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Anomalous Scattering and the Phase Problem

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The ambiguity of the phase obtained from the interference of normal and anomalous X-ray scattering by the method of 'Bijvoet pairs' with monochromatic X-rays can be resolved if diffraction is measured at several frequencies in the region of anomalous scattering. It is pointed out that for the anomalous region at the *K* edge of many atoms, a set of frequencies of just the right order of spread and spacing is provided by the characteristic *L* multiplet of an atom higher up the periodic table, so that all the information needed could be obtained in a single experiment if the *L* radiation could be produced. (A considerable white background could be tolerated.) Rough estimates suggest that for a unit cell containing a single anomalous scatterer, measurements of intensity with an accuracy of 1% should suffice to solve an organic structure containing 100 atoms. The method should be applicable to the crystallography of proteins containing sulphur atoms, where the sulphur *K* edge may be studied with Mo *L* radiation. A numerical example is discussed.

1. Introduction

The use of the interference between normal and anomalous scattering of X-rays in the determination of phases is well known. A difficulty of the method is that a unique solution for the structure factors cannot be obtained with certainty from a single experiment with monochromatic X-rays, but only if the information so obtained is supplemented in some other way, for example by using a second frequency (Okaya & Pepinsky, 1961; Ramaseshan, 1964). All the information necessary could be obtained in a single experiment if one had a source emitting several discrete frequencies spanning the anomalous region near the K edge of a particular atom. It would then be necessary to work with a group of diffraction spots corresponding to each reciprocal-lattice vector and extending over about 15% of the wavelength at the absorption edge, *i.e.* over about ten degrees in a typical case.

The object of this note is to remark that a set of X-ray lines of just the right properties is usually available in the characteristic L multiplet of some atom higher up the periodic table, and could be used to determine phases. It will be clear from what follows that radiation with a substantial white background would be satisfactory*, as long as the characteristic lines stood out sufficiently clearly to provide a scale of frequency.

The plan of the paper is as follows. In § 2, we discuss the determination of phases with a group of frequencies in the anomalous region. In § 3 we discuss the accuracy of intensity measurements required to use such a method of phase determination. § 4 treats the possibility of applying the method to solve small proteins, and also discusses the complications in dealing with a unit cell containing more than one anomalous scatterer. The conclusions are summarized in § 5.

2. The determination of phases

The structure factor for scattering with reciprocal lattice vector **k** is usually written in the form

$$F(\mathbf{k},\omega)=\sum_j f_j(\mathbf{k},\omega)\exp(+2\pi i\mathbf{k}\,.\,\mathbf{r}_j)\,, \qquad (1)$$

where j runs over the atoms in the unit cell. f_j is the scattering factor for the jth atom, and $\mathbf{r}_j$ its position in the unit cell. One can write

$$f_j(\mathbf{k},\omega)=f_{0j}(\mathbf{k})+\Delta f_j'(\omega)+i\Delta f_j''(\omega)\,, \qquad (2)$$

where f_{0j} is the normal component, and $\Delta f_j'$ and $\Delta f_j''$ are respectively the real and imaginary parts of the anomalous component (James, 1948). We shall denote the normal component of F by F_0, *i.e.*

$$F_0(\mathbf{k})=\sum_j f_{0j}(\mathbf{k})\exp(+2\pi i\mathbf{k}\,.\,\mathbf{r}_j)\,; \qquad (3)$$

this is the Fourier transform of the electron density. The anomalous component $(\Delta f'+i\Delta f'')$ is shown on an Argand diagram in Fig. 1 for two examples, copper and sulphur. The quantity x in Fig. 1 is defined as $x=\omega/\omega_c$, where ω is the frequency and ω_c the frequency at the K edge of the atom in question. Fig. 1 was calculated from equations (4·33), (4·34) and (4·41) in chapter 4 of James (1948), using the value $n=3$ for the parameter appearing there. This approximation should be adequate to illustrate orders of magnitude. More accurate calculations have been published by Cromer (1965).

The lines of the L multiplets of molybdenum and tungsten are marked in Fig. 1. The values of x correspond to ω_c(Cu) for tungsten, and $\omega_c(S)$ for molybdenum. It can be seen that anomalous scattering near the K edges is important in a band of frequencies whose width is of the order of 15% of ω_c, and that the appropriate L multiplets span a band of just this order.

The determination of phases by means of anomalous scattering is illustrated in Fig. 2. For the sake of simplicity, we consider a unit cell in which all atoms except

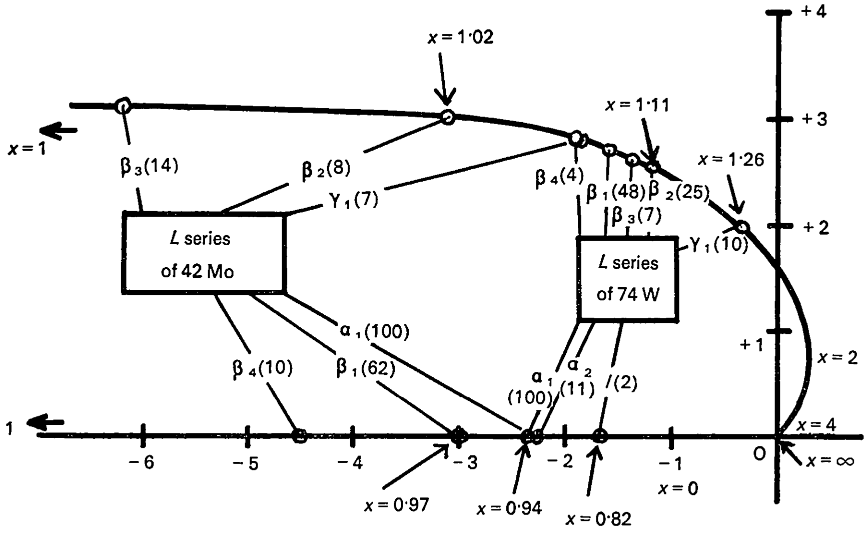

Fig. 1. The complex anomalous amplitude $(\Delta f'+i\Delta f'')$ for sulphur and copper in the neighbourhood of the K edges, divided by the oscillator strengths g_K ($g_K=1{\cdot}5$ for S, $g_K=1{\cdot}3$ for Cu). The quantity $x\equiv\omega/\omega_c$ gives the frequency with the edge frequency ω_c as unit. The strongest lines of the L multiplets of molybdenum and tungsten are marked, the ω_c values belonging to sulphur and copper respectively. The numbers in brackets next to the symbols designating the lines give the intensities as percentages of the strongest line in the multiplet. The units are such that the normal scattering amplitude in the forward direction equals the number of electrons in the atom.

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* This remark is due to Professor C. A. Taylor.

one have negligible anomalous components. For this case, equations (1), (2), and (3) reduce to

$$F(\mathbf{k},\omega)=F_0(\mathbf{k})+\Delta f'+i\Delta f'' , \qquad (4)$$

where $(\Delta f'+i\Delta f'')$ refers to the anomalous atom, which is taken to be at the origin. Fig. 2(*a*) illustrates the method of 'Bijvoet pairs' (Bijvoet, 1949) with a single X-ray frequency. Here one measures the intensity at pairs of reciprocal lattice vectors **k** and $\bar{\mathbf{k}}=-\mathbf{k}$. It follows from equations (1) and (2), and $f_{0j}(\mathbf{k})=f_{0j}^*(-\mathbf{k})$, and the fact that one measures only the modulus of F, that the measurement at $\bar{\mathbf{k}}$ is equivalent to a measurement at **k** with $(\Delta f'+i\Delta f'')$ replaced by its complex conjugate. Fig. 2(*a*) therefore shows curves for both $(\Delta f'+i\Delta f'')$ (full line) and $(\Delta f'-i\Delta f'')$ (broken line). We have marked an arbitrarily chosen structure factor $F_0(\mathbf{k})$, which has to be determined. Measurements at **k** and $\bar{\mathbf{k}}$ at a single frequency corresponding to points P and $\bar{P}$ now give two intensities $I(\mathbf{k},\omega)=|F(\mathbf{k},\omega)|^2$ and $I(\bar{\mathbf{k}},\omega)=|F(\bar{\mathbf{k}},\omega)|^2$. These imply that $F_0(\mathbf{k})$ must lie at the intersection of the two circles C and $\bar{C}$ of radius $\sqrt{I(\mathbf{k},\omega)}$ and $\sqrt{I(\bar{\mathbf{k}},\omega)}$ respectively. These circles have two points of intersection, at F_0 and F_0', so that the structure factor is not determined uniquely. Fig. 2(*b*) shows how a measurement at a second frequency ω', with intensity $I(\mathbf{k},\omega')$, would resolve the ambiguity by giving a circle which passes through only one of the two intersections of C and $\bar{C}$. Fig. 2(*c*) illustrates measurements at three frequencies ω_P, ω_Q, and ω_R, giving intensities $I(\mathbf{k},\omega_P)$, $I(\mathbf{k},\omega_Q)$, and $I(\mathbf{k},\omega_R)$ all at reciprocal lattice vector **k** without using $\bar{\mathbf{k}}$ at all; again a unique solution for F_0 is obtained.

The need for at least three frequencies to determine phases uniquely from measurements at a single reciprocal lattice vector, as in Fig. 2(*c*), is the reason why we have confined the discussion to the L multiplets. The prominent α and β lines in the K multiplets could also be used; (for example Cd K at the sulphur K edge,

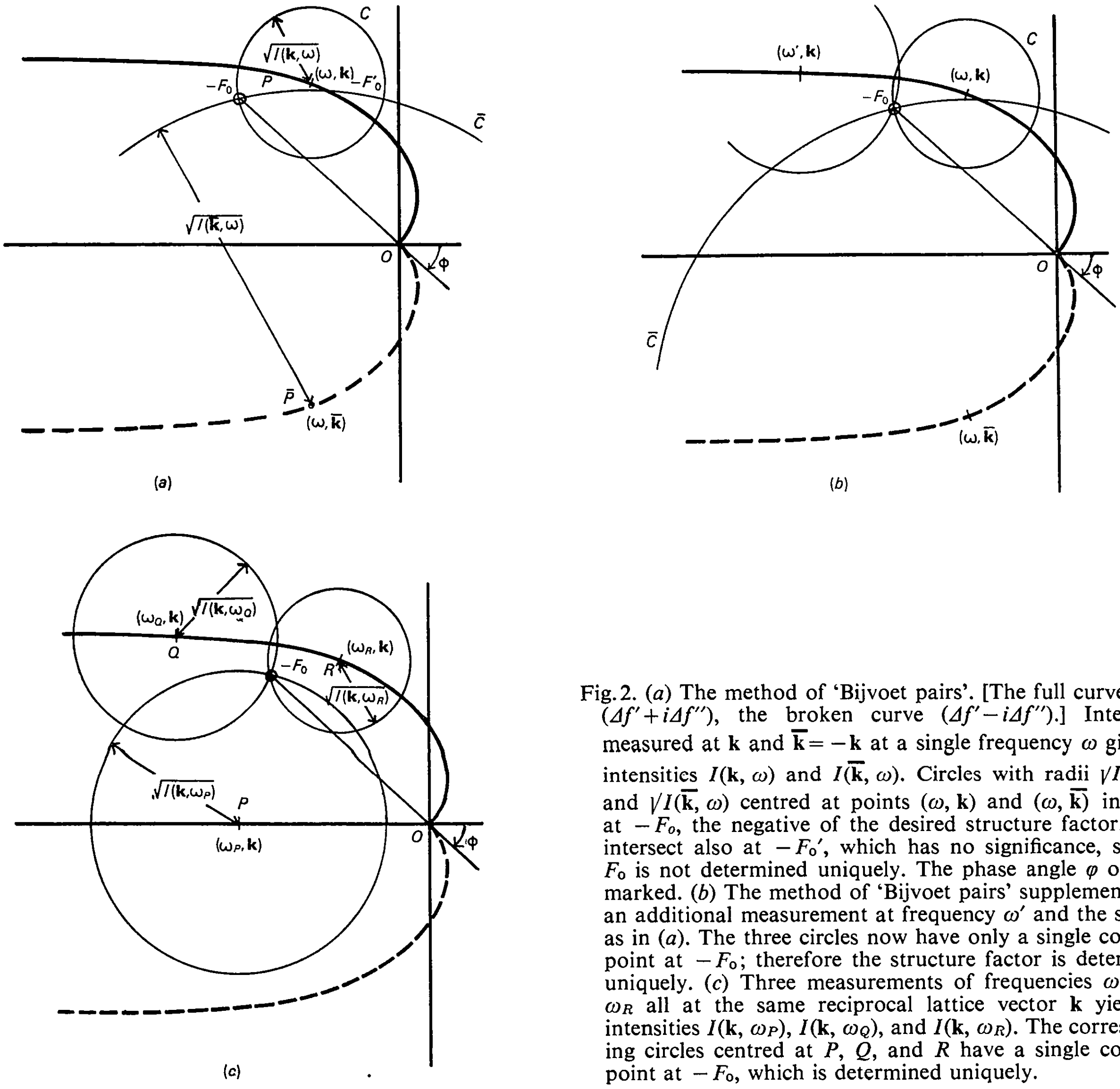

Fig. 2. (*a*) The method of 'Bijvoet pairs'. [The full curve gives $(\Delta f'+i\Delta f'')$, the broken curve $(\Delta f'-i\Delta f'')$.] Intensities measured at **k** and $\bar{\mathbf{k}}=-\mathbf{k}$ at a single frequency ω give the intensities $I(\mathbf{k},\omega)$ and $I(\bar{\mathbf{k}},\omega)$. Circles with radii $\sqrt{I(\mathbf{k},\omega)}$ and $\sqrt{I(\bar{\mathbf{k}},\omega)}$ centred at points $(\omega,\mathbf{k})$ and $(\omega,\bar{\mathbf{k}})$ intersect at $-F_0$, the negative of the desired structure factor. They intersect also at $-F_0'$, which has no significance, so that F_0 is not determined uniquely. The phase angle φ of F_0 is marked. (*b*) The method of 'Bijvoet pairs' supplemented by an additional measurement at frequency ω' and the same **k** as in (*a*). The three circles now have only a single common point at $-F_0$; therefore the structure factor is determined uniquely. (*c*) Three measurements of frequencies ω_P, ω_Q, ω_R all at the same reciprocal lattice vector **k** yield the intensities $I(\mathbf{k},\omega_P)$, $I(\mathbf{k},\omega_Q)$, and $I(\mathbf{k},\omega_R)$. The corresponding circles centred at P, Q, and R have a single common point at $-F_0$, which is determined uniquely.

and Zn K at the copper K edge). However, it would then be necessary to combine measurements from $\mathbf{k}$ and $\bar{\mathbf{k}}$ as in Fig. 2(*b*).

3. Experimental accuracy required

Whether this method of phase determination is of any practical use depends on the demands it makes for experimental accuracy. To see what accuracy is required, let $\varrho(\mathbf{r})$ be the sum of the Fourier components of the electron density which are accessible with an X-ray beam of given frequency. Thus

$$\varrho(\mathbf{r}) = \sum_{\mathbf{k}} F_0(\mathbf{k}) \exp(-2\pi i \mathbf{k} \,.\, \mathbf{r}) \,, \qquad (5)$$

the sum extending over the accessible vectors in the reciprocal lattice. Let $\Delta F_0(\mathbf{k})$ be the error in $F_0(\mathbf{k})$, and $\Delta\varrho(\mathbf{r})$ the consequent error in the synthesis. Write $F_0(\mathbf{k}) = \sqrt{I_0(\mathbf{k})} \exp[i\varphi(\mathbf{k})]$, and let $\Delta I(\mathbf{k})$ and $\Delta\varphi(\mathbf{k})$ be the errors in $I(\mathbf{k})$ and $\varphi(\mathbf{k})$. Then

$$\frac{\Delta F_0(\mathbf{k})}{F_0(\mathbf{k})} = \frac{\Delta I_0(\mathbf{k})}{2I_0(\mathbf{k})} + i\Delta\varphi(\mathbf{k}). \qquad (6)$$

It is now convenient to introduce a quantity E which is a measure of the accuracy of the synthesis. It will be defined by

$$E^2 = \frac{\int d\mathbf{r} |\Delta\varrho(\mathbf{r})|^2}{\int d\mathbf{r} |\varrho(\mathbf{r})|^2} = \frac{\sum_{\mathbf{k}} |F_0(\mathbf{k})|^2 \left[\left(\frac{\Delta I_0(\mathbf{k})}{2I_0(\mathbf{k})}\right)^2 + [\Delta\varphi(\mathbf{k})]^2\right]}{\sum_{\mathbf{k}} |F_0(\mathbf{k})|^2} . \qquad (7)$$

The integrals $\int d\mathbf{r} \ldots$ are to extend over a unit cell, and the sums $\sum_{\mathbf{k}} \ldots$ over the accessible part of the reciprocal lattice.

To estimate $\Delta\varphi$, write

$$\Delta f'(\omega) + i\Delta f''(\omega) = \sqrt{\delta(\omega)} \exp[i\alpha(\omega)] \,, \qquad (8)$$

and suppose that $\sqrt{\delta} \ll \sqrt{I_0}$, *i.e.* that the anomalous component of the scattering amplitude from the whole unit cell is small compared with the normal component. Then φ is given by

$$\cos[\varphi(\mathbf{k}) - \alpha(\omega)] = \frac{I(\mathbf{k},\omega) - I_0(\mathbf{k})}{2\sqrt{I_0(\mathbf{k})}\sqrt{\delta(\omega)}} . \qquad (9)$$

This relation may be used in place of the method of Fig. 2(*c*) if the anomalous component is small. The ambiguity in the solution of equation (9) for φ may be removed by making measurements at different frequencies in the anomalous region where $\alpha(\omega)$ sweeps over a large range (about π for measurements at both $\mathbf{k}$ and $\bar{\mathbf{k}}$). Denoting averages over many measurements by horizontal bars, it follows from (9) that $\overline{(\Delta\varphi)^2}$ is of order

$$\overline{(\Delta\varphi)^2} \simeq \overline{\left[\frac{\Delta(I-I_0)}{(I-I_0)}\right]^2} + \overline{\left(\frac{\Delta I_0}{2I_0}\right)^2} , \qquad (10)$$

where we have replaced $\sin^2[\varphi(\mathbf{k}) - \alpha(\omega)]$ by unity.

Suppose one wants $E \lesssim 10\%$. Then it follows from (7) and (10) that one must have $\sqrt{\overline{(\Delta I_0/I_0)^2}} \lesssim 0{\cdot}1$, and $\sqrt{\overline{[\Delta(I-I_0)/(I-I_0)]^2}} \lesssim 0{\cdot}07$. From Fig. 1 it appears that the anomalous amplitude is of the order of 5 electrons, or of the order of the scattering amplitude from a typical atom, other than hydrogen, in an organic molecule. Assuming the magnitude of the scattering factor from the molecule to vary roughly as the square root of the number of atoms, one finds that an accuracy of 1% in the measurement of intensity should suffice to solve a molecule containing about 100 atoms with a relative accuracy E of the order of 10%.

We have checked that this estimate is reasonable by calculating a Fourier synthesis for an artificial molecule consisting of 27 atoms, arranged at the corners of a cubic framework with 3 atoms on each side. (The calculation was done on the Manchester Atlas computer.) One of the atoms was copper, and the rest were H, C, N, and O, chosen at random, and spaced by 1·34 Å. The structure factors $F(\mathbf{k},\omega)$ were calculated for the characteristic lines α_1, β_1, γ_1 in the L multiplet of tungsten, and squared to give the intensities $I^t(\mathbf{k},\omega)$. The superscript t signifies that I^t is the exact theoretical intensity. An experimental X-ray analysis was then simulated as follows. An 'experimental' intensity $I^e(\mathbf{k},\omega)$ was constructed corresponding to each $I^t(\mathbf{k},\omega)$ by writing

$$I^e(\mathbf{k},\omega) = I^t(\mathbf{k},\omega)\,[1+\varepsilon_1(\mathbf{k})]\,[1+\varepsilon_2(\omega)] \,, \qquad (11)$$

where ε_1 and ε_2 were independent random errors chosen according to Gaussian distributions. In this way, the effect of varying the relative accuracy within the group of spots corresponding to each reciprocal lattice vector, and of varying the accuracy of these groups relative to one another could be checked independently. The phases were determined by the method of Fig. 2(*c*), the errors being allowed for by searching for the F_0 which minimized the expression

$$\{[|F_0(\mathbf{k})+P| - \sqrt{I(\mathbf{k},\omega_P)}\,]^2 + [|F_0(\mathbf{k})+Q| - \sqrt{I(\mathbf{k},\omega_Q)}\,]^2 + [|F_0(\mathbf{k})+R| - \sqrt{I(\mathbf{k},\omega_R)}\,]^2\} .$$

Here P, Q, and R are the complex anomalous amplitudes at the three frequencies ω_P, ω_Q, and ω_R. The Fourier synthesis was then calculated from the values of $F_0(\mathbf{k})$ obtained. A clearly recognizable picture was obtained even with $\sqrt{\overline{\varepsilon_1^2}} = \sqrt{\overline{\varepsilon_2^2}} = 10\%$.

A similar calculation was done with a sulphur atom in place of the copper atom, and three lines from the molybdenum in place of the tungsten L multiplet (α_1, β_4, and β_2). A truthful image was again obtained within the limited resolution of 2·5 Å attainable. These numerical experiments suggest that the accuracy of intensity measurement required is considerably less than the numerical estimates above.

4. Application to proteins

One may ask whether this technique could be of use in the crystallography of proteins, using the sulphur atoms in the cystine and methionine amino acid residues (see *e.g.* Setlow & Pollard, 1962). The best resolution attainable, 2·5 Å, would not be sufficient to resolve all the details, but would be better than the resolution of 6 Å which proved sufficient to produce the first synthesis of myoglobin (Kendrew, Bodo, Dintzis, Parrish, Wyckoff & Phillips, 1958).

The determination of phases with the aid of anomalous scattering becomes somewhat more complicated when there are several identical anomalous scatterers in the unit cell, because their distribution has to be determined first. We next consider a possible procedure in this case.

If the position of the jth sulphur atom in the unit cell is $\mathbf{r}_j^S$, the structure factor for the centres of the sulphur atoms is

$$F^S(\mathbf{k}) = \sum_j \exp\,(+2\pi i\mathbf{k}\,.\,\mathbf{r}_j^S)\,. \tag{12}$$

The scattering amplitude for the complete unit cell may then be written, near the sulphur K edge,

$$F(\mathbf{k},\omega) = F_0(\mathbf{k}) + [\Delta f'(\omega) + i\Delta f''(\omega)]F^S(\mathbf{k})\,; \tag{13}$$

here $(\Delta f' + i\Delta f'')$ is the anomalous amplitude from a sulphur atom at the origin. Then

$$I(\mathbf{k},\omega) = I_0(\mathbf{k}) + 2\sqrt{I_0(\mathbf{k})}\,\sqrt{I^S(\mathbf{k})}\sqrt{\delta}\cos\,[\varphi(\mathbf{k}) - \varphi^S(\mathbf{k}) - \alpha(\omega)]\,, \tag{14}$$

where $I^S(\mathbf{k}) = |F^S(\mathbf{k})|^2$, and $\varphi^S(\mathbf{k})$ is given by $F^S(\mathbf{k}) = \sqrt{I^S(\mathbf{k})}\exp\,[i\varphi^S(\mathbf{k})]$. Equation (14) is valid if the anomalous is small compared with the normal amplitude. By fitting the observed intensities $I(\mathbf{k},\omega)$ to an expression of the form $A(\mathbf{k}) + B(\mathbf{k})\sqrt{\delta(\omega)}\cos\,[\psi(\mathbf{k}) - \alpha(\omega)]$ for the groups of spots corresponding to each reciprocal lattice vector, one can determine I_0, I^S, and $\psi(\mathbf{k}) = \varphi(\mathbf{k}) - \varphi^S(\mathbf{k})$. One then has to do a Patterson analysis on $I^S(\mathbf{k})$ to determine the positions of the sulphur atoms, hence calculate $F^S(\mathbf{k})$ from (12), and thus determine $\varphi(\mathbf{k})$ from the measured $\psi(\mathbf{k})$.

The ratio of the two terms in (14) is of order $\sqrt{(\delta I^S/I_0)} \simeq \sqrt{(N_S/N)}$, where N_S is the number of sulphur atoms, and N the number of atoms of C, N, and O. Taking ribonuclease as an example, one has $N_S = 12$, $N \simeq 10^3$, so that $\sqrt{(N_S/N)} \simeq 0{\cdot}1$. Thus a measurement of intensity with 1% accuracy should determine the intensity I^S to better than 10%. A repetition of the argument based on equations (7) and (10) in § 2 then shows that a solution of a small protein containing about 10^3 atoms of C, N, and O with $E \simeq 10\%$ may be just about attainable with intensities whose relative accuracy within the group of spots corresponding to each reciprocal lattice vector is about 1%.

5. Conclusion

We have shown that the width of the frequency band in which anomalous scattering occurs at the K absorption edge of many atoms coincides roughly with the spread of the characteristic L multiplet of some atom higher up the periodic table. Therefore if the necessary L radiation could be produced, it could be used to determine phases from the interference between normal and anomalous X-ray scattering.

Two examples have been considered to estimate the experimental accuracy required to use the method:

1. An organic molecule containing a single copper atom scattering anomalously at its K edge illuminated by tungsten L radiation. Intensity measurements with a relative accuracy of 1% for the group of spots corresponding to each reciprocal lattice vector should make possible the solution of a molecule containing 100 atoms.
2. A small protein containing sulphur atoms, illuminated by molybdenum L radiation which covers the anomalous region near the sulphur K edge. Measurements of intensity with a relative accuracy of 1% within the group of spots corresponding to each reciprocal lattice vector may make possible the solution of a structure with up to 10^3 atoms of C, N, and O with a resolution of 2·5 Å.

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