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Image-seeking. A Brief Study of Its Scope and Comments on Certain Limitations

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With data for tosyl-L-prolyl-L-hydroxyproline monohydrate, $C_{17}H_{24}N_2O_7S$, image-seeking with groups of search points of different size and weight has been tested. For direct graphical superposition of the Patterson function and extraction of the derived function by summation or minimization, certain defects are revealed as due to the limited accuracy of the technique. For summation image-seeking, these defects may be overcome by direct calculation of the Fourier synthesis with terms $F_o^2.\varphi_c.\exp i\alpha_c$ where φ_c is the structure amplitude contribution of the search group and α_c the corresponding phase angle. Despite the improvement, both methods show that the use of an increasing number of light atoms without corresponding readjustment of the vector distribution does not contribute to the improved resolution of the remainder of the molecule, contrary to expectation.

Consideration of the product method of image-seeking suggested that a more direct approach to the final structure as represented by the electron density distribution would be by image-seeking involving a ratio method i.e. using Fourier terms $F_o^2/\varphi_c.\exp i\alpha_c$. This proposal, first made by Rogers and later by Ramanchandran & Raman, has been tested with the present data. It has been found much less useful than the product method for a small number of search points and to improve only as the number of search points tends towards that of the complete molecule. In this respect, therefore it may be considered complementary to image-seeking by the summation process. It is suggested that a combination of the two image-seeking functions, appropriately weighted, would provide a possible basis for a semi-automatic method of structure analysis once one or more of the weightier atoms were placed satisfactorily. A test is given in the present case where the location of approximately half the atoms in the molecule is known.

Methods of solving crystal structures are of three general types (*a*) by analysis of the Patterson syntheses, (*b*) by 'direct methods' (sign determination) and (*c*) by the study of molecular transforms. The formal equivalence of the three approaches, with particular reference to the first two, has been discussed by Cochran (1958). Due to the difficulties of visualising three-dimensional distributions, the transform method is generally restricted to two dimensions (Lipson & Taylor, 1958). The 'direct method', where unaided by reference to other techniques (e.g. Wright, 1958),* has been applied with success only to a limited number of problems of moderate magnitude e.g. *p*-dimethoxybenzophenone (Karle, Hauptman, Karle & Wing, 1958) and N-benzyl-1,4-dihydronicotinamide (Karle, 1961), both compounds being composed predominantly of planar groups. Furthermore it is at present restricted in practice to centrosymmetric structures or projections. By comparison the Patterson method encompasses non-centrosymmetric structures as well and so, of the three methods, is applicable to the widest range of problems, being of particular importance for compounds of natural occurrence which are predominantly asymmetric (see Mathieson, 1961). Because of the stress being laid at present on 'direct' and transform methods, it is appropriate to point out that the Patterson technique is still capable of dealing with relatively complex problems and in a manner which permits a direct and visual assessment of the progress of the analysis.

Of the various methods proposed for analysing vector distributions, the most logical process and the one permitting systematic development is image-seeking (otherwise Patterson superposition or vector coincidence), suggested by Wrinch in 1939. Much of the systematic development of image-seeking has taken place in the hands of Buerger (e.g. 1950*a*, 1951) while independent approaches to the resolution of vector distributions have been given by Robertson & Beevers (1950), Clastre & Gay (1950*a*, *b*) and Garrido (1950). Buerger (1959) has given an extended treatment of the theoretical development and examples of the application of image-seeking to selected analyses. The successful practical application of this method has been demonstrated by many other analyses e.g. Robertson & Beevers (1951), Thomas & McLachlan

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* In the Cochran & Douglas (1955) tests applied to glutathione, decision among the four main alternatives derived by the 'direct method' rested on the results of the three-dimensional vector distribution.

(1952), Pasternak, Katz & Corey (1954), Donohue, Lavine & Rollett (1956), Hahn & Buerger (1957). Structurally more complex problems have been resolved recently e.g. Nowacki & Bonsma (1958), Przybylska & Ahmed (1958), Beecham, Fridrichsons & Mathieson (1958), Jacobson, Wunderlich & Lipscomb (1959), King (1960), Dodge & Schomaker (1960), Romers & Fischmann (1960), Przybylska (1961), Trefonas, Mathews & Lipscomb (1961).

In these examples, the main use of image-seeking was to derive the crystal structures and no investigation of the potential of the method was attempted. To assess the effective scope of this technique and its usefulness compared with the other approaches to structure analysis, it will be necessary to apply it over a wide range of compounds, not only with regard to the solution of structures but also to provide extensive tests of the influence of (*a*) the condition of the experimental F_o data, (*b*) modification functions and (*c*) the types of image-seeking function. By these means, the scope and limitations of image-seeking can be more precisely defined, *vide* p. 328 Buerger (1959). With regard to this latter aspect, certain types of image-seeking functions were early investigated by Thomas & MacLachlan (1952), and Buerger (1959) has applied extensive tests mainly to inorganic compounds and Kraut (1960) has recently reported (in abstract) tests carried out on several compounds.

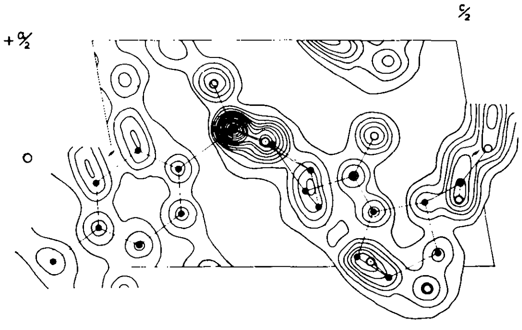

Fig. 1. The projection of the electron-density distribution down the *b* axis, $\varrho(x, z)$ with a diagram of the molecule superimposed.

During the analysis of *p*-tosyl-L-prolyl-L-hydroxyproline monohydrate ($C_{17}H_{22}N_2O_6S.H_2O$, space group $P2_1$), Fig. 1 (Beecham, Fridrichsons & Mathieson, 1958; Fridrichsons & Mathieson, 1962), the structure of which was solved by an image-seeking procedure, we took the opportunity to make a limited systematic study of practical image-seeking in two-dimensions to observe the influence of search groups of varying complexity. The molecule is suitable for such a test since it is reasonably complex—17C+2N+7O+S, a total of 27 atoms—while the sulphur atom is not of such weight as to dominate the structure. The heaviness index, $Z_H^2/\Sigma Z_L^2$, for the sulphur atom relative to the remainder of the molecule, 0·22, is small compared with values associated with molecules of similar complexity (Mathieson, 1955).

Preparation of the data

If, in practice rather than in theory, a fair comparison of the effectiveness of the Patterson technique (and the image-seeking process) is to be made with the formally equivalent methods of the Fourier transform and sign-determination then much depends on the collection of the experimental diffraction data and its conversion to vector space. Both transform and sign-fixing methods deal with unitary structure factors whereas the vector approach may appear to suffer by contrast since the vector map refers to real atoms with the consequent fall-off of data-magnitude for increasing s $(=\sin\theta/\lambda)$. Although it is permissible to 'sharpen-up' to a state corresponding to $B=0$, it is generally considered ill-advised to increase sharpening to the condition of point atoms (see however Abrahamsson & Maslen, 1960). Hence it would appear that the data cannot be handled in exactly the same condition for the three methods.* To achieve 'sharpening-up' to the effective experimental limit it is evident that, not only must the diffraction data be recorded to the limit of the wavelength used but also the percentage population over the experimental range must be high and reasonably uniform (Fridrichsons & Mathieson, 1961). This condition can be achieved either by lengthy exposures at room temperature or by shorter exposures at lower temperatures. In the present case, the former approach was used.

Packs of four films (Ilford G) were exposed in a Weissenberg goniometer for 250 and 8 hr. The intensities were estimated by eye against a set of standards. The F^2 data were subsequently sharpened-up by $\exp + 2Bs^2$, B being derived by Wilson's (1942) method. The resultant Patterson synthesis with the origin removed is shown in Fig. 2(*a*) and it was on this distribution that the first group of image-seeking tests was made. It will be evident that, from this projection alone, the selection of the vector corresponding to S–S would have been somewhat uncertain. In practice, the S–S vector was determined from the Harker section, $P(u, \frac{1}{2}, w)$ (Fridrichsons & Mathieson, 1962) and its location is indicated in Fig. 2(*a*). Since the origin peak had been removed completely, it was considered useful to introduce a small origin peak so that the search points should be reproduced in the image-seeking distribution. The electron-density distribution projected down the *b* axis, Fig. 1, provides a reference by which the various tests may be assessed.

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* On the basis of the formal equivalence of the three methods, this limitation for vector methods may be correlated with the corresponding limitation in transform and sign fixing methods arising from the omission of terms beyond the experimental limit of s (Cochran, 1958).

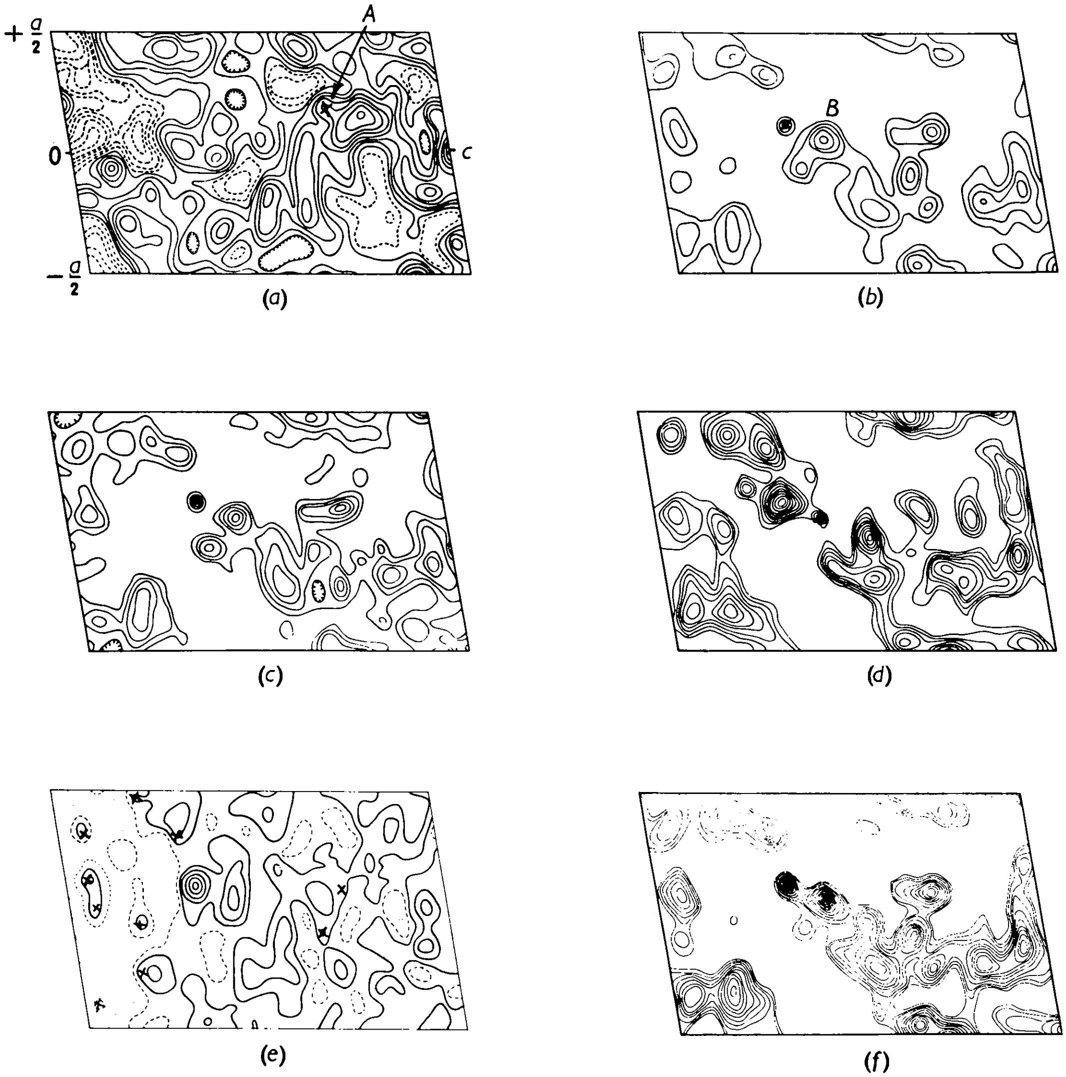

Fig. 2. Image-seeking by graphical superposition. Contour levels in all diagrams are arbitrary. The search group is indicated in each case. (*a*) The Patterson function with the origin peak removed. The S–S vector peak is at *A*. (*b*) Image-seeking summation using the (S–S) vector. (*c*) Image-seeking by minimum using the (S–S) vector. (*d*) Image-seeking by summation using the (ON–NO) vector. (*e*) Image-seeking by summation using 20 search points. (*f*) Image-seeking by summation using the (S–S) and (ON–NO) vectors.

Tests on image-seeking

1. *By direct operation on the vector distribution* (geometrical method)

For this purpose, the *ac* mesh, with *a* subdivided into 32 and *c* into 64 parts, was extended to cover the area $x=0$ to $2a$ and $z=-c/2$ to $+c/2$. The values of the Patterson function (3 figure accuracy) were entered adjacent to the mesh points. Instead of superimposing coloured contour maps to extract the image as generally advised by Buerger (1951, 1959), a method better adapted for dealing with a larger number of search points was selected (Thomas & McLachlan, 1952). A clear plastic sheet with the search-points marked by open circles was laid over the extended Patterson map. To avoid time occupied in interpolation, the values at grid points nearest to the open circles were combined in the appropriate manner and the final value entered at the relevant mesh point on a new *ac* grid. The search group is then moved from point to point, maintaining the correct orientation, to scan the required area.

Of the methods proposed for the combination of Patterson functions—addition, multiplication and minimization (Buerger, 1951)—only addition and minimization can be considered if the combination is to be carried out rapidly for a large number of operations and also applied to a progressively increasing number of search points. The first tests were a comparison of these two simple combinations using the principal inter-atomic through-centre vector, S–S. In the first case, the values at the two ends of the vector were added while in the second case only the lesser value was transferred to the grid. The results are shown in Figs. 2(*b*) and 2(*c*) respectively. Comparison of the two distributions indicated that the minimum function has a tendency to produce artefacts because of its mode of operation e.g. small peaks where none were likely, Fig. 3. Also, although selection of the minimum of two values is simple, the operation becomes rather confusing when attempting to deal rapidly with a large number of search points. Hence on the basis of simplicity of operation and of the smooth presentation of the final result with minimum influence from artefacts, the subsequent tests were carried out mainly on the basis of the summation function (see however Footnote p. 1068).

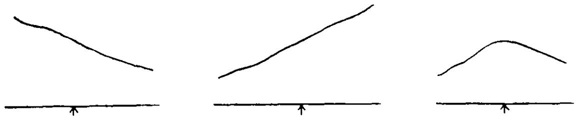

Fig. 3. Artefact peak arising from use of the minimum function.

Of the peaks revealed in Fig. 2(*b*), that at *B* appeared to arise from a superposition of atoms, later found to be about half the height of the sulphur peak in the electron density map, Fig. 1. It was therefore of interest to image-seek with the corresponding through-centre vector to determine the influence of a search point of smaller weight. The result is shown in Fig. 2(*d*). Again the main details are conserved but there are many odd distributions which do not appear to be significant. The next step was to combine the two vectors in image-seeking i.e. to form a four-point search group. To achieve this, it was only necessary to combine the values at grid-points in Figs. 2(*b*) and 2(*d*), weighted in the ratio 2:1 because of the probable weights of respective atom peak heights. The exact weighting is not critical at this stage. The result, Fig. 2(*f*), exhibits a close similarity to the final electron-density distribution, Fig. 1, there being only a few details which do not accord with the final structure. The effective weight of the search atoms relative to the remainder of the molecule, $\Sigma Z_H^2/\Sigma Z_L^2$, is 0·35, assuming provisionally that the smaller vector peak corresponds to the interaction of superimposed nitrogen and oxygen atoms (the completed analysis revealed the peak as due to overlap of three atoms but the peak height ratio is approximately 2 to 1).

Encouraged by the detail achieved so far with two vectors, it was decided to investigate the result of using a larger number of vectors. It has been claimed (Buerger, 1950*b*; Cowley & Moodie, 1957) and would appear intuitively correct that a progressive increase in the number of search points used on the original unchanged Patterson distribution should lead automatically to improved definition of the remainder of the molecule. The normal procedure would be to add the effect of the group of lighter atoms to that due to the weightier vectors above. But then the specific effect of the lighter atoms would be obscured by the dominant distribution derived from the use of the weightier vectors and it would be difficult to perceive the contributions of the lighter atoms and assess their value. To reduce this complication and attempt to provide a clearer test of this proposition, the direct effect of the lighter atoms was isolated by using only these in the search group. A new set of ten through-centre vectors, i.e. twenty search points, all of light weight corresponding to C–C, N–N and O–O interactions, was selected, Fig. 2(*e*). The result of this somewhat tedious image-seeking process (reading and adding 20 values at each point of a 32 × 32 mesh) is shown in Fig. 2(*e*). Not only is there no clear indication of the remainder of the molecule, apart from the S and N+O peaks which are thrown up again by this operation but even the search points are poorly defined. We believe that this experiment contradicts the simple deductions made from an intuitive viewpoint, indicating that other factors, not closely considered, become dominant as the number of search points increase.*

The following factors are relevant to our observations. First, the nature of the Patterson function, particularly for a relatively complex molecule, may be considered. In the present case, the Patterson distribution is composed of $\frac{1}{2} \times 54\,(54-1) = 1431$ peaks spread over the area $\frac{1}{2} \times ac \sin \beta = 60{\cdot}9$ Å^2 i.e. 23·5 peaks per Å^2. The majority of these vector peaks, i.e. $Z_L - Z_L$, overlap to provide a high plateau on which are superimposed the more obvious vectors arising from interaction of the heavier atoms with the light atoms. In image-seeking by summation methods, the result of using n search points is to obtain n values of the plateau $+m$ (where $m \ll n$) values of the peaks superimposed on the plateau. Since the peak height is considerably smaller than the plateau height, the larger n, the smaller becomes the significant peak plateau ratio of the derived function i.e. the signal-to-noise ratio drops. Secondly, the search points were necessarily selected at grid points and the resultant errors are accumulative with increase in the number of search points.

From the evidence, we conclude that with geometrical image-seeking which includes direct Patterson superposition by means of a digital computer (e.g. Pasternak, Katz & Corey (1954); Donohue, Lavine & Rollett (1956); Rossman, Jacobson, Hirshfeld & Lipscomb (1959), only a limited number of important, i.e. weighty, vectors yields significant results. Increase

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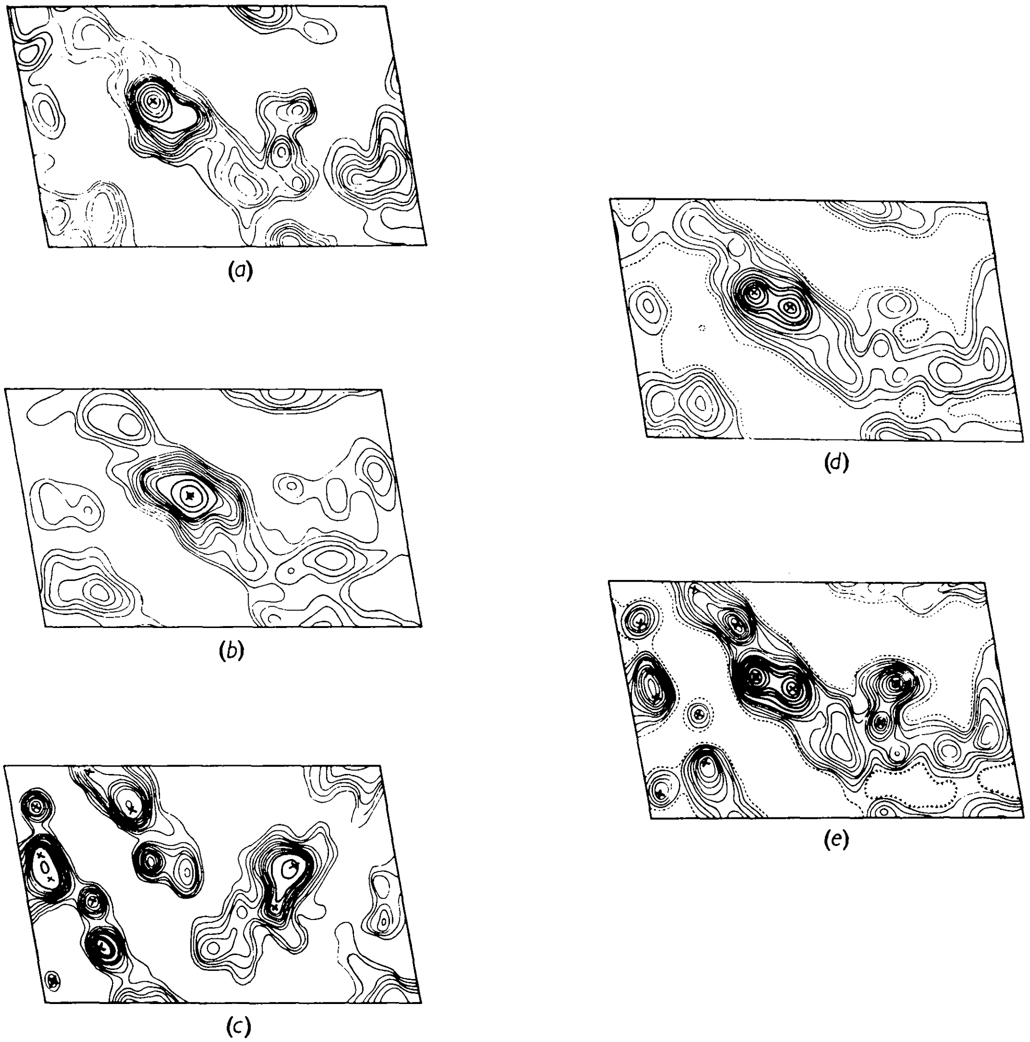
* In addition, minimum function values were derived for areas around the 20 search points. In certain of these regions, the value of the derived function corresponded to the lowest value of the Patterson distribution. In such cases, where the search point was not even reproduced as a broad peak, the minimum function yielded less than the simple summation function.



(a) (b) (c) (d) (e)

Fig. 4. Multiplicative $(F_o^2 . \varphi_c)$ image-seeking with (*a*) the S–S vector, (*b*) the (ON–NO) vector, (*c*) 20 search points, (*d*) (S–S) and (ON–NO) vectors, (*e*) combination of the three groups of vectors illustrated in (*a*), (*b*) and (*c*).

in the number of vectors, particularly lightweight ones, leads only to reproduction of the atoms constituting the vector set but does not resolve appreciably the atoms forming the remainder of the molecule. Under these circumstances, image-seeking with a progressive increase in search points can be successfully prosecuted only if, after each image-seeking operation, we use for the next step a new vector distribution from which the original vector set involved in the previous image-seeking is subtracted. With this procedure, progressive elimination is carried out until the whole molecule is extracted. This, however, is an idealized picture and it seems likely that, in practice, only a limited amount of image-seeking by geometrical methods is worthwhile.

2. *Summation image-seeking by calculation* (analytical method)

Image-seeking by graphical means with a large number of search points introduced problems, discussed above, which may be partly eliminated by carrying out the process by calculation. McLachlan & Thomas (1952), among others, pointed out that image-seeking by summation is equivalent to the calculation of a Fourier synthesis with terms $F_o^2(hkl) . \varphi_c(hkl) . \exp i\alpha_c(hk)$ where φ_c is the structure amplitude contribution calculated for the set of search points and $\alpha_c(hkl)$ the corresponding phase angle. By this means, the effect of (*a*) inaccuracy in the parameters of the search set involved in analogue image-seeking and (*b*) the summation of the vector distribution *n* times with the corresponding accumulation of errors are reduced. We may note that, from the viewpoint of image-seeking by Fourier syntheses, the zeroth order term $F_o^2(000) \times \varphi_c(000)$ increases at a greater rate than do the general terms $F_o^2(hkl) . \varphi_c(hkl)$ with increase of search points in accord with the observation above that the plateau increases at a greater rate than the heights of the significant peaks.

The image-seeking tests carried out directly on the

Patterson function were repeated and extended by the analytical method. The $\varphi_c(h0l)$ values were calculated with a temperature factor $B=0$ (*a*) for the sulphur atom, (*b*) for the superposition of an oxygen and nitrogen atom and (*c*) for the 10 atoms mentioned above. The corresponding values were then combined to give $\varphi_c(h0l)$ values for (*d*) the sulphur atom plus the superposition of oxygen and nitrogen and (*e*) for the combination $(a)+(b)+(c)$ in the set of search points. The Fourier terms, $s(h0l).F_o^2(h0l).\varphi_c(h0l)$ where s is the sign of the component $\varphi_c(h0l)$, were prepared and the five image-seeking functions computed and plotted, Fig. 4. In comparing similar distributions in Figs. 2 and 4, it must be noted that the regions adjacent to the search points may differ since the origin peak was largely removed from the Patterson distribution whereas this does not hold for the image-seeking by calculation for which the equivalent Patterson peak would be of full height. The following observations may be made with regard to Figs. 4(*a*), (*b*), (*c*), (*d*) and (*e*) respectively:

(*a*) The digital image-seeking is very similar to that derived by graphical means, Fig. 2(*b*) and is remarkably good, judged by the heaviness index for S, 0·22 or by the S peak height in the electron-density distribution, Fig. 1.

(*b*) As before, Fig. 2(*d*), there is a rapid fall-off in definition with the lighter-weight vector (ON–NO). While the main region of the molecule is defined, the effect of approximations necessary to carry out analogue Patterson image-seeking is evident, the two distributions, Figs. 2(*d*) and 4(*b*), differing considerably in certain regions.

(*c*) Use of the 20 search points reveals that the increased precision of parameter location by calculation yields an image of the original group, cf. Fig. 2(*e*), of definition superior to that by the graphical process but the remainder of the molecule is still largely undefined i.e. there appears little prospect of successful image-seeking with a group of light atoms. This deduction may be considered reasonably general since in the present circumstances sulphur can hardly be regarded as dominating the structure.

(*d*) The combined image-seeking with S+(N+O) yields a result much as by graphical means cf. Fig. 2 (*f*) —the whole molecule reasonably well defined.

(*e*) The final test with effectively half the molecule (13 atoms) as the search group yields a result close to the final electron-density map, Fig. 1.

Although not critical in the present case, experience with other compounds has shown that, particularly for space groups of higher symmetry, it is essential to subtract from the $F_o^2(hkl)$ terms the contribution of the search group i.e. $\varphi_c^2(hkl)$, before image-seeking otherwise artefact peaks of considerable weight may influence the structural deductions. The Fourier terms are then of the form

$$[F_o^2(hkl)-\varphi_c^2(hkl)].\varphi_c(hkl).\exp i\alpha_c(hkl)\,.$$

3. *Ratio image-seeking*

Carrying the process above to the limit i.e. using the whole molecule as the search group, the result would be (1) which approximates closely to (1*a*)

$$S(x,z)=\sum^h\sum^l|F_o^2(h0l)|.|F_c(h0l)|\times\cos 2\pi(hx/a+lz/c-\alpha_c(h0l)) \qquad (1)$$

$$\approx\sum^h\sum^l|F_o^3(h0l)|\cos 2\pi(hx/a+lz/c-\alpha_c(h0l))\,. \qquad (1a)$$

This distribution by its form would involve somewhat diffuse peaks and deviates rather far from an idealized process of image-seeking which would proceed from the vector (F_o^2) to the electron density ($|F_o(hkl)|.\exp i\alpha_c(hkl)$) distribution. A possible approach to such a procedure since we already had the necessary data, was to evaluate the distribution corresponding to (2) which in the limit yields (2*a*) approximating closely to (2*b*), the normal electron-density distribution.

$$R(x,z)=\sum^h\sum^l|F_o^2(h0l)/\varphi_c^*(h0l)|\times\cos 2\pi(hx/a+lz/c-\alpha_c(h0l)) \qquad (2)$$

$$=\sum^h\sum^l|F_o^2(h0l)/F_c^*(h0l)|\cos 2\pi(hx/a+lz/c-\alpha_c(h0l)) \qquad (2a)$$

$$\approx\sum^h\sum^l|F_o(h0l)|\cos 2\pi(hx/a+lz/c-\alpha_c(h0l))\,. \qquad (2b)$$

This type of image-seeking has already been proposed by Rogers (1951) with optimistic comments but no practical tests were presented. Loopstra & MacGillavry (1958) made some use of this type of synthesis to locate oxygen atoms in $KHSO_4$. More recently Ramanchandran & Raman (1959) have discussed theoretically this type of function among a general class of Fourier syntheses intended to reveal the remainder of a structure once certain structural information is available. Srinivasan & Aravindakshan (1961) have carried out several practical tests of these functions.

Tests on ratio image-seeking parallel to those in the previous group were carried out. The φ_c data had been calculated for $B=0$ and are therefore compatible with the 'sharpened-up' F_o^2 data so that the derived values F_o^2/φ_c should also be on a basis equivalent to $B=0$. For φ_c small, F_o^2/φ_c may be large so that an arbitrary level must be set for this process below which terms are discarded. (N.B. Such arbitrary choice is not involved in image-seeking by $F_o^2.\varphi_c$ terms which may be regarded as having the advantage of automatically weighting the F_o^2 data according to φ_c). The results, using the same set of search points as in the previous tests are shown in Fig. 5. The first test with the S–S vector is relatively satisfactory. The probable reason is that, with one important vector, F_o^2/φ_c is not drastically different from

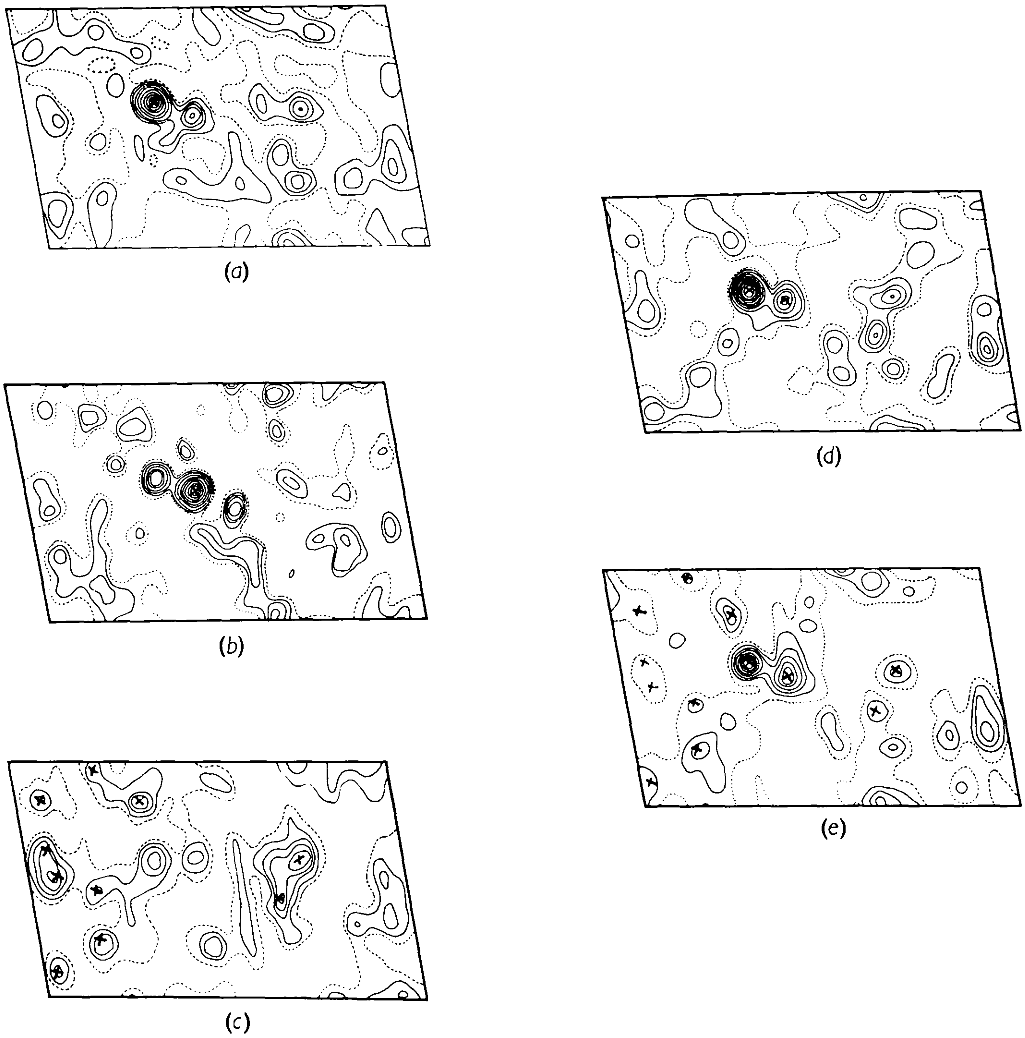


Fig. 5. Ratio (F_o^2/φ_c) image-seeking with (*a*) the S–S vector, (*b*) (ON–NO) vector, (*c*) the 20 search points, (*d*) combination of the vectors in (*a*) and (*b*), (*e*) combination of the vectors in (*a*), (*b*) and (*c*).

$F_o^2 . \varphi_c$ i.e. at this stage the sign rather than the magnitude of φ_c is dominant. In general, the tests with more complex search groups reveal rather disappointing results, contradictory to Rogers predictions. Even the last function, Fig. 5(*e*), with almost half the molecule (13 atoms) as search points is poor, comparing unfavourably with the corresponding $F_o^2 . \varphi_c$ image, Fig. 4(*e*). However the peak definition in the ratio image-seeking is much sharper, as expected from its form and the appearance of the function should improve considerably as one approximates to the complete molecule. It would therefore appear that, by comparison, product image-seeking is, in the early stages, greatly superior to ratio image-seeking both in ease of application and the lack of a need for subjective discrimination. In addition, the appearance and interpretation of the derived distribution is simpler and more direct.

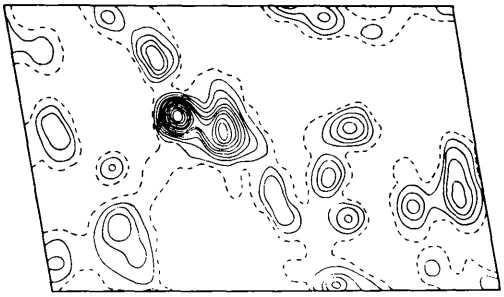


Fig. 6. A combination of multiplicative and ratio image-seeking.—Fig. 4(*e*) and 5(*e*) with equal weight.

Consideration of the properties of the two types of distribution suggests that their advantages and disadvantages at different stages may be counterbalanced by appropriate weighting so that a systematic procedure of moving from the Patterson vector map to the electron density distribution becomes feasible. This can be carried out by e.g. (3)

$$w_1S+w_2R=\sum^{h}\sum^{k}\sum^{l}K(hkl) \times\cos 2\pi(hx/a+ky/b+lz/c-\alpha_c(hkl))\,, \quad (3)$$

where

$$K=(1-r/N)F_o^2\,.\,\varphi_n+r/N\,.\,F_o^2/\varphi_n^*\,,$$

where N = number of atoms in the molecule

and n = number of atoms in the search group.

Initially, when n is small, the main contribution is from the product synthesis which we have shown to be less liable to misinterpretation whereas the ratio synthesis which is much less satisfactory at this stage is given small weight. As n tends to N, the function approximates more closely to the electron density distribution. As an illustration, we have combined the results in Figs. 4(*e*) and 5(*e*) giving each equal weight since n is approximately $N/2$. The result is shown in Fig. 6.

Discussion

The present experiments, although of limited range, suggest certain conclusions. With respect to image-seeking by graphical superposition (geometrical) as compared to Fourier (analytical) methods, most aspects favour the latter. The former is tedious, is liable to inaccuracies which accumulate and involves difficulties in carrying the minor details which produce a cumulative result in a multi-vector search. Although Buerger (1959) has shown that it is possible to deal with three-dimensional vector distributions by graphical combination, this was done with three sets of two-point search groups and to proceed further in this manner poses complex problems of handling and combining data. It would appear that graphical image-seeking when dealing with more than a pair of search points is convenient and practicable only in two dimensions. The Fourier method, however, is very easily extended to three dimensions and is flexible so far as the number of search points is concerned, being capable of use up to the full number of atoms in the asymmetric unit. An indication of the comparative value of the two approaches may be gained from the analyses of diglycine.HCl (Buerger & Hahn, 1957) and erythraline.HBr (Nowacki & Bonsma, 1958). For diglycine.HCl, $C_4H_{10}N_4O_2.HCl$, the three-dimensional vector distribution was handled by graphical means to yield by the minimum function peaks which were allotted as sites for the C, N and O atoms. Of the 17 peaks derived by this operation, five had to be rejected by non-crystallographic argument. For erythraline hydrobromide, $C_{18}H_{19}O_3N.HBr$, analytical image-seeking by $(F_o^2-\varphi_c^2)\,.\,\varphi_c\,.\exp i\alpha_c$ yielded in the first calculation 24 possible atom sites, only two of which required to be discarded.

In image-seeking, it is advisable to eliminate the influence of the vector set due to the search group before attempting to locate other structural features, particularly if weightier atoms are involved. For the geometric method, this necessitates the preparation of a new vector distribution with terms $F_o^2-\varphi_c^2$ each time the search group is elaborated and then image-seeking operations upon the new vector distribution. The analytical method, for a similar sequence of operations requires only one standard type of calculation—Fourier synthesis.

With regard to superposition of vector distributions by means of a computer (e.g. Pasternak, Katz & Corey, 1954; Rossman, Jacobson, Hirshfeld & Lipscomb, 1959) there is, in principle, little difference in the end-results from those derived by purely graphical techniques. In practice, the vastly increased storage and speed of computers permits exploitation of the enhanced possibilities of structure solution inherent in the increased vector resolution of three-dimensional distributions. The restrictions on geometrical image-seeking discussed above in terms of graphical superposition are therefore somewhat relaxed by the use of a computer but even here the addition of search points operating on the original Patterson synthesis is not likely to lead to sequential clarification and new vector distributions will be required to ensure successful location of further structural detail.

Image-seeking (as with other approaches to structure analysis) is markedly dependent on the original state of the diffraction data and how it is treated to yield up the information contained in it. By experimental means e.g. Fridrichsons & Mathieson (1961), it is possible to ensure that the diffraction data are extensive and the population high in all regions. Thus, in the analysis of jacobine bromhydrin (Fridrichsons, Mathieson & Sutor, 1960) for the solution of which analytical image-seeking methods with $F_o^2\,.\,\varphi_c$ played a part, 95% of the possible terms were measured. Such a high ratio of observed terms has the advantage that modification functions, particularly those of more extreme type, can be applied with confidence that significant features will not be omitted. The precise form of the modification function may itself be critical in achieving a solution. Thus, for L-leucyl-L-prolyl-glycine dihydrate, $C_{13}H_{22}N_3O_4$ image-seeking methods proved disappointing (Leung & Marsh, 1958) whereas for a compound of comparable size, cellobiose, $C_{12}H_{22}O_{11}$, Jacobson, Wunderlich & Lipscomb (1959), analysis by image-seeking was successfully prosecuted, the main difference lying in the type of modification function used.

The present series of tests carried out in 1958, followed a line of development essentially practical and heuristic. It is therefore of interest to observe that this approach led to types of Fourier synthesis for image-seeking which are identical with specific forms of the general classes arrived at by Ramanchandran & Raman (1959) following consideration of the relationship of the difference Patterson to the

Fourier synthesis point of view. The $F_o^2.\varphi_c.\exp i\alpha_c$ multiplicative synthesis corresponds to their α-synthesis and the $F_o^2/\varphi_c.\exp i\alpha_c$ ratio synthesis corresponds to their β-synthesis. The practical tests applied above deal in general with situations rather more complex than have been considered in relation to the theoretical approach. Raman (1959) gave a synthetic example based on a 6-atom cell of which three atoms are presumed known and the remaining three to be located. In such limited examples, the techniques work satisfactorily and smoothly. However with more complex structures various factors obtrude and the advantages apparent in the simple example are less evident. Srinivasan & Aravindakshan (1961) have provided practical tests of β-syntheses on tyrosine hydrochloride with the chlorines as search atoms which may be compared to those presented above for the sulphur atom alone, Fig. 5(a). The present examples provide rather more extensive tests. Thus for a β-synthesis with ten light atoms contributing to φ_c, Fig. 5(c), not much additional information is obtained beyond the heavier S and O+N. Even with half the atoms used to define φ_c, Fig. 5(e), the result must be regarded as disappointing relative to the comparable α-synthesis, Fig. 4(e). The experimental results would suggest that for small n, the α-synthesis is more valuable whereas the β-synthesis contains much spurious detail. For large n, the α-synthesis is poor in peak shape and resolution while the β-synthesis is much superior in this respect. Hence a combination of the two as proposed above with the comparative weights being adjusted in relation to n would seem a more practical approach.

Most who have used image-seeking in structure analysis have accepted Buerger's recommendation that the minimum function has complete superiority over other functions. Experience suggests however that this approach is restrictive in terms of increasing number of search points since it operates on the Patterson distribution. The experiments above and of Srinivasan & Aravindakshan (1961) in two dimensions and of Nowacki & Bonsma (1958) in three dimensions suggest that the multiplicative (α-synthesis) method has not been adequately exploited. Ratio (β-synthesis) image-seeking also warrants further extensive test to determine the range of useful application. Only Loopstra & MacGillavry, Raman, Srinivasan & Aravindakshan and the present authors have made what must be considered merely preliminary and incomplete tests of the scope of this function. In particular, tests of the β-synthesis in three dimensions will be of importance.

Combinations of the α- and β-syntheses weighted appropriately depending on the type and size of the search group offer a further development of the image-seeking technique of structure analysis, one which bears a certain similarity to the weighted phase method of Sim (1959) for ϱ_0 syntheses.

With regard to heavy-atom derivatives, it is of interest to determine whether image-seeking methods or direct ϱ_0 syntheses are more efficient in achieving a rapid and complete solution or whether a combination may not be more effective (Mathieson, 1961).

The Fourier syntheses and sets of structure amplitudes, were computed on SILLIAC 1, the electronic computer of the Department of Physics in the University of Sydney, using the programmes devised by Freeman (1957, 1958). We are grateful to Dr H. C. Freeman and Mr J. E. W. L. Smith for their assistance and cooperation in processing the data. We are indebted to Dr J. A. Wunderlich for discussion and argument regarding the contents of the manuscript.

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The Crystal Structure of Menthyl Trimethylammonium Iodide

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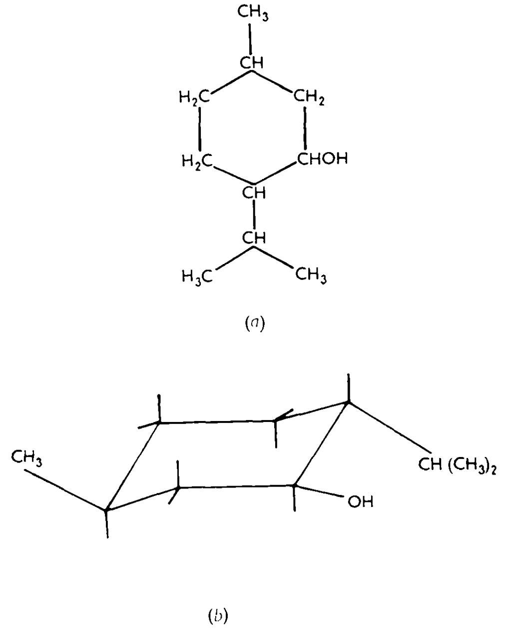
Menthyl trimethylammonium iodide ($[C_{10}H_{19}N(CH_3)_3]^+I^-$) crystallizes in the space group $P2_12_12_1$ with $a = 8{\cdot}4$ $b = 12{\cdot}4$ and $c = 15{\cdot}0$ Å. The structure was solved by three-dimensional Fourier and vector-convergence methods and refined by Fourier methods. The six-membered ring is shown to be boat-shaped and somewhat distorted, so that the large substituents, the trimethylammonium and isopropyl groups, are directed away from each other and on opposite sides of the ring. The iodine and the trimethylammonium group are electrostatically linked to form a spiral along a screw axis parallel to *a*.

1. Introduction

Menthol is the naturally occurring alcohol of the monocyclic terpene menthene. The chemical study of menthol has been extensive and has been of some importance in the stereochemistry of cyclohexane (Simonsen, 1947). The chemical constitution of menthol is shown in Fig. 1(*a*) and the chemically most favourable of the 16 stereo-chemical forms is shown in Fig. 1(*b*), where the ring is shown as chair-shaped with the three substituents in the equatorial position. Menthol and a number of its derivatives have been examined by X-ray methods (Grant & Rogers, 1954) with a view to confirming this configuration. Of those examined, the only crystalline derivative suitable for X-ray structural analysis was the trimethylammonium iodide. This derivative has two serious disadvantages, namely that the presence of the large trimethylammonium group could well change the stereochemical configuration from that of the parent alcohol, and also that the presence of one iodine to only 14 'light' atoms would mean that the accuracy of the structure determination would not be high. The ratio of the sum of the squares of the atomic numbers of the iodines to that of the light atoms is 5·3 to 1; thus



(*a*)

(*b*)

Fig. 1. (*a*) The chemical constitution of menthol. (*b*) Chair-shaped ring with the substituents in the equatorial position.