CRYSTALLOGRAPHY

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1 INTRODUCTION

In the hierarchy of methods for structure determination, crystallography is the monarch. A technically correct crystal structure determination on high-quality material approaches as close to infallibility as any human effort can do. This degree of certainty comes at a cost: It requires a properly crystalline sample and uses sophisticated expensive apparatus. This chapter first aims to give a general overview of what crystallography can contribute to drug discovery. A discussion of practical matters follows, covering required features of the crystalline sample, the radiation source, and the detector. Next, the essentials of the underlying theory are introduced so that the rationale for the steps in a crystal structure determination can be understood. Although crystallography is underpinned by mathematics, the treatment here will be as intuitive as possible with limited recourse to mathematics. The narrative then returns to specific examples of the use (and nonuse) of crystallography in drug discovery.

1.1 Discovering an Unknown Structure

For many years crystallography has provided the definitive proof of structure for a novel small molecule. Only one sample crystal is usually needed, and this specimen crystal remains available for further studies. Such economy of material is of particular value if, for instance, a very small quantity of a natural product has been isolated. If just the connectivity of the molecule is required, spectroscopy [especially nuclear magnetic resonance (NMR)] is generally sufficient, but crystallography removes any doubt and additionally provides geometric data like bond distances and angles. Crystallographic location of hydrogen atoms is less certain since X rays respond weakly to hydrogen atoms. Nevertheless, hydrogen atom positions can frequently be inferred from the molecular geometry and subsequently confirmed in a map. For instance, a carboxyl group in the free acid form has a short C=O bond and a longer C–OH bond, while a carboxylate ion has two similar C–O distances. If precise details of hydrogen atom geometry are necessary to understand the activity of a particular drug, neutron diffraction provides this information.

Crystallography is of key importance for macromolecules. Revolutionary technical advances have improved the productivity of macromolecular crystallography from a few structures per year in the 1960s to many thousands now. This is fortunate since the Human Genome Project has provided a wealth of new macromolecules whose structure and function need to be investigated. Once again, NMR provides a complementary technique. However, it has the great disadvantage of requiring inference, which could be wrong, although it does have the advantage of sampling all populated conformations in solution. Crystal growing necessarily freezes out most of the motion and selects one or a few conformations that pack together well.

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad