from room temperature up to their melting points and from this, the vibrational amplitudes of the individual ions calculated and estimates made of parameters arising from the non-Gaussian distribution of the thermal displacements at high temperatures.

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Successive Refinement of Structures with Data of Increasing Resolution: A Theoretical Study for Triclinic Space Groups

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The method of least squares could be used to refine an imperfectly related trial structure by adoption of one of the following two procedures: (i) using all the observed at one time or (ii) successive refinement in stages with data of increasing resolution. While the former procedure is successful in the case of trial structures which are sufficiently accurate, only the latter has been found to be successful when the mean positional error (*i.e.* $\langle|\Delta\mathbf{r}|\rangle$) for the atoms in the trial structure is large. This paper makes a theoretical study of the variation of the R index, mean phase-angle error, *etc.* as a function of $\langle|\Delta\mathbf{r}|\rangle$ for data corresponding to different resolutions in order to find the best refinement procedure [*i.e.* (i) or (ii)] which could be successfully employed for refining trial structures in which $\langle|\Delta\mathbf{r}|\rangle$ has large, medium and low values. It is found that a trial structure for which the mean positional error is large could be refined only by the method of successive refinement with data of increasing resolution.

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1. Introduction

Ramachandran & Shamala (1976) have recently described a new method of determining crystal structures, which consists of first obtaining a trial structure from an *a priori* knowledge of the molecular structure* by packing analysis using contact criteria (Ramachandran, Ramakrishnan & Sasisekharan, 1963) and then refining the trial structure thus obtained by a least-squares (hereinafter LS) method with an increasingly larger number of reflections of higher $(\sin\theta)/\lambda$ values in successive stages. Using this method they have solved the crystal structure of the cyclic hexapeptide *cyclo*(-Gly-Tyr-Gly-)$_2$ containing 41 non-hydrogen atoms and belonging to the triclinic space group $P1$ (Shamala, 1977, hereinafter S, 1977). During this process the following features regarding this method were observed (see S, 1977 for fuller details). (i) Though the packing analysis using contact criteria gave a few possible trial structures, only one of these, referred to for convenience as the correct trial structure, could be eventually refined. (ii) From among the different trial structures suggested by the packing analysis, the correct one could be identified from the values of the R index and from a study of the behaviour of the LS refinement of the different possible alternatives using a few hundred reflections with low $(\sin\theta)/\lambda$ values. (iii) Even though the correct trial structure obtained from packing analysis had a mean coordinate error (*i.e.* $\langle|\Delta\mathbf{r}|\rangle$, the mean value of the magnitudes of the positional errors of the atoms in the asymmetric unit) as large as 0·8 Å, it could be eventually refined to a high degree of accuracy provided the LS refinement was carried out in stages, starting with low-resolution data, and subsequently increasing the number of higher-angle reflections in each stage in a stepwise manner. (iv) Even the correct trial structure for which $\langle|\Delta\mathbf{r}|\rangle = 0{\cdot}8$ Å could not be refined by the conventional LS method (*i.e.* the LS method of refining a trial structure using all the observed reflections within the Cu $K\alpha$ limit at a time). These results point to the necessity of carrying out a detailed theoretical study of the method of successive refinement with data of increasing resolution (hereinafter the SRDIR method) when the value of $\langle|\Delta\mathbf{r}|\rangle$ for the trial structure is as large as 0·8 Å. Such a study can evidently be carried out by analysing how closely (on the average) the calculated values of the structure factor magnitudes and phase angles of structure factors of a trial structure would agree with the corresponding true values of the crystal structure for data of different resolutions. These, in turn, can be studied by considering the behaviour of the overall values of the R index and mean phase-angle error $E(|\theta^c|)$ [where $\theta^c = \alpha_{\text{true}} - \alpha_{\text{cal}}$; see Parthasarathy & Parthasarathi (1974) – hereinafter PP (1974)] as functions of $\langle|\Delta\mathbf{r}|\rangle$ for data with different resolutions. In the case of a centrosymmetric crystal the quantity analogous to θ^c is s^c which is defined as the product of the signs of the calculated and true structure factors of a given reflection (PP, 1974). Since $s^c = +1$ for those reflections whose signs are correctly determined by the trial structure, for the analysis of the present problem in the centrosymmetric case we have to study the variation of the overall value of the probability that $s^c = +1$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for data with different resolutions.

Another related problem of interest arises in connection with the Patterson function approach to structure analysis *via* the Nordman vector-space search (Nordman, 1966). This procedure could be applied even when only a part of the molecular structure is known (*e.g.* a rigid group of atoms forming a part of the molecule) and the mean positional error for the trial structure obtained by this procedure would in general be less than 0·4 Å. In connection with this method it is natural to ask whether or not the conventional LS method would be successful for refining an *incomplete* trial structure for which $\langle|\Delta\mathbf{r}|\rangle \simeq 0{\cdot}4$ Å. We shall analyse this problem as well in this paper.

We shall use the abbreviations C and NC for the terms centrosymmetric and non-centrosymmetric respectively. We shall use the symbol S to denote $(\sin\theta)/\lambda$ and σ_1^2 to denote the fractional contribution to the local mean intensity from the atoms in the trial structure relative to all the atoms in the unit cell of the given structure. In a structure with similar atoms, σ_1^2 is practically equal to the ratio of the number of atoms in the unit cell of the trial structure to that of the true structure. Also $2S(=H)$ denotes the length of the reciprocal-lattice vector $\mathbf{H}$.

For convenience in our discussion we shall use the symbol X to stand for any one of the quantities: the normalized discrepancy index $R_1(F)$ (Srinivasan & Ramachandran, 1965), the cumulative function $N(|\theta^c|)$, the expectation value $E(|\theta^c|)$ or the probability $P(s^c = +1)$ [hereinafter $P(+)$]. In this paper we shall characterize the resolution by using S even though $1/(2S)$ is the quantity usually employed in protein crystallography. We shall also denote the maximum value of S for the reflections used in the refinement by $S_{\max}$. Thus the larger the value of $S_{\max}$, the greater the resolution obtained. X is a function of S and its overall value for the data for which $0 \le S \le S_{\max}$, denoted by $\langle X\rangle_{S_{\max}}$, could be evaluated theoretically from the expression (Parthasarathi & Parthasarathy, 1974)

$$\langle X\rangle_{S_{\max}} = \frac{3}{S_{\max}^3}\int_0^{S_{\max}} XS^2\,dS.$$

* This could be established to an accuracy needed for the present method from stereochemical considerations and from the results of studies such as NMR.

Since the largest possible value of S_{max} for Cu $K\alpha$ radiation is 0·6485, the quantity $\langle X\rangle_{0\cdot6485}$ would be denoted by $\langle X\rangle_{Cu\,K\alpha}$.

2. Theoretical considerations

Consider a triclinic crystal (C or NC) containing N atoms in the unit cell of which P atoms are known (these P atoms constitute the trial structure). Let $\langle|\Delta\mathbf{r}|\rangle$ be the mean positional error for the atoms in the trial structure.

Non-centrosymmetric case

In the case of an NC crystal the probability density function of θ^c has been shown to be (PP, 1974)

$$P(|\theta^c|) = \frac{\sigma_B^2}{\pi(1-\sigma_A^2\cos^2\theta^c)} \times \left\{1 + \frac{\sigma_A\cos\theta^c}{1-\sigma_A^2\cos^2\theta^c)^{1/2}}\left[\frac{\pi}{2} + \sin^{-1}(\sigma_A\cos\theta^c)\right]\right\} \quad (1)$$

where

$$\sigma_A = \sigma_1\exp(-\pi^3\langle|\Delta\mathbf{r}|\rangle^2 S^2), \quad \sigma_B = (1-\sigma_A^2)^{1/2}. \quad (2)$$

From (1) we can obtain the expectation value and cumulative function of θ^c using the formula

$$E(|\theta^c|) = \int_0^{\pi} \theta^c P(|\theta^c|)\,d\theta^c \quad (3)$$

$$N(|\theta^c|) = \int_0^{|\theta^c|} P(|\theta^c|)\,d\theta^c. \quad (4)$$

The theoretical expression for the conventional R index in the normalized form has been shown to be (PP, 1975)

$$R_1(F) = \frac{3\sigma_B^3}{2}\int_0^1 \frac{{}_2F_1(-\frac{1}{4},-\frac{3}{4};1;\sigma_A^2x^2)}{(1-\sigma_A^2x^2)^2(1+x)^{1/2}}. \quad (5)$$

Centrosymmetric case

The theoretical expression for $P(+)$ for this case has been show to be (PP, 1974)

$$P(+) = \tfrac{1}{2} + \frac{1}{\pi}\sin^{-1}(\sigma_A) \quad (6)$$

and that for $R_1(F)$ to be (Srinivasan & Ramachandran, 1965)

$$R_1(F) = [2(1+\sigma_A)]^{1/2} + [2(1-\sigma_A)]^{1/2} - 2. \quad (7)$$

Equations (3) to (7) show that $R_1(F)$, $P(+)$, $E(|\theta^c|)$ and $N(|\theta^c|)$ are functions of σ_A which is, in turn, a function of the three quantities: σ_1, $\langle|\Delta\mathbf{r}|\rangle$ and S [see equation (2)]. Of these σ_1 and $\langle|\Delta\mathbf{r}|\rangle$ are fixed quantities for a given trial structure. In the presence of coordinate errors (*i.e.* $\langle|\Delta\mathbf{r}|\rangle > 0$) the quantity σ_A for a given trial structure is a systematically decreasing function of S [see (2)]. Thus the quantities X are in general expected to vary markedly as a function of S. For practical applications we are interested only in their overall values for the given data (*i.e.* $\langle X\rangle_{S_{max}}$). Such an overall value of X for given values of σ_1^2, $\langle|\Delta\mathbf{r}|\rangle$ and S_{max} can be obtained by first substituting the appropriate equation of (3)–(7) in the equation given at the end of § 1, and carrying out the resulting integration numerically. For each X, this process can be repeated for different values of $\langle|\Delta\mathbf{r}|\rangle$ by keeping σ_1^2 and S_{max} fixed. The whole calculation can in turn be repeated by varying S_{max} in steps (*e.g.* 0·1, 0·15, . . ., 0·6485) keeping σ_1^2 fixed all the while. We can thus obtain the variation of the overall value $\langle X\rangle_{S_{max}}$ for a given trial structure (*i.e.* σ_1^2 fixed) as a function of $\langle|\Delta\mathbf{r}|\rangle$ for data with different resolutions (this is determined by the value of S_{max}).

3. Discussion of the theoretical results

The method of evaluating $\langle X\rangle_{S_{max}}$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for any given value of σ_1^2 has been described in § 2. The variation of $\langle X\rangle_{S_{max}}$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for different fixed values of S_{max} are shown in Figs. 1–4 for the quantities $R_1(F)$, $P(+)$, $E(|\theta^c|)$ and $N(|\theta^c|)$ respectively. We shall presently analyse the nature of these curves in order to understand the characteristics of refinement by the SRDIR method. We shall consider two types of trial structures: (*a*) an imperfectly related complete type (*i.e.* $\sigma_1^2 = 1$) and (*b*) an imperfectly related incomplete type [*i.e.* $\sigma_1^2 < 1$; see Srinivasan & Parthasarathy (1976) for the terminology]. We shall take 0·6 as a typical value of σ_1^2 for an incomplete trial structure and this corresponds to the case when 60% of the atoms in the unit cell are known.

The case of an imperfectly related complete model

We shall take 1·0 Å as a typical value of $\langle|\Delta\mathbf{r}|\rangle$ and study the effect of refinement of such a model (*i.e.* $\langle|\Delta\mathbf{r}|\rangle \rightarrow 0$ starting from 1·0 Å) on $\langle X\rangle_{S_{max}}$ when S_{max} assumes different fixed values. Following the example of the hexapeptide (Ramachandran & Shamala, 1976) we shall take 0·25 as the value of S_{max} for the starting data set.

(i) *Behaviour of* $\langle R_1(F)\rangle_{S_{max}}$. From Fig. 1(*a*) it is clear that in the C case, even when the value of $\langle|\Delta\mathbf{r}|\rangle$ is as high as 1·0 Å, the value of $\langle R_1(F)\rangle_{0\cdot25}$ is 75·9%, which is less than the value 82·8% expected for a completely wrong structure (Wilson, 1950). Further as $\langle|\Delta\mathbf{r}|\rangle$ decreases from 1·0 Å, the curve for $\langle R_1(F)\rangle_{0\cdot25}$ shows a systematic decrease. However,

when $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, the value of $\langle R_1(F)\rangle_{\mathrm{Cu}K\alpha}$ is 82·4%, which is practically the same as the value, 82·8%, expected for a completely wrong structure. Further, the curve for $\langle R_1(F)\rangle_{\mathrm{Cu}K\alpha}$ is practically flat in the neighbourhood of the point $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, In the NC case also the curves for $\langle R_1(F)\rangle_{0\cdot25}$ and $\langle R_1(F)\rangle_{\mathrm{Cu}K\alpha}$ exhibit corresponding similar features (Fig. 1*b*). Thus it appears that successful refinement of a trial structure with mean coordinate error as large as 1·0 Å could be achieved only by the SRDIR method, not by the conventional method.

(ii) *Behaviour of* $\langle P(+)\rangle_{S_{max}}$: It is seen from Fig. 2(*a*) that when $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, the value of $\langle P(+)\rangle_{0\cdot25}$ is 0·62. Thus in the data for which $S_{max} = 0{\cdot}25$, the fractional number of reflections whose signs are correctly determined by the trial structure is 0·62, which is well above the value 0·5, expected for a completely wrong trial structure. However, when $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, the value of $\langle P(+)\rangle_{\mathrm{Cu}K\alpha}$ is 0·509, which is very close to the value 0·5 expected for a completely wrong structure. Further, while the curve for $\langle P(+)\rangle_{\mathrm{Cu}K\alpha}$ is practically flat in the neighbourhood of the point $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, that for $\langle P(+)\rangle_{0\cdot25}$ shows a systematic increase as $\langle|\Delta\mathbf{r}|\rangle$ decreases from 1·0 Å.

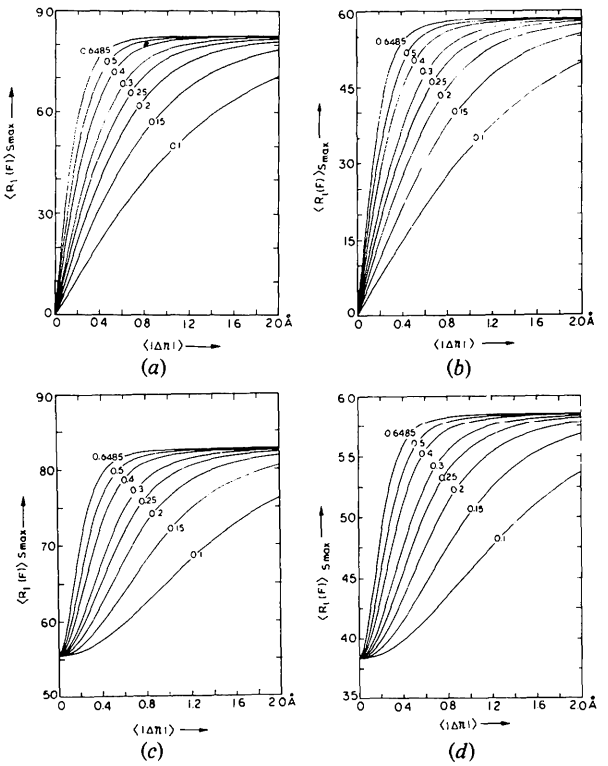

Fig. 1. $\langle R_1(F)\rangle_{S_{max}}$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for different fixed values of S_{max}. The number near each curve denotes the value of S_{max}. Curves in (*a*) and (*b*) are for an imperfectly related complete trial structure with $\sigma_1^2 = 1{\cdot}0$, while those in (*c*) and (*d*) are for an imperfectly related incomplete trial structure with $\sigma_1^2 = 0{\cdot}6$. While curves in (*a*) and (*c*) are for the C case, those in (*b*) and (*d*) for the NC case. The value of $\langle R_1(F)\rangle_{S_{max}}$ is given as a percentage.

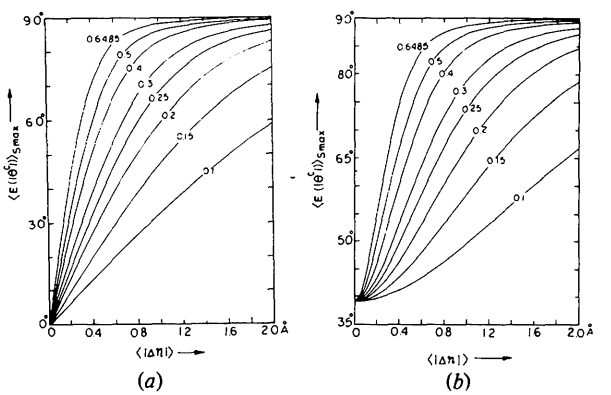

Fig. 3. $\langle E(|\theta^c|)\rangle_{S_{max}}$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for different fixed values of S_{max} for the NC case. Curves in (*a*) and (*b*) are for the cases $\sigma_1^2 = 1{\cdot}0$ and 0·6 respectively. The number near each curve denotes the value of S_{max}.

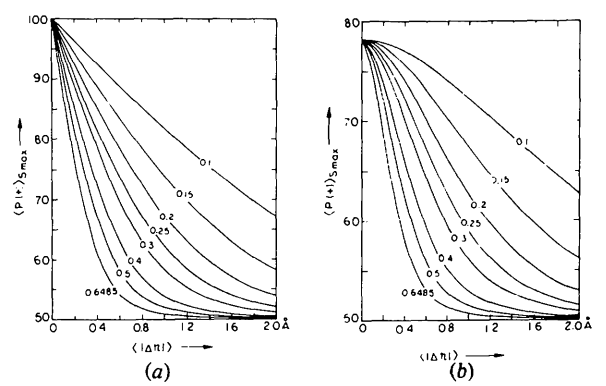

Fig. 2. $\langle P(+)\rangle_{S_{max}}$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for different fixed values of S_{max} for the C case. Curves in (*a*) and (*b*) are for the cases $\sigma_1^2 = 1{\cdot}0$ and 0·6 respectively. The number near each curve denotes the value of S_{max}.

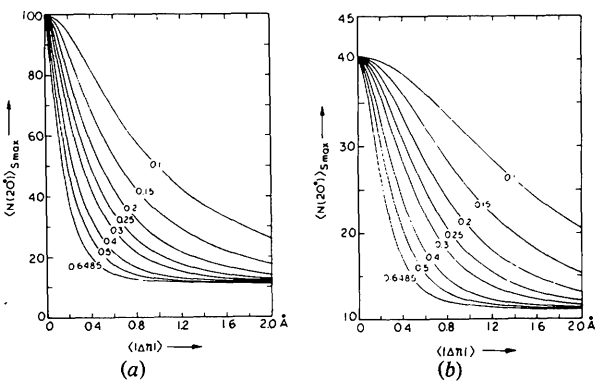

Fig. 4. $\langle N(20°)\rangle_{S_{max}}$ as a function of $\langle|\Delta\mathbf{r}|\rangle$ for different fixed values of S_{max} for the NC case. Curves in (*a*) and (*b*) are for the cases $\sigma_1^2 = 1{\cdot}0$ and 0·6 respectively. The number near each curve denotes the value of S_{max}.

This again points to the necessity of adopting the SRDIR method for a successful refinement of a trial structure for which $\langle|\Delta\mathbf{r}|\rangle$ is as large as 1·0 Å.

(iii) *Behaviour of* $\langle E(|\theta^c|)\rangle_{S_{max}}$. It is seen from Fig. 3(*a*) that when $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å the value of $\langle E(|\theta^c|)\rangle_{0{\cdot}25}$ is 68° while that of $\langle E(|\theta^c|)\rangle_{\mathrm{Cu}K\alpha}$ is 88°. The latter is very close to 90°, which is the value expected for a completely wrong trial structure, while the former is much less than the value expected for a completely wrong model. Further, while the curve for $\langle E(|\theta^c|)\rangle_{\mathrm{Cu}K\alpha}$ is practically flat in the neighbourhood of $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, that for $\langle E(|\theta^c|)\rangle_{0{\cdot}25}$ systematically decreases as $\langle|\Delta\mathbf{r}|\rangle$ decreases from 1·0 Å. Thus, it appears that to refine successfully a trial structure with large mean coordinate error one must use the SRDIR method.

(iv) *Behaviour of* $\langle N(20°)\rangle_{S_{max}}$. From Fig. 4(*a*) it is seen that when $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å, $\langle N(20°)\rangle_{0{\cdot}25} = 0{\cdot}208$ and $\langle N(20°)\rangle_{\mathrm{Cu}K\alpha} = 0{\cdot}118$. Thus while the former value is well above the value 0·111 expected for a completely wrong trial structure, the latter is very close to 0·111. Further, while the curve for $\langle N(20°)\rangle_{0{\cdot}25}$ systematically increases as $\langle|\Delta\mathbf{r}|\rangle$ decreases from 1·0 Å, that for $\langle N(20°)\rangle_{\mathrm{Cu}K\alpha}$ is practically flat in the neighbourhood of the point $\langle|\Delta\mathbf{r}|\rangle = 1{\cdot}0$ Å. This shows that even though the value of $\langle N(20°)\rangle_{0{\cdot}25}$ is as low as 0·208 it could increase as the structure is refined. Thus it is again seen that the SRDIR method should be used for the successful refinement of trial structures for which $\langle|\Delta\mathbf{r}|\rangle$ is as large as 1·0 Å.

So far we have considered the case of a trial structure for which the value of $\langle|\Delta\mathbf{r}|\rangle$ is quite high, say 1·0 Å. For the sake of completeness, we shall examine the case of a trial structure for which the value of $\langle|\Delta\mathbf{r}|\rangle$ is neither high nor low (say, 0·4 Å), in order to find out whether or not such a structure could, in principle, be refined by the conventional LS method. From a similar study of the nature of the curves for $\langle X\rangle_{S_{max}}$ for different fixed values of S_{max} in the neighbourhood of the point $\langle|\Delta\mathbf{r}|\rangle = 0{\cdot}4$ Å (Figs. 1 to 4) it appears that when the positions of the atoms of the trial structure are determined to an accuracy better than 0·4 Å on the average, the trial structure could in general be refined by the conventional LS method. It is also relevant to note here that when the trial structure is sufficiently accurate (say, $\langle|\Delta\mathbf{r}|\rangle < 0{\cdot}2$ Å), the change in the value of $\langle X\rangle_{S_{max}}$ for a given small decrease in the value of $\langle|\Delta\mathbf{r}|\rangle$ (*i.e.* the slope) is greatest when $S_{max} = 0{\cdot}6485$. Thus it follows that for refining such a trial structure the conventional LS method would be preferable to the SRDIR method.

The case of an imperfectly related incomplete model

We shall take 0·4 Å and 0·6 as typical values of $\langle|\Delta\mathbf{r}|\rangle$ and σ_1^2 respectively and study the effect of refinement of such an incomplete trial structure on $\langle X\rangle_{S_{max}}$ for different fixed values of S_{max}. A study of the curves for $\sigma_1^2 = 0{\cdot}6$ in Figs. 1–4 shows that they are quite similar to the corresponding curves for the case $\sigma_1^2 = 1{\cdot}0$ considered earlier. Thus the results obtained for the case of an imperfectly related complete model could be expected broadly to hold good for the present case as well.

4. Conclusion

This study indicates that an imperfectly related trial structure which is of either the complete or incomplete type could be refined only by the SRDIR method whenever the mean positional error $\langle|\Delta\mathbf{r}|\rangle$ for the atoms in the trial structure is large (≃1·0 Å, say). The conventional LS method could be successful whenever the mean positional error has medium value (≃0·4 Å, say). For refining a trial structure which is sufficiently accurate, (*i.e.* $\langle|\Delta\mathbf{r}|\rangle < 0{\cdot}2$ Å), the conventional LS method appears to be preferable to the SRDIR method.

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