An overview of solvent use and solvate formation in the CSD

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As part of an ongoing investigation into solvate formation [1], [2], a database of over 90,000 solution-based crystallisation experiments has been extracted from the Cambridge Structural Database [3]. For each compound crystallised, the solvent(s) used and any solvent(s) included in the resulting crystal are listed.

Three categories of solutes were distinguished in the initial analysis of the data: organometallic compounds, organic salts and neutral organic molecules. The most frequently used solvents for organometallic compounds are hexane, dichloromethane, diethyl ether, toluene, pentane and their binary mixtures. Organic salts are most frequently crystallised from methanol, ethanol, water and acetonitrile, with the use of mixed solvents being less common for this group. Common solvents for neutral organic compounds include methanol, ethanol, hexane, dichloromethane, ethyl acetate and acetone.

The overall frequency of solvate formation is higher for organic salts and organometallic compounds than for neutral organic molecules. Surprisingly, this trend also holds for solvate formation with apolar solvents, which do not interact more strongly with ions than with neutral molecules.

The most frequently included solvent is water, which is often present in crystals grown both from water and from organic solvents. The relative frequencies of solvates with various organic solvents are similar to those found earlier by Görbitz [4]. Solvate formation propensities are obtained from these frequencies by taking into account the frequency of using each solvent for crystallisation [5]. There is a large variation in these propensities: 18% of the crystals grown from water are hydrates, but only 0.4% of the crystals obtained from ethyl acetate include solvent molecules. In fact, hydrates are more frequent than ethyl acetate solvates even among crystals grown from solutions in ethyl acetate.

Solvate formation propensities depend on whether crystals with only metal-coordinated solvent molecules are counted as solvates or not. For strongly coordinating solvents (e.g., ethanol, DMF), the difference can be more than twofold.

Data on crystallisation from mixed solvents can be used to test competition between different solvents and to make small differences between similar overall solvate formation propensities more clearly visible. Unfortunately, the exact composition of solvent mixtures is rarely reported, so these results may be biased if mixtures rich in one of the components are used more frequently than mixtures rich in other(s).