distribution of conformational states represented in the PDB. A systematic review of multiple deposits shows that a single protein is rarely represented by a single structural conformer. This result sheds light on the first link and demands the reformulation of the protein-folding problem. A vast majority of proteins shows significant number of distinct conformational states with, sometimes large, structural divergence (up to ~24Å). The results suggest that every single protein evolved according to its own optimization principles combining different proportions of rigid (solid-like) and mobile (liquid-like) structural elements. The results suggest further that the optimization process that produced the particular combination of those elements is intricately connected with the function of individual proteins. Therefore, the structural description of the protein, besides the folding class (the architecture represented by the SCOP database), should include the natural structural divergence (width of the distribution) as two main attributes. Additionally, our analysis suggested the principles of functional evolution by use of the Dual Personality sequences (sequences with incomplete representation in the atom records that have distinctive sequence features from regularly folded and intrinsically disordered fragments).

Keywords: redundant structure database, distribution of conformational states, protein folding

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Analysis of the organic X-ray powder diffraction database and its use with pharmaceutical substances

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The crystals of small molecule pharmaceutical substances are usually of low symmetry, often have hydrogen-bonding-induced polymorphs [1], and frequently exhibit anisotropic crystal habits leading to preferred orientation in X-ray powder diffraction (XRPD) experiments. Statistical studies and cluster analyses have been used to show the prevalence of polymorphs and low symmetry space groups for these materials. Such statistical analyses can be performed using permutations of 40 different property and data searches with the PDF-4/Organics database (PDF-4). The XRPD patterns for these materials can exhibit overlapping peaks over small ranges of two theta angles, peak asymmetry at low angles, and preferred orientation. However, the proper choice of diffractometer and specimen configuration can minimize the two latter effects. Examples of XRPD data from experiments with thermodynamically stable polymorphs [2] will be given to illustrate this optimization. Modern crystallographic software can index XRPD patterns, determine unit cell dimensions and assign space group symmetry. Using this information and the PDF-4 searches lead to the model selection from the Cambridge Structural Database (CSD), followed by Rietveld refinement to verify both crystallographic parameters and indexing assignments of the experimental XRPD pattern. The experimental XRPD pattern then becomes a powerful reference for quality control measurements, quantitative analysis and polymorph identification. Systematic analysis examples of data from XRPD experiments for active pharmaceutical ingredients will be given.
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Keywords: X-ray powder diffraction, polymorphs, preferred orientation

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Studying conformational preferences for mechanistic purposes: Using database mining and computation

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It has long been known that phosphine and phosphite ligands can adopt various conformations depending on coordination environment. Containing over 400,000 structures more than half of which are metal complexes, the Cambridge Structural database (CSD)[1] has an extensive amount of information regarding ligands, the attached metal centre and the coordination environment of the complex. By combining the information from database mining with computational (DFT) studies it is possible to explore the response of ligands to different coordination environments. This enables us to have a better understanding of conformational behaviour when exploring mechanistic pathways, which often involve coordination changes. The chosen systems, tribenzylphosphine $P(CH_2Ph)_3$ and triphenylphosphite $P(OPh)_3$, are part of a synthetically relevant series of phosphorus ligands for catalytic studies. Although DFT is known to give reasonable agreement with molecular structure,[2] these systems are far too large to be studied by DFT conformational searching. The combination of DFT studies with database mining results has accurately predicted the conformational preference and lowest energy profile for these ligands across a series of coordination environments, and has been utilised in mechanistic studies undertaken in our group. Further analysis of the data retrieved from the CSD has highlighted conformational interconversion pathways. These have been explored and structures along the pathways have been used to predict transition states between conformers. This furthers our understanding of ligand conformation during reactions.
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Ligand substructure validation in macromolecular crystallography using the CSD

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Structural studies of protein-ligand complexes have become essential to modern drug discovery processes. The quality of results delivered by X-ray crystallography has a direct effect on downstream computational chemistry studies, therefore thorough validation - especially that of small molecule substructures - should be considered as a key step in structure determination. However, the final geometry of a ligand is influenced primarily by the restraints applied to it during refinement, as a consequence of the typical resolution range of macromolecular crystal structures. Therefore critical assessment of the initial geometrical parameters should carry equal weight, particularly in a high throughput environment. Validation of chemical structures in the context of macromolecular crystallography