Materials science

# Ordered absences out of the blue

Adam Jaffe & Jeffrey R. Long

Prussian blue analogues are archetypes of coordination solids, in which metal ions are bridged by ligands to form extended network structures. An analysis reveals a surprising ordering of the gaps found in their crystal lattices. **See p.256**

The centuries-old pigment Prussian blue and its analogues are archetypes of compounds known as coordination solids, and have had an unparalleled role in advancing our understanding of inorganic chemistry and materials[1,2]. The wide-ranging structural, electronic, magnetic and optical properties of Prussian blue analogues (PBAs) have been repeatedly leveraged towards applications that include energy storage[3], catalysis[4], ion trapping[5] and gas storage[6]. However, studying the surprisingly complex atomic-scale structures of PBAs remains a long-standing challenge. On page 256, Simonov *et al.*[7] report that they have successfully grown single crystals of PBAs, which have previously been notoriously elusive. By coupling X-ray measurements of the crystal lattices with a simple but effective theoretical model, the authors reveal an unexpected ordering of vacancies — absent nodes in the lattices that correspond to missing metal–anion units. This structural insight could enable yet another means of adjusting the properties of these extraordinary materials.

Prussian blue ($Fe_4[Fe(CN)_6]_3{\cdot}14H_2O$) was first reported[8] in 1710 and was widely used as a deep-blue pigment. The eventual determination of its crystal structure greatly expanded the conceptual boundaries of inorganic chemistry. X-ray diffraction experiments performed on powders[9], and later on single crystals[10], of Prussian blue revealed the parent structure shared by all PBAs: a cubic framework in which two different types of metal cation act as 'nodes' linked in three dimensions by cyanide anion ($CN^-$) 'struts' (Fig. 1a). PBAs therefore have the general formula $M[M'(CN)_6]$, in which M and M′ are chemically distinct metal ions; the $[M'(CN)_6]^{3-/4-}$ complex ion unit (Fig. 1b) is known as a hexacyanometallate ion, and carries either three or four negative charges. The study of the PBA parent structure enriched our fundamental understanding of the coordination chemistry of transition metals (how ligand molecules or ions bind to transition-metal ions such as iron, cobalt and copper), and demonstrated that coordination solids that have multidimensional connectivity can act as porous framework materials through which molecules and ions can move.

The idealized crystal structures of PBAs correspond to the cubic framework described above, but belie a hidden degree of complexity that is crucial in determining their physical properties. The true atomic-scale structures contain vacancies corresponding to absent hexacyanometallate ions (Fig. 1b), which form pores that are typically filled with water molecules. The concentration and ordering (networking) of vacancies control the pathways through which mass can move within the materials, and can therefore tune the ability of PBAs to reversibly transport ions or small molecules. Insight into how vacancy ordering is affected by the chemistry of PBAs, or by the conditions used to synthesize them, can thus provide guidelines on how to tailor the properties of these compounds for applications.

X-ray-scattering measurements on PBA powders, beginning with the early diffraction studies on Prussian blue[9], yielded structural information for these compounds. But the random orientation of millions of crystallites in powders leads to loss of information that is retained if measurements are performed on single crystals. To gain this extra insight and illuminate vacancy behaviour, Simonov *et al.* sought to produce crystals of a series of PBAs that contained different metal-ion combinations. Growing single crystals of PBAs is challenging because of the rapidity with which microcrystalline powders precipitate when solutions of PBA precursors are combined. However, the authors found that controlled mixing of these solutions over the course of weeks produced single crystals suitable for X-ray-scattering analysis.

Simonov and co-workers observed clear indicators of non-random ordering of vacancies in the scattering data for their PBA crystals. This ordering depends on each crystal's chemical composition and the conditions used to crystallize it. To understand the diversity of the vacancy networks, the authors developed a simple two-part model to simulate vacancy ordering. The model considers only the trade-off between the preference of these compounds to adopt a uniform vacancy distribution, and the preference for lattice sites to have a certain local symmetry, yet it effectively reproduces the experimental X-ray scattering results.

Notably, the authors' insights enable the vacancy-network architectures of PBAs to be predicted by considering only a few factors

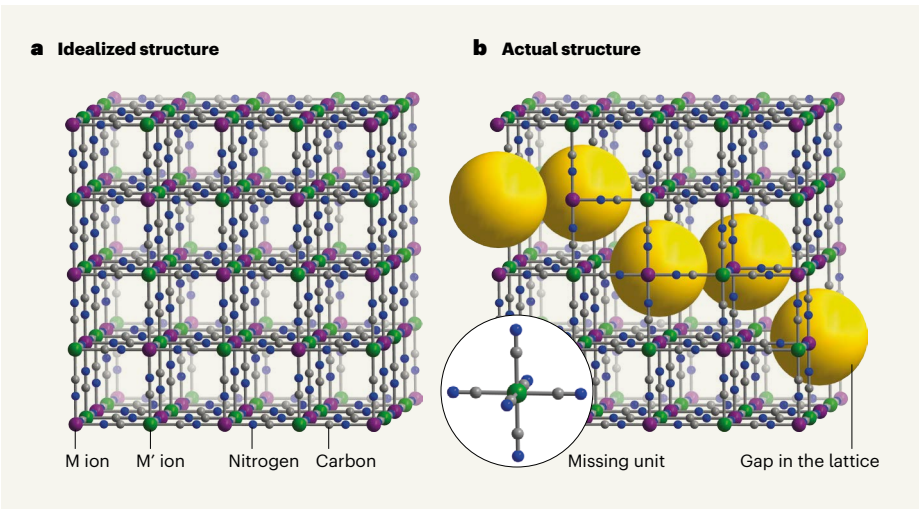


**Figure 1 | Vacancies in Prussian blue analogues. a**, Compounds known as Prussian blue analogues (PBAs) have the formula $M[M'(CN)_6]$, where M and M′ are two chemically distinct metal atoms. The idealized crystal structure of a PBA is a cubic framework in which M and M′ ions act as 'nodes' connected by cyanide ions ($CN^-$), which act as 'struts'. **b**, The actual crystal structures contain vacancies — gaps in the lattice that correspond to missing $[M'(CN)_6]^{3-/4-}$ units. Networks of vacancies can form pathways that allow molecules or ions to be transported through PBAs, a potentially useful characteristic. Simonov *et al.*[7] have used X-ray measurements of single crystals of PBAs and numerical modelling to reveal the hidden order of vacancies in PBAs.

that depend on the two model parameters, such as the choice of metal, precursor concentrations and the temperature of crystallization. Some networks turn out to have relatively direct pathways through which a molecule or ion could move, whereas other networks' pathways are more tortuous. By selecting PBAs that have direct pathways facilitating mass transport, these materials can be optimized for use as battery electrodes, catalysts or ion-exchange materials.

Simonov and colleagues' work addresses a long-standing lack of detailed knowledge about the structural vacancies that determine the physical properties of Prussian blue and its analogues. But numerous challenges remain before the predictive potential of their results can be fully realized. Although remarkably effective, the modelling analysis does not consider further possible complexities, such as the effects of ionic species that dwell in the PBA pores. Extrapolation of the findings from these single-crystal studies to powder samples, which are more technologically relevant, will require further challenging experiments and enhanced modelling that considers the surface structure and chemistry of microparticles. Great care will also be needed to work out how each of the variables in a PBA synthesis correlate with the resulting vacancy ordering and material properties.

Although these challenges necessitate substantial further work, they also represent an opportunity to exert even greater control over the properties of PBAs, guided by a deeper understanding of structure–property relationships. Refinement of more-complex models will dictate how to take advantage of the many variables of a PBA synthesis. Not only has this work resulted in new-found control over the optimization of PBAs for applications in energy storage, ion capture and catalysis, but it also represents a platform on which to build a similar understanding of other framework materials, such as zeolites[11] and metal–organic frameworks[12], which have their own sets of challenges and promising applications.

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Neurodegeneration

# A protein's structure used to diagnose disease

**Juan Atilio Gerez & Roland Riek**

Parkinson's disease and multiple system atrophy involve the protein α-synuclein. Proof that aggregated α-synuclein adopts a different structure in each case suggests that its conformation underlies the distinct disorders. **See p.273**

A snowflake begins life as a tiny crystal that acts as a seed on which water molecules aggregate, increasing the size of the snowflake as it descends to earth. Proteins can also act as seeds – for instance, in a class of age-related disorders called amyloid diseases, in which thousands of copies of a type of protein known as an amyloid adopt an abnormal structure and aggregate in harmful clumps. In Parkinson's disease, aggregates of the amyloid protein α-synuclein accumulate in neurons. A rarer neurodegenerative disease, multiple system atrophy (MSA), involves α-synuclein aggregates in neuron-supporting cells called glia. It can be difficult to distinguish between the two disorders, given their overlapping symptoms, but they require different treatments. Shahnawaz *et al.*[1] provide an explanation for this difference on page 273: like two dissimilar snowflakes composed of identical water molecules, α-synuclein aggregates form distinct 3D architectures in each disease.

*In vitro* and animal experiments have previously indicated that different aggregate structures of α-synuclein, called strains, yield different effects[2]. The various α-synuclein strains not only can have distinct cell-killing abilities and different seeding and propagation properties, but also can target different cell types and areas of the mammalian brain[3,4].

Shahnawaz *et al.* built on these previous findings using a technique called protein misfolding cyclic amplification (PMCA), which amplifies small amounts of α-synuclein aggregate, allowing thorough examination of minuscule samples. An amyloid-specific fluorescent dye is incorporated into the newly formed aggregates, enabling their analysis.

Impressively, the authors amplified and analysed samples from the cerebrospinal fluid of more than 200 people who had either Parkinson's disease or MSA, or who were healthy (Fig. 1). They found that samples taken from people with Parkinson's disease displayed more fluorescence than those from people with MSA. Thus, PMCA could be used to discriminate between Parkinson's disease and MSA.

The different levels of fluorescence suggested that the amyloid dye interacted with each α-synuclein aggregate differently, and that distinct α-synuclein strains are involved in the two diseases. The authors confirmed this result by showing that the two strains could also be distinguished by using proteinase K digestion (an enzymatic treatment that breaks down strains that have different structures in different ways), and through other biophysical characterizations, including a microscopy approach called cryo-electron tomography.

Shahnawaz and colleagues' work has two major implications. First, it demonstrates that PMCA can be used as a diagnostic tool to discriminate between diseases involving α-synuclein. However, it should be noted that the samples analysed in this study were obtained from people who had already been diagnosed, and it remains unclear whether the approach could be used as a predictive tool to detect disease at earlier stages. Moreover, it is possible that PMCA is affected by the medication given to the participants who had Parkinson's disease. These people typically receive the hormone dopamine (L-dopa), which has been shown to affect α-synuclein aggregation *in vitro*[5].

Second, the study adds to a growing body of evidence supporting the 'one polymorph, one disease' hypothesis[6–8], which states that different structural forms (polymorphs) of the same aggregated protein can cause distinct pathologies and symptoms. What might lead a protein to adopt different structures? *In vitro*, distinct fold structures can result