tetrahedral intermediate. The scaffold seems to displace the Zn(II)-bound water molecule, and form a covalent bond to the Zn-bridging nucleophilic water molecule, resulting in an sp^3-hybridized bicyclic boronate. The boronate ester oxygen forms a dative bond with Zn_2, and two boron-bound exocyclic oxygens coordinate with Zn_1.

Schofield, Brem and co-workers discovered that InCs are potent MBL inhibitors using high-throughput screening of a compound library and subsequent optimization of hits. By tuning components in the C-3 and C-7 of InC, the inhibition could be enhanced by 100–1,000 fold compared with VNRX-5133. A comprehensive structure–activity relationship study uncovered new information with additional insight provided by a large number of X-ray structures of the enzymes with inhibitors. For example, the InCs were found to resemble both a β-lactam substrate — because most β-lactamases bind their substrates with remarkable efficiency — and a bound MBL-carbapenem complex. Surprisingly, the team observed an unprecedented mechanism of action that locks the Zn(II)-bound hydroxide, which is in contrast to the mechanism of previously developed inhibitors that work by displacing it. The Zn(II)-complexed hydroxide forms H-bonding with the nitrogen from the indole ring, and the C-7 isopropyl methyl groups simultaneously block the hydroxide (Fig. 1, bottom). Blocking this hydroxide was also confirmed from the identical distances between the two Zn^{2+} ions in the intact enzyme and the enzyme with the inhibitor bound (Zn–Zn distance of 3.5 Å). In contrast, ANT-2681, another MBL inhibitor in preclinical trial[10], binds to Zn_2 with Zn–Zn distance of 4.15 Å.

The inhibitors developed by Schofield, Brem and co-workers are highly selective, and possess a good safety profile on mouse infection models. One of the lead InC compounds, **58**, can be well-translated to an in vivo model. Taken together, these studies are supportive of the potential of InCs for clinical utilization with meropenem/imipenem to combat antimicrobial resistant bacteria. Importantly, the approach mimicking multiple elements of key interactions between an enzyme and a substrate may open a new horizon for drug development. It would also be of interest to see whether InCs work on the B2 subclass of MBLs. There is a lot to be done before InCs can be deployed in a clinical setting, but the work by Schofield, Brem and co-workers will inspire other researchers working to develop new methods of combating antibiotic resistance. ❐

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Competing interests

The authors declare no competing interests.

AQUEOUS SOLUTIONS

Hydration determines anion accumulation

Why do bulky anions solubilize macromolecules in water but precipitate out the corresponding monomers? The answer lies in the differences in local water structure. Polymers have now been shown to disrupt water structure more than their monomers, leading to an accumulation of anions near the polymers that increases their solubility.

Aniket U. Thosar and Amish J. Patel

The celebrated Hofmeister series organizes ions according to their ability to precipitate proteins from aqueous solutions[1]. Bulky anions that are weakly hydrated, such as iodide or thiocyanate, appear at the bottom of the Hofmeister series because they are drawn to non-polar surfaces, and can weaken hydrophobic interactions, enabling them to solubilize proteins. Interestingly, in contrast to their solubilizing effect on macromolecules[2], weakly hydrated anions tend to precipitate out non-ionic small molecules[3]. In fact, weakly hydrated anions can enhance the solubility of certain polymers, but suppress the solubility of their monomeric building blocks. Now, writing in *Nature Chemistry*, Cremer and colleagues resolve this apparent paradox by showing that weakly hydrated anions affect polymers and monomers in different ways due to subtle differences in how the solutes perturb water structure[4].

Surfactants can compatibilize oil and water by accumulating at the oil/water interface and lowering the interfacial tension[5]. Similarly, weakly hydrated anions can solubilize a hydrophobic polymer in water by accumulating in its hydration shell and reducing the aversion between the polymer and water. Conversely, anions can lower the solubility of a solute if they are excluded from its vicinity. Given that weakly hydrated anions solubilize polymers and precipitate out monomers, it stands to reason that they must accumulate near polymers and be excluded from the hydration shells of monomers. By characterizing the interactions of weakly hydrated thiocyanate ions with ethylene oxide monomers, oligomers and polymers, Cremer and colleagues find that this is indeed the case; the anions bind to the polymers, but not the monomers. By using site-specific NMR spectroscopy, they further show that thiocyanate ions are excluded from the terminal regions of the polymer but bind to the rest of it. Because terminal regions comprise a small fraction of the polymers, there is a net accumulation of anions in their hydration shells; in contrast, monomers possess only terminal regions and exclude anions (Fig. 1a). Cremer and colleagues complement their experiments with molecular dynamics simulations, which

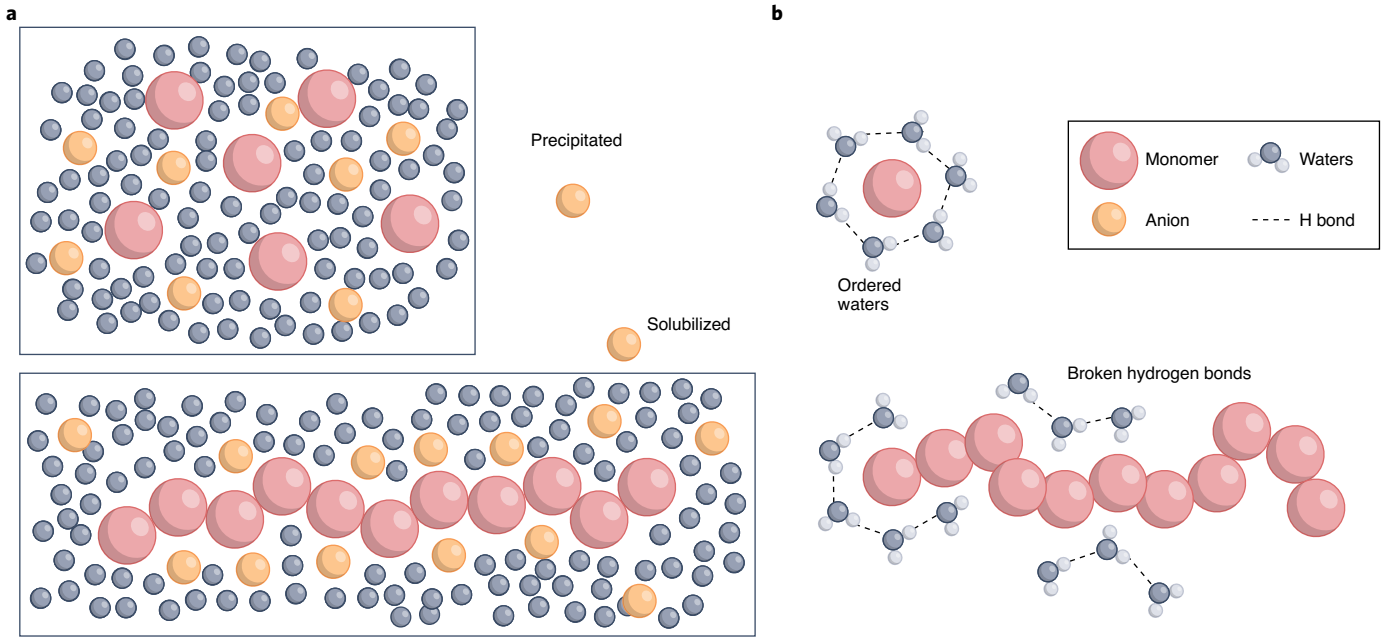

Fig. 1 | Solute hydration determines the accumulation of weakly hydrated anions and their influence on solubility. a, Weakly hydrated anions are excluded from the hydration shells of monomers, thereby suppressing monomer solubility. Anions are also excluded from polymer termini but bind to the remainder of the polymer resulting in a net accumulation of anions in the polymer hydration shell and an increase in polymer solubility. **b**, Monomers and polymer termini are better accommodated within the hydrogen bonding network of water than the central regions of polymers, enabling the latter to bind weakly hydrated anions.

confirm that anions are indeed excluded from polymer termini but bind to other polymer regions.

Given that the chemical moieties comprising the terminal and central regions of the polymer are identical, why are weakly hydrated anions excluded from the former, but bind to the latter? Cremer and colleagues use Raman spectroscopy with multivariate curve resolution to show that the answer to this question lies in the extent to which water structure is perturbed in these regions. This method enables them to subtract the trivial contribution of bulk water from an aqueous solution's Raman spectrum and focus on the signal from the solute hydration shell; features in the spectra are then used to characterize the disruption of hydration water structure.

Cremer and colleagues find that water molecules near terminal polymer regions are ordered, whereas water structure away from polymer ends is relatively disordered and is therefore more accommodating of the weakly hydrated anions (Fig. 1b). Using simulations, the authors further show that water molecules near the polymer termini have enhanced tetrahedrality relative to the rest of the polymer hydration waters. Furthermore, both experiments and simulations display a strong correlation between how tightly the weakly hydrated anions bind to certain regions of the polymer and the extent to which those regions disrupt water structure. Thus, the aversion of weakly hydrated anions for monomers and their preference for polymers, which leads to those ions precipitating out monomers and solubilizing polymers, can be traced back to subtle differences in how those solutes perturb water structure.

These differences in water structure can be rationalized by modern theories of the hydrophobic effect, which have highlighted that the size of a non-polar solute, or alternatively its curvature, influences how the solute perturbs water structure[6]. Solutes smaller than 1 nm constrain but do not disrupt water's tetrahedral network of hydrogen bonds, whereas larger solutes, which cannot be accommodated within the network, break hydrogen bonds. Moreover, because constraining the hydrogen bonding network is entropically unfavourable, the hydration shells of small solutes become less stable from a thermodynamic standpoint as temperature is increased. In contrast, the relatively disordered hydration shells of larger solutes are stabilized at higher temperatures. Given the findings of Cremer and colleagues that polymer terminal regions order water molecules like small non-polar solutes, whereas the rest of the polymer disorders them like larger solutes, temperature could serve as a lever to amplify the subtle differences in the hydration of different polymer regions and enhance the contrast in the binding of weakly hydrated anions to those regions.

In terms of their preference for water, weakly hydrated ions lie at the fuzzy boundary between non-polar molecules, such as methane or argon, and strongly hydrated ions, such as sodium or chloride. Cremer and colleagues have shown that such ambivalence for water allows weakly hydrated anions to discriminate between seemingly indistinguishable chemical moieties, such as the terminal and central regions of polymers, which perturb water structure in different ways. The uncanny ability of weakly hydrated anions to tease out subtle differences in hydration may have wide-ranging implications. For example, non-polar residues on the surface of a protein can vary widely in the extent to which they perturb water structure[7]; characterizing regions of the protein surface that bind or exclude weakly hydrated anions may thus provide a way to characterize protein hydrophobicity and uncover regions that mediate protein interactions[8]. Weakly hydrated anions could also be used to perform challenging separations involving chemically similar components that differ only in how they perturb water structure. For example, weakly hydrated anions may provide routes for separating polymers with slightly different architectures, even when they are composed

of the same building blocks and have the same molecular weight.

Importantly, Cremer and colleagues have highlighted that the intriguing characteristics of weakly hydrated anions can be rationalized by treating them as discriminating hydrophobes; they don't bind all non-polar solutes, only those that perturb water structure substantially. More broadly, their findings emphasize that an understanding of aqueous assembly demands an accurate accounting of the collective reorganization of water structure in response to not just the chemistry of the solute, but also its shape. Although such a context-dependent characterization of solute hydration can be challenging, particularly when solutes display chemical and topographical heterogeneity at the nanoscale, it can also provide rich insights in diverse contexts, ranging from biomolecular assembly to supramolecular chemistry. To this end, the creative techniques employed by Cremer and colleagues, which offer a site-specific characterization of solute hydration, offer tremendous promise. ❐

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MECHANOCHEMISTRY

Defogging the view through a milling jar

Innovations in instrumentation together with new strategies of data collection and processing have been shown to solve the problem of data quality for time-resolved in situ X-ray diffraction studies on ball milling, opening new horizons in mechanochemistry.

Elena Boldyreva

How does a mechanical impact cause atoms or molecules — trapped in different solids — to break existing bonds, mix, and form new bonds? It has been known since ancient times that mechanical action on solids (impact or rubbing) can yield chemical transformations. These transformations, referred to as mechanochemical, can give access to products that cannot be obtained otherwise. They are also typically carried out in much higher yields compared with reactions in solution and significantly reduce (or exclude completely) the consumption of solvents. In these respects, mechanochemical transformations are considered a significant step towards environmentally benign chemical processing, and highlighted by IUPAC amongst the "10 chemical innovations that will change our world"[1].

What remains unclear, however, is how mechanochemical processes actually occur. The vessel in which the transformation occurs (the mechanoreactor — the jar in the ball mill containing the reagents and ball(s) for grinding) is often considered to be a 'black box'. An approach has now been proposed by Giulio Lampronti, Adam Michalchuk, Paolo Mazzeo and co-workers in *Nature Communications* that combines a new construction of the milling jar with innovations in data collection and processing strategies to provide a clearer 'looking glass' for mechanochemistry[2]. It enables researchers to observe and analyse even fine details of the reactions at play, and in turn explore the mechanisms of inorganic and organic mechanochemical transformations. Moreover, low sample loadings can now also be measured, allowing mechanochemical investigations of expensive and/or toxic compounds.

Typically, one cannot see what occurs inside the vessel walls during mechanical treatment without interrupting the treatment, opening the vessel, extracting a sample and analysing it ex situ. However, interrupting mechanical treatment alone, and more significantly opening the mechanoreactor and extracting a sample, can have a pronounced effect on the process and corrupt the picture entirely[3–5]. New analytical techniques have emerged in recent years that can probe in real time chemical and structural changes during mechanical treatment directly in a mechanoreactor in situ[6].

Of particular note is the use of synchrotron-based X-ray powder diffraction (XRPD). In principle, XRPD provides simultaneous insight into both the overall reaction profile and details of the crystal structures of the components. However, established protocols for time-resolved in situ (TRIS) XRPD give data of poor quality. The X-ray scattering signals are broad and their shapes are corrupted. This happens because the stationary X-ray beam interacts with a permanently moving powder or slurry within the vessel, while also being absorbed, scattered and diffracted by the walls of the mechanoreactor itself and the moving milling bodies. This is analogous to capturing an image of an object that is not in focus and is permanently changing its location, all while looking through a poorly transparent and light-scattering glass. Moreover, for an inhomogeneous sample (which is usually the case), the composition of the sample can differ at every moment. Different parts of the sample are exposed to the probing beam as the sample moves, and the powder composition changes as the mechanochemical process evolves.

Combining innovations in the design of the ball milling apparatus, data acquisition methodology, and data processing algorithm, the researchers have presented a strategy that overcomes many pitfalls of TRIS XRPD