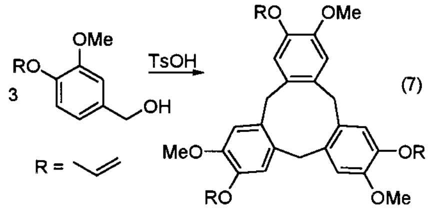


1a R^1, R^2 = Me; R^3 = H
1b R^1, R^3 = Me; R^2 = H

Etherification of Alcohols. Treatment of alcohols with equimolar amounts of *p*-toluenesulfonic acid (TsOH) has been reported as a method to synthesize the corresponding ethers in the solid state.[7c] We find, however, that equimolar amounts of diphenylmethanol (benzhydrol) and TsOH ground together (eq 6) form a sticky white liquid, which solidifies after 10−15 min to give the reported ether.



Oligomerization of Benzylic Alcohols. We have previously reported[23] that the bowl-shaped supramolecular host compounds such as cyclotriveratrylene[24] (CTV) and the analogous tris-(*O*-allyl)-CTV may be synthesized in the absence of a solvent (eq 7).



Grinding of 4-allyloxy-3-methoxybenzyl alcohol with 1 equiv of TsOH yields a viscous melt which solidifies over a period of days as tris-(*O*-allyl)CTV is formed and separates as a microcrystalline solid. Once again, this solvent-free reaction is not a solid−solid reaction despite the relatively high melting points of both reagents (86 and 103−105 °C, respectively). One mole of water is produced for each mole of benzyl alcohol condensed, yet we do not believe the presence of free water accounts for the apparent liquefaction of the reaction mixture. Although the viscosity of the monomer/acid mixture was lowest directly after the grinding of the two components, TLC analysis reveals <5% product at this point. Thus, the water present is derived chiefly from the monohydrate catalyst and would be insufficient to account for the degree of liquefaction noted (particularly given the low aqueous solubility of the benzyl alcohol monomer[25]).

Discussion

The above results show clearly that many of the so-called “solid−solid” reactions are not reactions in the solid state. With only one exception, all of the reactive systems investigated exhibited a clear change to a liquid (melt) phase. Even without this ample experimental evidence, the occurrence of a rapid (i.e., faster than in solution) chemical reaction in the solid state is hard to come to terms with on the basis of chemical intuition. True, for a reaction in solution one would expect that the concentration of substrates A and B would be lower than for the pure compounds, and even when two molecules collide the reaction may not take place (depending on reactive cross-section and orientation).[26] However, in the case of two solid particles, although substrate “concentration” may be high, the actual number of active substrate molecules would be low because only those molecules on the particle surface would be able to react.[27] Furthermore, the orientation of the molecules in the solid is fixed, making for a lower cross-section, and the energy required to disrupt the crystal lattice to enable the individual molecules to react is often considerable.[28] Solid−solid reactions

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(21) Rothenberg, G.; Clark, J. H. *Green Chem.* **2000**, *2*, 248−251.

(22) Rothenberg, G.; Clark, J. H. *Org. Process Res. Dev.* **2000**, *4*, 270−274.

(23) Scott, J. L.; Raston, C. L.; MacFarlane, D. R.; Teoh, C. M. *Green Chem.* **2000**, *2*, 123−126.

(24) Systematic name: 2,3,7,8,12,13-hexamethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene.

(25) BzOH (1 g) dissolves in 25 mL of water: *The Merck Index*, 11th ed.; Merck & Co.: Rahway, NJ, p 1137.

(26) Levine, R. D.; Bernstein, R. B. *Molecular Reaction Dynamics and Chemical Reactivity*; Oxford University Press: New York, 1987; pp 26−66.

(27) Mukhopadhyay, S.; Rothenberg, G.; Wiener, H.; Sasson, Y. *New J. Chem.* **2000**, *24*, 305−308.

(28) The typical energy barrier for molecular reorientation in a crystalline organic compound is 10−20 kcal mol^{-1}. See: Gavezzotti, A.; Simonetta, M. *Chem. Rev.* **1982**, *82*, 1−13.

occurring between two discrete crystalline solids, without intervention of a mobile phase and which allows a large number of productive molecular collisions, would be expected to exhibit diffusion-controlled kinetics.[29] Thus, the rapid rates exhibited by most of the reactions studied ($\tau_{1/2,25\,°C} < 60$ s in some cases) do not support the theory of two solids reacting together without intervention of a new (liquid) phase which would enable higher substrate mobility.

Another issue which the solid−solid interpretation is incomplete in addressing is the phenomenon of substrate deactivation via the formation of a solid product layer on the substrate particle surface. If there is no solvent and no liquid phase, a chemical reaction of A with a molecule of B on the crystal surface of B would form the solid product C on, or in close proximity to, the crystal surface of B (see Figure 1, bottom). Since no melting is supposed to occur in the solid−solid reaction, in most cases this would result ultimately in the formation of an microcrystalline layer, coating B with C.[30] This could arrest the reaction before full conversion is achieved (in fact, we have observed a similar phenomenon even in the case of a solid/liquid system, viz. the coating of CaF_2 particles with $CaSO_4$ in the in situ production of HF from liquid H_2SO_4 and solid CaF_2).[31]

We propose the following description of such systems: upon mixing of the reagents, a melt of mutually miscible A and B exists, so that these may be considered to be *mutually soluble*. At this point, the phase diagram is that of two largely immiscible solids, which do not exhibit the formation of a molecular complex, as shown in Figure 6i.[32,33]

In the reaction, A + B ⟹ C, the overall phase equilibria may be represented by a triangular prism as shown in Figure 6ii. In this prism each rectangular face represents one binary diagram (AB, AC, etc.).[34] Since the reactions are not thermally isolated, these approximate to systems at constant temperature, and the chemical and phase composition may be represented by triangular cross-sections of the prism [cf. Figures 6iii and (6iv, which represent cross-sections at T1 and T2, respectively]. Figure 6iii shows the situation where the temperature is above that of the binary eutectic formed by A and B (and above the binary eutectics formed by A and C, B and C, and the ternary eutectic formed by A, B, and C). Thus as A and B react in 1:1 stoichiometry (as in the azomethine reactions) to form product C, the composition changes along the line qC. The liquid phase, initially composed of 1:1 A:B, becomes enriched in C until the liquidus line is crossed and C begins to crystallize out of the melt. At complete conversion, the only phase present will be a solid, crystalline C. As the quantities of A and B, relative to each other, remain constant throughout the reaction, a vertical section of the triangular prism [such as the one shown in Figure 6v] can be used to depict the phase equilibria occurring.

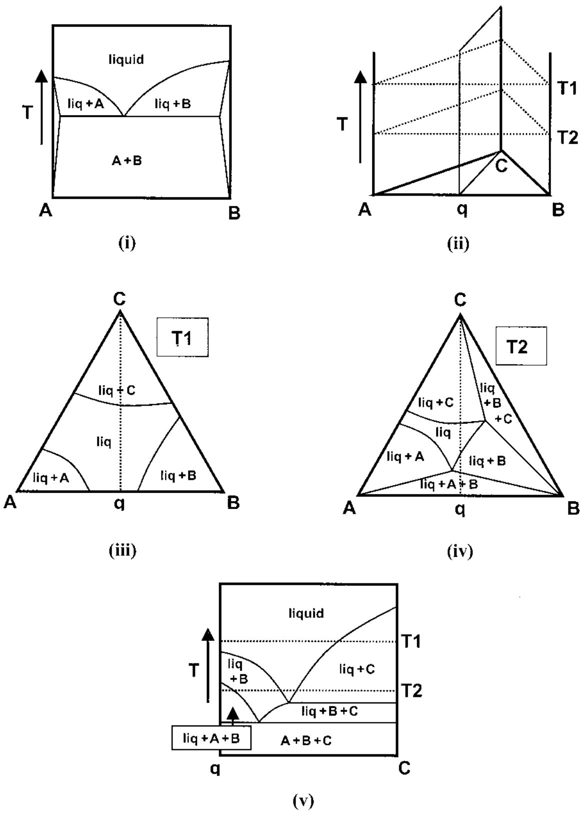

Figure 6. (i) Simple eutectic diagram (at constant P) for two components, A and B, that are completely miscible as liquids but practically immiscible as solids. (ii) Triangular prism basis for a three-component phase diagram at constant P with vertical axis representing increasing temperature. Consideration of cross-sections such as T1 and T2 allow analysis of the phases occurring at various component concentrations at a specific, constant temperature. (iii) and (iv) represent cross-sections of this prism at particular temperatures. (iii) Three-component phase diagram at temperatures greater than the AB, BC, AC, or ABC eutectic temperature. Note liquid phase at C = 0. (iv) Three-component phase diagram at temperatures greater than the AC and ABC eutectic temperature but below AB and BC eutectic. Note a liquid phase coexists with solid A and solid B at any point where C ≠ 0 (i.e., even a reaction which begins as a solid−solid reaction could liquefy upon formation of product). (v) Diagram representing constant A and B composition of 1:1 molar ratio with increasing temperature. Moving along the dotted lines marked T1 and T2 indicates the phase changes occurring as C increases.

In several of the above examples, water is produced as the condensation reaction proceeds and should be considered as a fourth chemical component in the phase diagram. The same is true of any reaction intermediates, such as the β-hydroxy ketones formed in the Aldol type reactions, and of the catalysts where appropriate (e.g. NaOH). However, the above description is adequate for those cases where the quantities of catalysts are small, the reaction intermediates are short-lived, and the components A, B, and C have very low aqueous solubility. Indeed, the inclusion of further miscible components only serves to increase the proliferation (and likelihood of occurrence) of possible liquid phases, as was shown by Epple et al. in the case of the reductions of benzophenones with sodium borohydride.[35]

It is interesting to consider the situation where the temperature at which the reaction is conducted is above the eutectic temperature of the reagents A and B. If A and B react in a solid−solid reaction, whether by grain boundary diffusion or surface migration,[4] product C begins to form and, should there exist an AC, BC, or ABC eutectic which occurs below the

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[29] Rastogi, R. P., Singh, A. K., Shukla, C. S., *J. Solid State Chem.* **1982**, *42*, 136−148.

[30] Such passivation would not be expected only in the special cases where the newly formed phase would incur a larger molar volume, e.g., the oxidation of Fe by O_2 to Fe_2O_3. The issue is further complicated by the fact that mechanical stress, such as grinding, may disrupt this passivating surface layer, exposing fresh unreacted reagent.

[31] Rothenberg, G.; Royz, M.; Arrad, O.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1491−1494.

[32] Moore, W. J. *Physical Chemistry*; Prentice Hall: Englewood Cliffs, NJ, 1968; pp 146−149.

[33] There are numerous examples of reactivity in systems that *do* exhibit molecular complex formation (cf. ref 10c), but these describe reactions in a single solid phase containing both reagents and are thus not reactions between discrete solid phases.

[34] Masing, G. *Ternary Systems; introduction to the theory of three component systems*; Dover Publications Inc., New York, 1944; pp 9−31.

[35] Epple, M.; Ebbinghaus, S.; Reller, A.; Gloistein, U.; Cammenga, H. K. *Thermochim. Acta* **1995**. *269*, 433−441.

reaction temperature, a liquid phase may again intervene. Thus, a reaction which begins as a solid−solid reaction may proceed much more rapidly by intervention of a liquid phase arising due to the existence of a lower melting eutectic formed by the product and the reagent or reagents. This too could account for the appearance of liquid phases and for the rapid kinetics observed in some of the examples studied.

We have noted that, in some binary reactions which require a catalyst for reaction, e.g., 6-methoxytetralone **4** and veratraldehyde **5**, incomplete conversion to a liquid phase is observed prior to addition of the catalyst. This implies that while above the eutectic temperature, these mixtures do not exhibit the eutectic composition and one component is present in the mixture as a solid as would occur in region A + liquid (or B + liquid) in Figure 6i.

Conclusion

We have demonstrated that few covalent bond forming bimolecular organic transformations that proceed rapidly and to a high degree of completion between two solid reactants actually occur in the solid state. Instead, a *liquid or melt phase*, which imbues the individual molecules with the required mobility for productive (or reactive) collision, intervenes, allowing rapid reaction between the two solid reagents. These reactions should therefore be classified together with classical liquid/liquid and liquid/solid systems that react in the absence of an added solvent.

Experimental Section

Powder XRD analysis was performed on a Syntag PAD5 diffractometer at 294 K using Cu Kα radiation ($\lambda = 1.54059$ Å) in the range 6−36° 2θ. DSC analysis was performed on a Perkin-Elmer DSC-7 system in sealed 50 μL aluminum pans on ground samples of 4−10 mg at a heating rate of 10 °C/min. The system was calibrated using two standards with appropriate melting points. ^{1}H NMR spectra were recorded on a Varian Mercury AM 300 MHz spectrometer in $CDCl_3$ with TMS reference. Melting points were measured using an Electrothermal digital melting point apparatus in open capillary tubes or with a Reichert hotstage microscope and temperature controller and are uncorrected.

Binary phase diagrams were constructed from data obtained using the thaw−melt method of Rastogi[36] and measurement of the liquidus temperatures using the visual-polythermal method.[13]

Single-crystal X-ray diffraction data were collected on an Enraf Nonius CCD diffractometer at 123 K using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The data were corrected for Lorentz polarization effects. Structures were solved by direct methods using the SHELXS-97 program[37] and refined by full matrix least squares refinement on F^2 using the SHELXL-97[38] and XSEED[39] programs. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms, except that of the OH group, were inserted at geometrically determined positions with temperature factors fixed at 1.2 times (methine and methylene) and 1.5 times (methyl) that of the parent atom. The OH hydrogen atom position was located from electron density difference maps and refined with a simple bond length restraint. Calculated X-ray powder patterns were generated using the LAZYPULVERIX[40] program as modified and included in the XSEED program.[39]

All reagents were of 98% purity or greater and were used as purchased from the supplier unless noted otherwise. Reagent grade *m*-CPBA (Aldrich) was assessed prior to reaction to contain 50% *m*-CPBA, 15% *m*-CBA, and ca. 35% water (this compound is a solid and was kept refrigerated prior to reaction; no data are given regarding the type of *m*-CPBA used in the previous study, and we assumed that the highest commercial grade solid, i.e., similar, was used). *p*-Toluenesulfonic acid (monohydrate) was used without further drying while NaOH was dried to remove water absorbed on storage. Satisfactory spectral data were obtained for all products.

Extreme care was taken to repeat all procedures exactly as reported. Thermal reactions were carried out in Pyrex tubes immersed in a thermoregulated silicon-oil bath (Heidolf MR 3003). Temperature was monitored throughout the reactions using both thermocouple and mercury thermometers, and the heated oil was stirred continuously to maintain an even temperature. Temperatures obtained using this setup were accurate to ±1.0 °C. Grinding experiments were performed with agate or porcelain mortar and pestles, which were acid washed and dried prior to use. In all cases grinding was quite gentle and in many cases a similar effect, albeit slower, could be achieved by pregrinding of the reagents (to achieve particle size reduction) and subsequent mixing.

Aldol Condensation. A total of 0.67 g (5.1 mmol) of 1-indanone and 0.84 g (5.1 mmol) of 3,4-dimethoxybenzaldehyde were gently ground together at 22 °C. A clear light brown liquid formed which, upon addition of solid NaOH (approximately 1 molar equiv) and further grinding, solidified to yield a brownish solid. This solid was reground, slurried in approximately 2 mL of 0.02 M HCl, filtered, washed with 1 mL of water, and dried to yield 1.33 g of 2-(3,4-dimethoxybenzylidene)indan-1-one (94%), mp 183−185 °C (lit.[41] mp 175−177 °C). Other condensation reactions with the ketones and aldehydes listed in Table 1 were carried out similarly. The products were identified by ^{1}H NMR analysis and melting point.

Ketone Oxidation. A total of 1.12 g (3.24 mmol) of *m*-CPBA and 0.25 g (1.62 mmol) of 4-*tert*-butylcyclohexanone were ground together at 25 °C. A glassy liquid formed which quickly solidified into the product 3-*tert*-butylcaprolactone (preparative TLC; hexane:EtOAc 2:1), mp 49 °C (lit.[42] mp 51−54 °C).

Naphthol Coupling. A total of 1.00 g (7.0 mmol) of 2-naphthol and 3.80 g (14.0 mmol) of $FeCl_3\cdot 6H_2O$ were ground separately and then ground together at 25 °C and heated to 50 °C. The mixture melted and then solidified. Recrystallizing (from EtOH/water) afforded 1.70 g of 2,2′-dihydroxybinaphthalene (85% based on 2-naphthol), mp 212 °C (lit.[43] mp 215−217 °C).

Azomethines. A total of 300 mg (2.8 mmol) of 4-aminotoluene and 510 mg (2.8 mmol) of 4-bromobenzaldehyde were ground together to give a yellow liquid melt which rapidly solidified to give (4-bromobenzylidene)-*p*-tolylamine quantitatively as a white solid, mp 144−147 °C. Reactions with the benzaldehyde and aniline derivatives listed in Table 2 were performed in similar manner to yield the appropriate azomethines. In the case of 4-nitroaniline and 4-nitrobenzaldehyde, the ground mixture was heated until melted and maintained at this temperature for 10 min during which time it solidified to the yellow product.

Phenol Bromination. A total of 61.1 mg (0.50 mmol) of 3,4-dimethylphenol and 266 mg (1.50 mmol) of NBS (white powder) were ground together to yield a yellow liquid melt which solidified to give a mixture of 2,6-dibromo-3,4-dimethylphenol and 2,3,6-tribromo-4,5-dimethylphenol. The reaction of 3,5-dimethylphenol was performed similarly.

Benzhydrol Etherification. A total of 92.1 mg (0.50 mmol) of benzhydrol and 95.1 mg (0.50 mmol) of TsOH were ground together at 25 °C to form a sticky white liquid, which solidified after 10−15 min to give 1,1,1′,1′-tetraphenyldimethyl ether.

Oligomerization of Benzylic Alcohols. A total of 0.33 g (1.68 mmol) of 4-allyloxy-3-methoxybenzyl alcohol and 0.32 g (1.69 mmol) of *p*-toluenesulfonic acid monohydrate were ground together to produce a sticky, pale brown syrup which solidified over a period of 2 days to yield tris-(*O*-allyl)CTV. The solid material was dissolved in dichloromethane, insoluble material was removed by filtration, and the pure crystalline product was obtained by slow evaporation of the solvent.

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(36) Rastogi, R. P.; Rama Verma, K. T.; *J. Chem. Soc.* **1956**, 2097.

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(38) Sheldrick, G. M. SHELXL-97, University of Gottingen, 1997.

(39) Barbour, L. J. 1999, X-Seed − a graphical interface to the SHELX program suite, University of Missouri.

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(41) Poirier, Y.; Lozac'h, N. *Bull. Soc. Chim. Fr.* **1966**, 1052−1068.

(42) Allinger, N. L.; Greenberg, S. *J. Am. Chem. Soc.* **1962**, *84*, 2394−2402.

(43) Akimoto, H.; Yamada, K. *Tetrahedron* **1971**, *27*, 5999−6009.

The white crystalline product (0.16 g, 54%) obtained proved to be pure tris-(*O*-allyl)CTV when compared with authentic samples by melting point, TLC, and ^{1}H NMR analysis.

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Supporting Information Available: DSC of the 4-aminotoluene and 4-hydroxybenzaldehyde system showing changes effected by heating to melt. Phase diagrams of mixtures of 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin)/(2-hydroxy-3-methoxybenzylidene)-*p*-tolylamine (azomethine product), and 4-aminotoluene/(2-hydroxy-3-methoxybenzylidene)-*p*-tolylamine. Data pertaining to the crystal structure analysis of the condensation product of *p*-aminotoluene and *p*-hydroxybenzaldehyde [(4-hydroxybenzylidene)-*p*-tolylamine] as an X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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