

## Predictive Synthesis

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### **Kirill Kovnir Bio**

Kirill Kovnir studied chemistry and received Ph.D. at the Lomonosov Moscow State University scrutinizing inverse clathrates. As a postdoc he explored itinerant catalytic potential and magnetism of intermetallics. Kirill started his independent career at UC Davis and soon after promotion to Associate Professor relocated to Iowa State University. Kirill's research interests are in the broad field of solid-state and materials chemistry aiming at understanding of synthesis, crystal structure, chemical bonding, and physical properties.

## Abstract

Current solid state synthesis intrinsically involves a multi-dimensional space which is challenging to parametrize and predict. Diversity of extended structures comes from the diversity of basic properties of elements of the Periodic system which may exhibit a variety of bonding modes. The fundamental challenges of prediction of the preparative outcome are further complicated by practical synthetic issues. Current development in computational and experimental methods calls for collaborative efforts to make solid state synthesis more predictable. This Perspective discusses several steps in this direction, including integration of predictions of synthetic conditions with new structure predictions, widespread of *in-situ* studies to obtain a panoramic view of the reaction mechanism, and creation of synthetic database to properly document all synthetic efforts, including the unsuccessful ones.

Chemical synthesis relies on the ability to make and break chemical bonds in a controlled manner. Organic chemistry has demonstrated a high degree of predictability in synthesis by applying both kinetic and thermodynamic controls arising from advances in the understanding of the relative stabilities of reactants, products, and intermediates as well as their electronic structures. Combinations of in-situ spectroscopic studies and computational characterization uncover organic reaction mechanisms allowing for better control of the reaction outcomes. In contrast to organic chemistry, solid state chemistry is less predictive, especially when a new compound, thermodynamically stable or metastable, having no structural or compositional analogues is targeted. The low degree of predictability of any solid state synthetic outcome is a general consequence of extended 1D, 2D, or 3D bonding in crystal structures in contrast to the molecules in organic synthesis. Note, that predictions of packings of organic molecules in crystals are much less successful as compared to predictions of molecules themselves. Similarly, in molecular organic frameworks and covalent organic frameworks (MOFs and COFs) one can predict the local fragments and overall structural motifs based on the rigidity of the organic linkers and coordination chemistry of the metal cations but predicting complete crystal structure, such as stacking sequence of layers in COFs is still a challenge.

Solid state chemistry deals with 82 stable elements of the Periodic system and some radioactive ones, including such inert elements as He [1,2]. Such chemical diversity leads to a variety of compounds with ionic, covalent, and metallic bonding and combinations therein. In solid state compounds elements exhibit various oxidation states, coordination numbers, and bond lengths. Compounds of interest often contain *d*- or *f*-elements with open electronic shells, which complicates their computational treatments. For the arbitrarily chosen combination of *A*, *B*, *C*, and *D* elements there is no obvious way to predict the composition and crystal structure of the compound formed by those elements, other than by an analogy with existing compounds. The fundamental challenges of prediction of the preparative outcome are further complicated by practical synthetic challenges:

1. Solid state reactions are conducted at a wide temperature range from  $-100^{\circ}\text{C}$  to  $2000^{\circ}\text{C}$  and beyond when arc-melting and other high-temperature techniques are considered.
2. Multiple aggregate states (solid, liquid, gas) of reactants, products, and intermediates are often involved impeding diffusion limitations and concentration gradients across the sample.
3. Reactants, either elements or compounds, showcase a wide range of thermal and chemical stabilities. For example, melting points for the elemental metals range from  $-39^{\circ}\text{C}$  (Hg) to  $3400^{\circ}\text{C}$  (W).

Drastic differences in the aggregate states and reactivities often create issues with proper mixing of the reactants and substantial diffusion limitations even at elevated reaction temperatures. In certain cases, a specific design of synthesis is required to overcome the diffusion limitations, for example by layer-by-layer precursor deposition allowing to control composition and diffusion lengths. Self-assembly of such precursors upon thermal treatment resulted in synthesis of a variety of unique compounds with interesting properties [3,4].

Nevertheless, solid state chemists have synthesized and continue to prepare a wide range of complex and novel solid state compounds. Although some of these compounds are produced due to serendipity, a number of fundamental chemical bonding concepts are used to rationalize and, to some extent, predict the outcomes of solid state synthesis. Such concepts include trends in atomic and ionic radii, cationic and anionic hardness and acidity, electronegativity and charge transfer, Zintl-Klemm concept,

valence electron counting rules or valence electron concentrations, bond valence sums, and chemical bonding analyses in direct space [5-15]. A combination of fundamental chemical concepts, intuition, and serendipity have guided solid state synthetic efforts for decades with great success. Is it time to change the paradigm and make solid state synthesis more predictable? This viewpoint discusses several general steps to consider for the solid state chemistry community to move towards this direction.

### **Why do we need more predictable synthesis? What are the desired traits which are currently lacking?**

1. To form targeted chemical bonds and local coordination environments that can induce specific functions. This is an analogy of introducing functional groups in organic chemistry, but these functional groups must be incorporated into the 1D-2D-3D bonding framework. For example, non-centrosymmetric building blocks linked together with strong covalent bonds lead to overall non-centrosymmetric structures [16-17].

2. Clearing out “blank spots” in binary and ternary systems may lead to the discovery of unprecedented structures and properties. Divergent reactivities of starting materials often lead to understudied binary and, more often, ternary and multinary systems. For example, among non-oxide ternary systems containing refractory hafnium and boron Hf-B-X, only ternary compounds for X = transition metals, Si, and Al are reported [18]. Those X elements have high boiling points and low vapor pressures, and are therefore suitable for arc-melting, which is the method used to overcome the refractory natures of hafnium and boron. No examples of ternary compounds with X = chalcogen or pnictogen are reported due to comparatively high vapor pressure of pnictogens and chalcogens at elevated temperatures. Hf-B-X systems is one out of many examples where exploration of ternary compounds is hindered by synthetic limitations rather than any fundamental stability or bonding preference issues. Replacement of refractory hafnium (melting point of 2230°C) with low-melting and reactive alkali metal leads to over 50 reported A-B-X compounds for A = Li-Cs; X = pnictogen or chalcogen [18].

3. Realization of a computational chemistry *Holy Grail*, e.g., the reverse approach to materials engineering – when the desired band structure is constructed first, followed by the prediction and preparation of the compound in which the desired band structure can be realized [19].

The author can imagine numerous skeptical grins on the faces of experimental chemists reading this part. Solid state synthesis intrinsically involves a multi-dimensional space which is challenging to parametrize and predict. However, specific steps in this direction should be taken, keeping in mind high-end goals.

### **Step 1. Computational predictions of synthesis (from a naïve purely experimental point of view).**

Theoretical analysis of band structures and chemical bonding is an important part of solid state chemistry. Many great chemists (just to name a few: Myung-Hwan Whangbo, Roald Hoffmann, Jeremy Burdett, and Linus Pauling) contributed to make theoretical and computational analysis a useful tool in understanding and predicting trends in crystal structure and properties of solid state compounds [6, 20-23]. Recent advances in computer speed and algorithms make possible numerous predictions of crystal structures which in some cases were experimentally verified. With the encouragement of funding agencies there are multiple examples of successful computational-experimental collaborations [24-32], but, in the author’s opinion, the integration of computational and experimental communities still needs to be improved. When experimental or computational groups work separately from each other, they

often may not recognize the limitations and interests of other party and prefer to stay inside their comfort zone, i.e. predict or synthesize compounds they are good in predicting or synthesizing.

As an experimentalist, when I glance over computationally predicted structures, I am sometimes amazed with structures that seem unconstrained by basic chemical concepts. I can hardly imagine such structures based on my chemistry knowledge alone, see for example [33,34]. As an experimentalist, I often start to think – how can I synthesize this? Perhaps, at low temperatures if the structure is metastable; maybe from precursors with pre-formed chemical bonds – the analog of protected functional groups in organic chemistry; maybe templating this structure somehow and then removing the template. Computations give very few, if any, suggestions along these lines of any synthetic strategy.

Thousands of new compounds have been recently predicted, of which only tens have been realized. This gap between prediction and outcome may arise, in part, because computations are cheaper and faster than experiments. Another reason for the discrepancy between predictions and experimental verifications is the absence of predicting synthetic conditions. From the experimental point of view, predicting the thermodynamic stability of a new compound at 0 K has limited value if the compound cannot be synthesized. It allows to identify highly metastable compounds which are less likely to be synthesized and computational methods to evaluate the limits for synthesizability of metastable compounds were suggested [35]. Nevertheless, even for the thermodynamically stable compounds the prediction of the synthetic conditions is highly desirable. One should not expect computational prediction of specific reaction conditions, but rather their estimation, as well as identification of likely reaction dead-ends which should be avoided. To make predictions practically relevant, the following goals might be considered:

**Compt1.** Predictions of basic thermodynamic properties (*e.g.* melting point or vapor pressure) of the target phase at reaction conditions, such as finite temperature, pressure, or chemical potential of the solvent) including consideration of decomposition pathways with identification of the decomposition products. Such computational guidance can eliminate a significant set of dead-end synthetic routes. To be practically relevant, high accuracy of such predictions is required.

**Compt2.** Analysis of kinetic barriers and reaction mechanisms. For example, a thermodynamically feasible reaction with negative Gibbs energy,  $A+B+C \rightarrow ABC$ , should be considered an experimental dead-end if this reaction proceeds via formation of stable solid intermediates  $A_2B$  and  $BC_2$ , whose reaction with each other requires high activation energy, that exceeds any available thermal energy at the reaction temperature. The reaction temperature is often limited by the thermal stability of the target compound, although  $ABC$  still can be synthesized by a different reaction pathway (*i.e.*  $AC+B$ ), which brings us to the next goal.

**Compt3.** Screening and ranking of potential precursors and reaction pathways. Solid-solid reactions often suffer in not providing single phase products. The atoms need to diffuse and as the product nuclei grow, regions form that become low in concentrations/amounts of one component. For the hypothetical compound  $AB_3C_4D_2$ , in addition to making it from stoichiometric reaction of the elements, it can be made from binary compounds, such as  $AB_3 + 2C_2D$ . Advantages of this method could be in averaging reactivity of inert element  $A$  and highly reactive element  $B$  and bringing them in close spatial proximity to each other to minimize diffusion limitations [3,4,16,17,36] or unifying aggregate states (using metal oxide precursors instead of elemental oxygen). Another potential advantage is inducing a

particular type of chemical bonds between elements *C* and *D* which will be preserved in the product [37].  $AB_3C_4D_2$  also can be made by the reaction of  $AZ + 3BZ + 4C + 2D$  when a foreign element *Z* is introduced to ensure easiness of mixing (NaH instead of Na [38-40]), or handling (CsCl instead of Cs [41],  $K_2CO_3$  instead of  $K_2O$  [42]), or reduction of reactant's melting point (CuCl instead of Cu [43]). *Z* may also be added to facilitate diffusion for otherwise solid-solid reactions. Flux synthesis is a common example of introducing additional element(s) serving as high-temperature metallic or ionic solvents [41, 44-49]. Another common method is gas transport reactions utilizing transport agents, such as iodine, to increase reactivities of refractory precursors by making volatile iodides that can successfully react in the gas phase precipitating the desired product [50,51]. Removal of byproducts containing the foreign element *Z* is an integral part of the synthetic design, achieved by either self-elimination during reaction ( $CO_2$  evaporation from open crucible in oxide synthesis), by post-synthetic chemical treatment (dissolving metal chloride in water), or by mechanical treatment (high-temperature centrifugation of liquid flux or crystal polishing). Computational efforts in screening and ranking potential precursors are limited, and predictions of novel compounds are seldom accompanied by these synthetic considerations.

For the computational community, the **Compt1** goal can be achieved and there is significant progress in this direction, see for example [29,52,53]. The **Compt2** goal implies knowledge of reaction mechanisms. Achieving this goal can be accomplished with the help of *in-situ* experimental feedback discussed in the next section. Successful computational efforts for **Compt3** goal notwithstanding [54,55], further development of the methodology requires a close consultation with experimentalists to account for certain precursor characteristics going beyond thermodynamic or kinetic stability that will be crucial for any successful synthesis. Including important precursor parameters, such as easiness of handling and mixing, overall vapor pressure, compatibility with reaction container material, and cost (e.g., Pt crucibles should not be top choices) into consideration will significantly increase the value of any prediction.

## 2. In-situ diffraction studies.

Traditional solid state synthesis is a “black box”: reactants placed in a container at ambient conditions, some treatment (temperature, pressure, radiation) is applied, products are brought back to ambient conditions, extracted from the container, and analyzed. What happens at reaction conditions is an educated guess. For example, it is not always clear during high-temperature syntheses when a target phase forms: during heating, upon annealing at the highest temperature, or upon cooling. One can perform a set of control experiments eliminating certain parts of the thermal treatment process, combine it with the quenching experiments from different temperatures and DSC/TGA (differential scanning calorimetry/thermogravimetric analysis) studies to improve the initial guesses. Except of simple yet powerful DSC/TGA experiments the overall workflow is tedious. Moreover, when a synthesis of a new compound is considered, there is no ready-to-use recipe on how to prepare the target in a single-phase form. Instead, the target phase is often present as an admixture in the products of initial syntheses or even only computationally predicted.

Soon after first ambient condition X-ray diffraction experiments, techniques to perform X-ray diffraction measurements at either elevated temperature or applied pressure were developed [56,57] allowing to study polymorphic transformations and phase transitions. These types of measurements received a boost with development of more powerful X-ray sources at synchrotrons, for example allowing to study compounds unstable at ambient pressure using diamond anvil cells. In 2014, the power and applicability

of *in-situ* diffraction methods to solid state synthetic processes were demonstrated in pioneering work on a reaction of Cu and K<sub>2</sub>S [58]. This study revealed several hidden phases formed during heating and cooling that were not detected using conventional “black box” synthetic attempts. Since that work, numerous groups have applied *in-situ* studies which provide a panoramic view of a reaction landscape to advance solid state synthesis. In some cases, these studies confirm the initial guesses about reaction pathways. In other cases, they provide crucial information for successful synthesis. For example, the quaternary layered compound BaCuSi<sub>2</sub>P<sub>3</sub> is only stable within a very narrow temperature window of ~940-960°C [59]. In such a case, guessing the correct synthetic temperature from trial-and-error attempts is highly improbable.

There are certain practical limitations of *in-situ* studies to advance synthesis. One of them is the identity of starting materials. For example, high-temperature X-ray studies are often conducted in sealed silica capillaries to ensure sufficient transmission of X-rays when working with heavy elements due to their high X-ray absorptions. For ductile starting materials, such as elemental Cs or Ba, placing correct amounts of reactants and ensuring their proper mixing with other precursors inside a small capillary is a challenge. To resolve the issue of poor mixing, a pre-reaction is performed in the lab using larger containers to ensure that ductile elemental precursors react with other components to form more stable and grindable intermediates [59]. For example, to study reactions containing Cs and As, a pre-reaction of Cs and As resulting in a brittle mixture of binary Cs arsenides in the desired overall Cs:As ratio can be performed [60]. Precise measurement of the sample temperature is also an issue because the thermocouple is placed externally, in close proximity to the sample but outside the capillary. Additionally, depending on the type of heaters used and the average temperature, a temperature gradient across the sample could be induced. Similar to DSC experiments, measurement of appropriate standards may help to calibrate the system, but such determinations need to be repeated frequently. When working with heavy elements used as fluxes, such as Bi or CsI, high X-ray absorption of the sample may lead to low-quality data even for high-energy X-rays of ~50 keV,  $\lambda \sim 0.25 \text{ \AA}$ . In such cases, neutron diffraction studies should be considered [61]. Overall larger size of reaction vessels used for neutron studies is useful for mimicking lab reactions, especially for cases of gas-solid reactions which are volume- and pressure-sensitive [62]. Finally, *in-situ* experiments are suitable to study relatively fast reactions. The small diameter and internal volume of the capillaries may help to overcome certain diffusion limitations. Nevertheless, the typical length of a variable-temperature X-ray experiment is a few hours, and information for the reactions requiring multiple days of treatment is limited [62].

Experimentalists should consider using *in-situ* studies to guide and expedite their synthetic efforts. Often, one hour of beamtime may save months of experimental trials. Keeping in mind the aforementioned limitations, one needs to “choose their battles” wisely. In the author’s experience, it may take one or two beam time sessions until all methodology is adjusted for group-specific research. Consulting with beam scientists who are willing to modify and develop experimental capabilities is highly recommended. To secure beamtime, one needs to apply well ahead of time, which is often considered as the main entry barrier. Due to recent COVID-imposed limitations, significant progress in mail-in capabilities was achieved, including those for studies at non-ambient conditions.

*In-situ* studies, in general, are not limited to diffraction. Total scattering data are essential to study local ordering, amorphous phases, nucleation intermediates, and potentially structure of high-temperature melts [63-66]. Diffraction and total scattering experiment can be combined with other spectroscopic

*operando* techniques to obtain complimentary information regarding liquid and/or gas phase present during the reaction.

*In-situ* studies generate a tremendous amount of priceless data to refine computational predictions of reaction mechanisms. Unfortunately, such data are currently published mainly in graphical, not-machine-readable form. Implementation of machine-assisted analysis (indexing, phase identification and quantification) of the diffraction, total scattering, and spectroscopic data and creating opportunities to deposit such data in an open access database (pending a publication or student thesis) is a crucial step that will significantly raise the importance of the *in-situ* studies. Machine-assisted analysis of *in-situ* data is similar to routine analysis of *ex-situ* data but for the large number of datasets. Beside routine analysis of the each datapoint, i.e. indexing of an X-ray diffraction pattern, general methods to extract information from series of ranked correlated data are required [67,68]. This methodology is important for the desirable on-the-fly analysis of the data. Such analysis would allow to tune the *in-situ* experiments to maximize useful outcome. Currently, experiment is designed prior to beamline with little to no influence of the acquired data. One can envision more rational use of the beamtime utilizing adaptive control by consecutive analysis of several identical samples with synthetic conditions for next sample derived from data acquired for previous samples. Cloud-based applications may provide required computational power for on-the-fly data analysis, such as developed by Billinge *et al.* PDFitc platform [69,70].

### **3. Make every synthetic effort count.**

It is common to run tens of reactions to optimize the preparation of a single novel compound. Eventually, only one successful set of conditions and perhaps a few representative unsuccessful reactions are published leaving off a large chunk of synthetic data. As an example, a graduate student in my group performs ~1000 synthetic reactions during ~5 years of PhD studies. Assuming the student is highly successful, s/he publishes ~10 peer-reviewed publications reporting ~20-30 compounds. This clearly shows that >90% of the synthetic data remain in lab notebooks and may never be published, although the synthetic research is funded by national funding agencies or local universities and is required to be publicly available. The unpublished synthetic data is a valuable resource for multiple reasons. Such data might help other experimentalists to look for an alternative way to synthesize reported compounds or develop synthesis of analogous compounds or a completely novel compound in the reported or similar systems. Something originally considered as an “undesired admixture” might be a valuable product for another group [71]. In the authors’ experience, sentences like “all our synthetic attempts to produce this compound in a single-phase form failed” have a variety of meanings ranging from attempting only a couple of alternative reaction temperatures to, indeed, a detailed study with dozens of reaction conditions tested. Knowing what has been tried will, at the very least, avoid unnecessary repetitions of the synthetic conditions.

Results of “unsuccessful” syntheses of a target compound are also valuable for computational chemists trying to predict basic thermodynamic properties, parts of phase diagrams, or synthetic conditions. Finally, unsuccessful synthetic results will be valuable for machine-learning approaches where negative results are crucial for proper training of the machine-learning algorithms [72-75]. The author is highly doubtful that machines will eventually replace human experimentalists, but machine-learning algorithms may provide helpful guidance. If we cannot prevent the rise of machines, we should lead it.



Even the published synthetic data are often reported in a random non-standardized format with a mixture of text, tables, and diagrams. Perhaps it is time for the synthetic community to develop a standard for reporting synthetic data. Inspiration can come from the crystallographic community. The crystallographic information file (CIF) is currently a standard for reporting structural data. It has been developed with strict and simple syntax and is compatible with any software dealing with structural data. For documenting synthetic procedures, an analogous synthetic file (SyF) could be developed. Formalizing synthesis is a less obvious task than formalizing crystal structure data, but it can be accomplished with feedback from multiple and diverse synthetic groups. SyF should be simple and compatible with any software currently used for lab notebooks, ranging from simple google sheets to fancy specialized software, to ensure all groups, including those with limited funding, have no barriers to work with SyFs. Continuing the analogy with crystallography, the author envisions that SyF can be deposited into an open access synthetic database. Authors concerned with revealing the data of unfinished projects may request reasonable delay prior to releasing their data to public. While other experimental or computational researchers may benefit from using a synthetic database as discussed above, why should an experimentalist make an effort to deposit data in the SyF database? It is a feature of human nature to avoid extra work if possible.

Benefits for researchers to fill the synthetic database include:

- Upon preparing a publication, all relevant SyFs can be effortlessly deposited to the synthetic database and reference numbers provided to reviewers and editors. Upon publication and after selected trial period the data will become publicly available.
- Similarly, the entries can be used for preparing reports for funding agencies. The annual outcome of 3 papers and 200 SyFs better represents project efforts rather than just 3 papers. Note that for many funding agencies, making data publicly available is a requirement.
- For graduate students and postdoctoral researchers, the motivation is similar: you perform hundreds of chemical reactions and publish only a small fraction of it. Would you like the other >90% of your synthetic efforts to be documented?
- For PIs, the SyF format will ensure the research transparency and sustainability, especially when group members leave, and other(s) take(s) over the project.
- Last but not least, the implementation of SyF and corresponding database might be eventually encouraged by funding agencies and publishers.

Obviously, the SyF will be not free from errors ranging from typos and careless copying of previous entries to inaccurate temperature readings and incorrect interpretation of diffraction patterns. Unlike for CIFs, there are no simple validation procedures for SyF. One potential validation procedure can be to include powder diffraction patterns in a commonly accepted ASCII format. In such a case, tools developed for data analysis for *in-situ* studies can be utilized for partial SyF entries verification.

In summary, current development in computational and experimental methods calls for collaborative efforts to make solid state synthesis more predictable. The current perspective is a good starting point in this direction.

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