References

BERGHUIS, J., HAANAPPEL, IJ. M., POTTERS, M., LOOPSTRA, B. O., MACGILLAVRY, C. H. & VEENENDAAL, A. L. (1955). *Acta Cryst.* **8**, 478.

HUGHES, E. W. (1941). *J. Amer. Chem. Soc.* **63**, 1737.

ROOF, R. B., JR. (1955). *Acta Cryst.* **8**, 739.

SCHREWELIUS, N. (1942). *Ark. Kemi Min. Geol.* 16B, No. 7.

WHITTAKER, E. & ROBINSON, G. (1944). *The Calculus of Observations*, p. 214. London: Blackie.

Acta Cryst. (1956). **9**, 969

The isomorphous-replacement method applied to molecules containing like atoms.

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The introduction of a 'heavy atom' into a compound often provides a convenient method of analysing its crystal structure. The coordinates of the heavy atom can generally be obtained from the Patterson function, and then it may be a relatively simple matter to locate the rest of the molecule. The method suffers from the disadvantage that the presence of the heavy atom results in less accurate values for the atomic coordinates than are usually obtained for a compound containing only like atoms. This disadvantage can be overcome by using, instead of the conventional heavy atom, one containing a similar number of electrons to the atoms comprising the rest of the molecule. Except for certain cases, such as those in which the compound can be obtained with varying amounts of water of crystallization, this extra atom will be part of the molecule. For example, in organic crystal structure analysis this method can be applied to two similar molecules one of which contains an extra substituent atom.

The two compounds chosen must show a close correspondence in unit-cell dimensions so that the atomic positions are not very different. A comparison of the two Patterson functions will then show whether the molecules not only have the same orientation but also occupy closely similar positions in their unit cells. I have applied the method with success to caffeine and theophylline, whose crystal structures I had not succeeded in solving by other means. In this case, the extra atom is the carbon of the methyl group, substituted in the five-membered ring of caffeine (see Fig. 1). The two *hk*0 Patterson functions

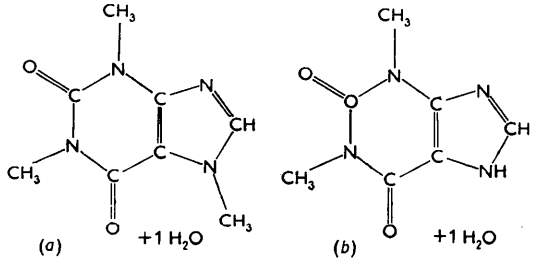

Fig. 1. (*a*) Caffeine. (*b*) Theophylline.

showed that the orientation and position of the molecules are similar, but indicated that the plane of the theophylline molecule is more steeply inclined to the short (*c*) axis. This is to be expected from the unit-cell dimensions as the *c* axis shows an increase of 12% in theophylline whereas the *a* and *b* axes are 11% and 8% shorter respectively.

The difference Patterson introduced by Buerger (1942), and preferably sharpened, is used to locate the positions of the molecules in the unit cell, as this function will contain images of the molecules as seen from the extra atoms. In the calculation of the difference Patterson, terms which are sensitive to the non-exact correspondence of like atoms in the two compounds are not included. These terms are of two types, first a few reflexions occurring at low angles where the difference in F values for the two compounds is greater than can be due to the extra atom, and secondly, all reflexions occurring at high angles where the correspondence between the observed structure amplitudes is no longer good. Omission of these latter terms causes no errors due to series termination since it is a difference series which is used.

The difference Patterson (*hk*0 projection) of caffeine and theophylline, sharpened and with the origin peak removed, is shown in Fig. 2(*a*). The space group is $P2_1/a$, which has four general positions, and therefore this function represents sixteen images of the molecule as seen from the four extra atoms with each of the four molecules in turn. These sixteen images constitute four sets of four molecules related by the space-group elements, and the choice of one such set fixes the molecule with respect to one of the origins in this projection. The location of a set proved to be comparatively easy: the obvious starting point was the molecule situated with the extra atom on the origin of the difference Patterson. Positive regions could be obtained for the majority of atoms and the orientation of the six-membered ring agreed with that obtained from the ordinary sharpened Patterson functions of both caffeine and theophylline. By a process of trial and error lasting less than half a day, three other molecular positions were found satisfying the space-group symmetry and placing as many atoms as possible on positive regions. These four positions are shown in Fig. 2(*a*). Of the remaining maxima, those marked with crosses are the only ones compatible with the positions for the water molecules forming hydrogen bonds. More accurate coordinates for this water molecule were obtained from the first Fourier refinement and it is these coordinates which are marked in Fig. 2(*a*). Spurious maxima occur, due to the non-exact correspondence of like atoms in the two compounds, but there are very few peaks which have not been used. At present both structures have R factors below 20% and refinement is proceeding.

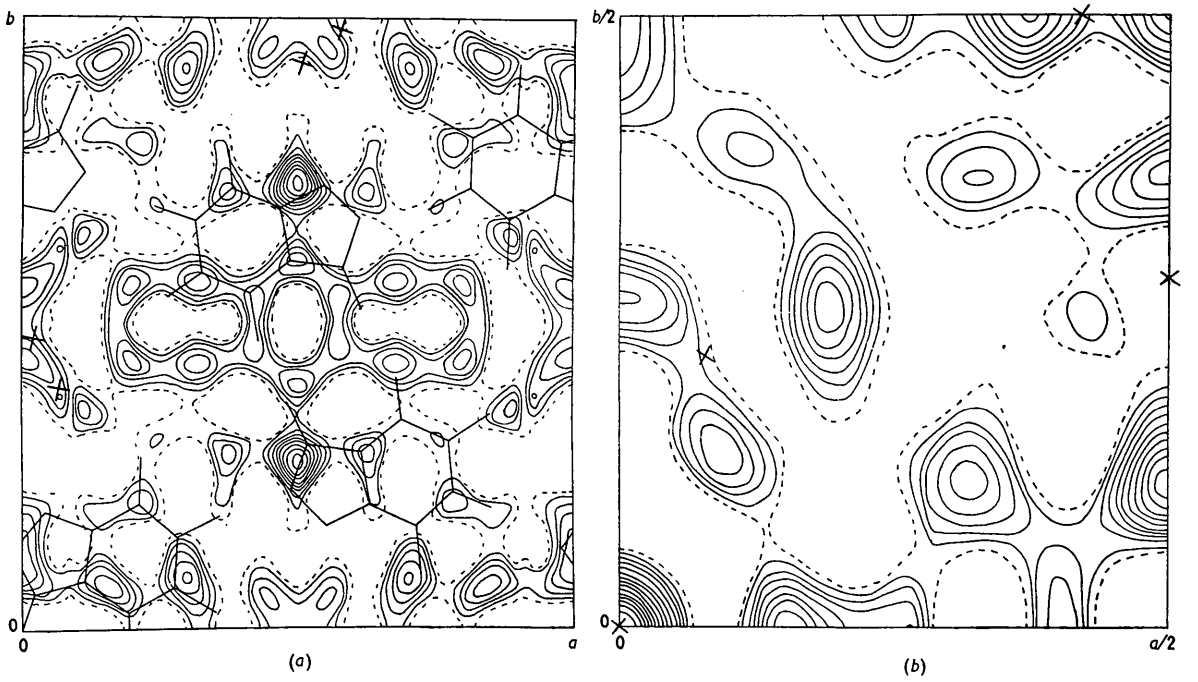

Fig. 2. (*a*) The *hk*0 difference Patterson of caffeine and theophylline. The four positions of the caffeine molecule related by the symmetry elements are shown, and the water molecules are indicated by crosses. Contours at arbitrary intervals; zero contour broken. (*b*) The *hk*0 Patterson of the difference structure of caffeine and theophylline. The positions of the vectors due to the extra atoms are marked by crosses, other peaks are spurious. Contours are at arbitrary intervals; zero contour broken.

As a check on the correctness of the coordinates obtained by this method, the Patterson of the difference structure can also be calculated, using for coefficients the square of the difference between the moduli of the structure factors instead of the difference between the squares. This function should in theory contain only maxima corresponding to the vectors between the extra atoms, but spurious peaks will again occur. The *hk*0 Patterson of the difference structure for caffeine and theophylline is shown in Fig. 2(*b*) and the positions of the vectors due to the extra atoms are shown. The existence of many large spurious peaks in this function indicates that its usefulness is rather limited.

The usefulness of the method depends on a close correspondence between the two compounds. How exact this should be to ensure that the difference map will not contain too much spurious detail is difficult to assess. In the present case, with R factors of 17% and difference syntheses about to be used for refinement, the deviations in the coordinates of the atoms in the molecule are in the range 0·003–0·018 for x (the average value is 0·011) and 0·001–0·045 for y (the average value is 0·018). The water molecules differ by 0·042 in x and 0·018 in y. The largest deviations occur in the five-membered rings due undoubtedly to the presence of the extra methyl group in caffeine. Its close proximity to the keto grouping in the six-membered ring is causing the methyl group, and the nitrogen atom to which it is attached, to move outwards. The deviations in the y coordinates of these carbon and nitrogen atoms, 0·042 and 0·045 respectively, are quite considerable.

To my knowledge, this method has not been used in structure determinations before. In the present case, it has been tested not on compounds whose crystal structures are known but on two new compounds which I had not succeeded in solving by other methods. It has the advantage that two chemically different structures are determined at the same time and hence the effect of a substituent atom on the rest of the molecule can be found by a comparison of bond lengths etc. The method is likely to be of value particularly in organic crystal structure analysis, where it should not be difficult to obtain two compounds satisfying the required conditions.

Work is still in progress on caffeine and theophylline and their detailed crystal structures will be published later.

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Reference

BUERGER, M. J. (1942). *Proc. Nat. Acad. Sci., Wash.* **28**, 281.