located in the region $3 < q < 10$. Therefore, the presence of this feature in observed peak profiles, resulting from samples where a demixing process has probably occurred, will make the use of the aforesaid analytical expression quite advantageous. From a numerical point of view, in fact, the use of (19) is only slightly more complicated than that of pseudo-Voigt functions. Besides, with $\delta = \delta_{LSW}$, it involves only one parameter, D_0 or equivalently D_c. This result is interesting for three reasons: (*a*) it makes it possible to test whether the conditions underlying the LSW theory are met or not, directly using WAXS results; (*b*) one could use SAXS experimental results for testing the applicability of the LSW model. In the affirmative case, one knows the ideal WAXS profiles. Thus any deviation ought to be ascribed to disorder effects; (*c*) with δ as a free parameter, one has another simple expression for fitting peak profiles. If it turns out that the overall agreement is better than that obtained by using Voigt functions, one would find a v.f.w.d. skewed in a direction opposite to the ones so far observed.

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BYPASS: an Effective Method for the Refinement of Crystal Structures Containing Disordered Solvent Regions

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Abstract

A method is described for the least-squares refinement of the atomic parameters of the ordered part of a crystal structure in the presence of disordered solvent areas. Potential solvent regions are identified automatically. The contribution of the observed contents to the total structure factor is calculated *via* a discrete Fourier transformation, and incorporated in a further least-squares refinement of the ordered part of the structure. The procedure is iterated a few times to convergence. It is found that this mixed discrete-atom and continuous solvent-area model refinement approach greatly improves the quality of discrete atomic parameters, *i.e.* the geometry and the e.s.d.'s. An electron count over the solvent region in the final difference electron-density map provides a convenient estimate for the number of solvent molecules present in the unit cell. The application of the method to four structures is described.

Introduction

The completion of an otherwise successful structure determination is frequently hampered by the presence of statically or dynamically disordered solvent of crystallization filling voids in the structure (*e.g.* Raston & White, 1976; Read & James, 1980). The problem of disordered solvent areas is very common in protein crystallography. Several methods are used

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in that field to handle disordered solvent regions (mainly water), as described by Blake, Pulford & Artymiuk (1983), Savage & Wlodawer (1986) and Smith, Corfield, Hendrickson & Low (1988). Although solvent molecules are often essential to obtain single crystals of the compounds to be studied, their detailed structure is usually not of particular interest. A statistical analysis (van der Sluis & Kroon, 1989) of structures contained in the Cambridge Structural Database (Allen, Kennard & Taylor, 1983) reveals significantly higher R values for structures containing solvent molecules than for those without. This indicates a need for more effective methods to take care of the contribution of solvents to the diffraction intensities. Special techniques are needed for the calculation of the contribution of the disordered solvent to the total structure factor. The usual procedure in cases of orientational disorder involves the inclusion in the least-squares refinement of two or more overlapping instances of the solvent molecule in order to model the observed electron density in the solvent region. Constraints and restraints are then nearly always necessary to obtain stable refinement and chemically reasonable geometries, making this discrete-atom approach laborious and seldom fully satisfactory. Structures with additional high anisotropic thermal motion of the solvent molecules pose particularly severe problems,* resulting in still relatively high residual densities in a difference Fourier map that are not taken into account, correspondingly high final R values and large e.s.d.'s on the structural parameters of interest. Structures that virtually preclude the application of the discrete-atom approach to model the disorder are those that contain areas or channels with a nearly homogeneous density distribution. Spherically averaged molecular scattering factors may be used instead (Jones, Schwarzbaum, Lessinger & Low, 1982). Often the nature of the disordered solvent molecules is not even known, for example cases where several solvents were used in the preparation and crystallization of a small batch of crystals. In such cases the difference electron-density map is normally left uninterpreted. The most intense peaks are then taken into account in the refinement with the assignment of pseudo-atom parameters including occupancy factors (*e.g.* Boge, Mockler & Sinn, 1977).

An alternative way to proceed in such cases is to calculate the discrete Fourier transform of the observed density in the solvent area as a whole and to incorporate this as the solvent contribution to the structure factors in the structure factor and refinement calculations. The application of such a procedure was reported by Wehman, van Koten, Jastrzebski, Rotteveel & Stam (1988). The present paper presents a more elaborate and automated implementation of, and experience with, such a procedure.

Method

The calculated structure factor $F_{\mathbf{h}}^c$ for the reflection $\mathbf{h}$ of a structure containing disordered solvent may be divided into two parts (Fig. 1). The first part originates from the ordered part of the structure, $F_{\mathbf{h}}^m$, the second part, $F_{\mathbf{h}}^s$, represents the solvent contribution. $F_{\mathbf{h}}^m$ is readily calculated from the structural parameters of the model. The solvent contribution is derived from the electron-density difference map $\Delta\rho(\mathbf{r})$ as calculated according to

$$\Delta\rho(\mathbf{r}) = V^{-1}\sum_{\mathbf{h}}[s|F_{\mathbf{h}}^o|\exp(i\varphi_{\mathbf{h}}^c) - |F_{\mathbf{h}}^m|\exp(i\varphi_{\mathbf{h}}^m)]\exp(-2\pi i\mathbf{h}\,.\,\mathbf{r}), \quad (1)$$

where $|F_{\mathbf{h}}^o|$ is the observed structure factor, $\varphi_{\mathbf{h}}^c$ the phase of $F_{\mathbf{h}}^c$, $\varphi_{\mathbf{h}}^m$ the phase of $F_{\mathbf{h}}^m$ and V is the volume of the unit cell. $F_{\mathbf{h}}^s$ is obtained by discrete Fourier transformation of this function restricted to the solvent region using

$$F_{\mathbf{h}}^s = V_g \sum_{\mathbf{r}_j \in S} \Delta\rho(\mathbf{r}_j)\exp(2\pi i\mathbf{h}\,.\,\mathbf{r}_j), \quad (2)$$

where V_g is the volume per grid point and S is the set of grid points $\mathbf{r}_j$ within the solvent area.

The structure refinement is broken up in a sequence of two subrefinement processes in which the contribution of the ordered part of the structure, $F_{\mathbf{h}}^m$, and the disordered solvent contribution, $F_{\mathbf{h}}^s$, are optimized alternatingly until convergence. Refinement of the ordered part of the structure is done by standard least squares taking the solvent contribution into account as a fixed contribution to the structure factor. Optimization of the solvent contribution consists of an iteration with (1) and (2). The correct values of

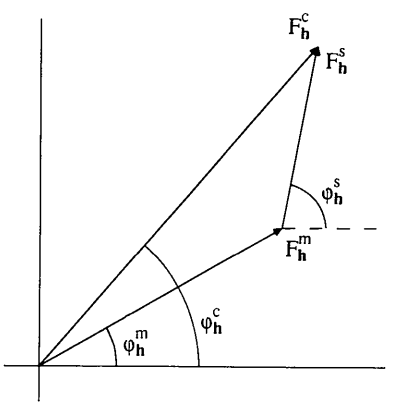

Fig. 1. Argand diagram showing subdivision of the calculated structure factor, $F_{\mathbf{h}}^c$, into the contributions of the ordered structure, $F_{\mathbf{h}}^m$, and the solvent, $F_{\mathbf{h}}^s$.

* Data collection at low temperature will usually diminish the problems related to dynamic disorder, but rarely those of static disorder.

$\varphi_{\mathbf{h}}^c$ and s, needed to apply (1) and (2), are not known initially. Therefore the iterative calculation of $F_{\mathbf{h}}^s$ is started with $\varphi_{\mathbf{h}}^c = \varphi_{\mathbf{h}}^m$ and $s = s_m$ as initial values, where s_m is the scaling factor to put $|F_{\mathbf{h}}^o|$ on the same scale as $|F_{\mathbf{h}}^m|$. Subsequent optimization cycles of $F_{\mathbf{h}}^s$ start from $\varphi_{\mathbf{h}}^c$ values calculated with the provisional solvent contribution obtained in the previous run. The solvent area (S) acts as a filter in direct space to obtain improved phases, $\varphi_{\mathbf{h}}^c$, and an improved scale factor s in (1).

Iteration of (1) and (2) starting with $\varphi_{\mathbf{h}}^m$ phases will be slow for non-centrosymmetric structures. This is because the solvent density will show up only at half height in a difference Fourier map (Lipson & Cochran, 1966). The convergence is speeded up with the introduction of a scaling factor ε (typically in the range 1 to 2) to $F_{\mathbf{h}}^s$ in the calculation of $F_{\mathbf{h}}^c$:

$$F_{\mathbf{h}}^c = F_{\mathbf{h}}^m + \varepsilon F_{\mathbf{h}}^s. \tag{3}$$

The value of ε is varied and the corresponding s is obtained by a least-squares procedure and that combination of ε and s is chosen that minimizes

$$R = \sum_{\mathbf{h}} |s|F_{\mathbf{h}}^o| - |F_{\mathbf{h}}^c||/\sum_{\mathbf{h}} s|F_{\mathbf{h}}^o|. \tag{4}$$

The number of electrons in the solvent region, $F_{\mathbf{0}}^s$, is obtained from the difference Fourier map (1), that is calculated without such a contribution, by summation of $V_g \Delta\rho(\mathbf{r}_j)$ over the grid points in the solvent area S, yielding the value F_0. A similar count over the region outside S will necessarily obtain $-F_0$. A good approximation of $F_{\mathbf{0}}^s$ can be calculated by raising the average density level from zero such that the electron count outside the solvent region will yield zero:

$$F_{\mathbf{0}}^s = F_0[V/(V - V_S)], \tag{5}$$

where V_S is the volume spanned by the solvent grid points and V is the unit-cell volume spanned by all grid points. A corresponding contribution $F_{\mathbf{0}}^s/V$ is added to $\Delta\rho(\mathbf{r}_j)$ before the application of (2). The number of electrons, $F_{\mathbf{0}}^s$, is also useful in deducing which solvent might be present in the structure and in what quantity.

An essential step in the procedure is the assessment of the possible solvent areas (S).* This is achieved with the help of an additional three-dimensional map with a grid step half that of the difference Fourier map calculated with (1). The difference Fourier map is calculated using a grid with $2 \times \text{index}_{\max} + 1$ grid points (index = h, k, l) for the three dimensions. This number is increased, if necessary, to match optimal conditions for fast Fourier transformation. Grid points are assigned a value in the range 0 to 3 following a procedure described below. In this map the value of grid points within the van der Waals sphere (Bondi, 1964) of atoms belonging to the ordered part of the structure is set to zero and the value of grid points that fall outside is set to one (Fig. 2*a*). Even in a structure without disordered unaccounted solvent, about 30% of the grid points will still be outside the van der Waals volume of the constituent atoms (Kitaigorodskii, 1961). We are only interested in grid points that are situated in cavities that are large enough to contain at least one water molecule. Therefore only grid points within cavities larger than a certain solvent radius (r) are considered. To that effect grid point values in the centre of these cavities with a distance greater than r Å to grid points with value zero are set to two (Fig. 2*b*). The radius r, called solvent radius, is usually taken as 1·30 Å. In order to mark all grid points of the solvent area, grid points with value still one in Fig. 2(*b*), but within solvent radius of a grid point with value two, are given the value three. The solvent region is now the set of grid points with values greater than one Fig. 2(*c*). This set is analysed to identify connected areas. Space-group symmetry is applied to identify crystallographically independent areas and the grid points are labelled accordingly. This makes it possible to identify and optionally exclude 'natural' cavities near symmetry elements (*e.g.* mirror planes) from the calculations or to perform calculations for independent areas separately, which in turn makes identification of the solvent easier when more than one crystallographically independent cavity is present.

Implementation

The logical procedure to follow would be the addition of the solvent contribution $F_{\mathbf{h}}^s$ to the discrete model part $F_{\mathbf{h}}^m$ according to (3), followed by refinement on $|F_{\mathbf{h}}^o|$ (where $F_{\mathbf{h}}^m$ is variable and $F_{\mathbf{h}}^s$ is fixed). Alternatively, it is possible to subtract the solvent contribution from the observed structure factors to obtain modified structure factors $F_{\mathbf{h}}^{o'}$ against which refinement of the discrete-atom model parameters can proceed. We took the latter approach in order to use our current least-squares refinement program (*SHELX*76: Sheldrick, 1976). Modified observed structure factors are calculated with

$$F_{\mathbf{h}}^{o'} = s|F_{\mathbf{h}}^o| \exp(i\varphi_{\mathbf{h}}^c) - \varepsilon F_{\mathbf{h}}^s, \tag{6}$$

where ε converges to 1.

The full procedure, called the BYPASS procedure, can be summarized as follows:

Step 1. Refinement of the ordered part of the structure on $|F_{\mathbf{h}}^{o'}|$. When applicable, a provisional discrete-atom approach is used for the solvent region as a better starting point to speed up convergence. This step optimizes $|F_{\mathbf{h}}^m|$ and the corresponding $\varphi_{\mathbf{h}}^m$. Step 1 is called FM cycle.

* For an alternative algorithm for identification of solvent areas see Gavezzotti (1983).

Step 2. Determination of the solvent area map according to the procedure schematized in Fig. 2, in which of course provisional atoms belonging to the disordered solvent are discarded.

Step 3. Calculation of a difference Fourier map according to (1), the number of electrons in the solvent region with (5) and solvent structure factors according to (2). This is repeated until convergence, which is assumed when the integral over the difference Fourier map in the solvent area, F_0^s, has reached convergence. This step optimizes $|F_h^s|$ and the corresponding φ_h^s. Step 3 is henceforth called FS cycle.

Steps 1, 2 and 3 are repeated until the integral over the difference Fourier map in the solvent area has reached convergence. Steps 1, 2 and 3 together are henceforth called MAIN cycle. A MAIN cycle consists of one FM cycle and a few FS cycles.

From the second MAIN cycle on, the starting value of φ_h^s in step 3 is taken as the end value of φ_h^s in the previous MAIN cycle.

A number of utilities were developed to display the automatically determined solvent regions and difference Fourier maps on an Evans & Sutherland PS300 system in order to visualize and monitor the procedure.

Tests

A number of test calculations were carried out in order to investigate the validity of the BYPASS procedure. Results are summarized in Tables 1 and 2 and discussed in the last section. In all eight test cases the parameters of one solvent molecule and symmetry-related ones were omitted from the parameter set of a previously refined discrete-atom model and the procedure run to recover the solvent contribution. The indicated grid step used is that of the grid used to calculate the solvent map. The Fourier transforms are calculated with twice this grid step.

Compound I

[*N*-(5-Methyl-2-thienylmethylidene)-L-methionyl]-histamine silver triflate methanol solvate (Modder, van Koten, Vrieze & Spek, 1989) crystallizes in the non-centrosymmetric space group $P2_12_12_1$, $a = 11{\cdot}339$, $b = 13{\cdot}122$, $c = 17{\cdot}451$ Å, and contains one methanol molecule in the asymmetric unit. The methanol is hydrogen bonded to the triflate anion and the parent molecule. Four calculations were carried out with this compound. In all cases two MAIN cycles with two FS cycles were needed to reach convergence. Test calculation I^a, in fact, converged after one cycle, but calculations were continued as a check. Grid used = 0·187 Å. The first test is a null test (I^a in Tables 1 and 2). The methanol molecule was omitted from the refined structural model and structure factors calculated for this solvent-free model were taken as F_h^o to check whether any significant electron density leaked into the solvent region. The integral over the solvent Fourier map yielded F_0^s less than 0·00005 electrons, which is quite satisfactory. As a second test (I^b), the methanol molecule was omitted and the procedure was started without prior least-squares refinement using structure factors calculated from the model including the methanol molecule as F_h^o. In a third test (I^c), the methanol molecule was omitted and the procedure was started with prior least-squares refinement using again structure factors calculated from the model including the methanol molecule as F_h^o. In (I^d), the methanol molecule was omitted and the procedure was started with prior least-squares refinement using experimental values of F_h^o.

Compound II

Neoandrographolide monohydrate (Smeets, Spek, Duisenberg, Labadie, De Silva & Ratnayake, 1987) crystallizes in the non-centrosymmetric space group $P2_1$, $a = 7{\cdot}377$, $b = 6{\cdot}235$, $c = 28{\cdot}569$ Å, $\beta = 95{\cdot}73°$, and contains two water molecules. The positions of the H atoms of the water molecule could not be determined in that study. Two MAIN cycles with two FS cycles were needed to reach convergence. Grid used = 0·217 Å. For this very small solvent area the optimal solvent radius turned out to be 1·20 Å.

Compound III

{2,2′-Bis[(methylphenylamino)methyl]phenyl}bis-(triethylphosphine)nickel(II) bromide (van Beek, van

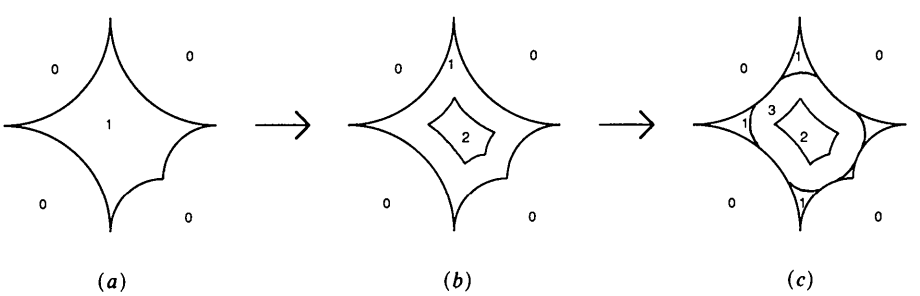

Fig. 2. Schematized solvent-area determination procedure.

Table 1. *Results of the solvent BYPASS method for the five test structures and the four applications*

V_s is the volume occupied by the solvent molecule as determined by the procedure. V_l is the molecular volume of the solvent in liquid at room temperature. All volumes refer to one solvent molecule. N_m is the number of solvent molecules found by electron count in the asymmetric unit, for the test cases I–V, divided by the number omitted.

	Before		After BYPASS application				
Compound	Solvent	R (%)	R (%) start	N_m	R (%) end	V_s	V_l
I[a]	MeOH	0·00	0·00	-	0·00	53	67
I[b]	MeOH	0·00	7·35	0·985	0·72	53	67
I[c]	MeOH	0·00	6·17	0·991	0·78	53	67
I[d]	MeOH	3·70	7·56	0·987	3·66	52	67
II	H_2O	5·37	12·10	0·998	5·55	41	30
III	Et_2O	5·52	8·99	1·063	5·24	209	173
IV	DMSO	4·40	15·73	0·979	4·77	141	118
V	THF	5·24	12·32	0·999	4·49	125	135
VI	H_2O	-	9·60	4·518	4·26	41	30
VII	MeOH	-	10·34	2·220	4·68	83	67
VIII	Toluene	-	7·94	1·040	5·84	216	177
IX	Pentane	-	11·00	1·075	6·32	218	191

Table 2. *Results of the BYPASS method showing the improvement in geometry concerning the* C *atoms of five test structures*

Compound identification corresponds to Table 1 and the text. For each parameter the mean of the discrepancies relative to the starting model is given. The left columns refer to refinement with omission of solvent, the right to results of the BYPASS method. Mean e.s.d.'s in parentheses.

Compound	Bond length (Å)		Bond angle (°)	
I[a]	0·000 (0)	0·000 (0)	0·00 (0)	0·02 (0)
I[b]	- (-)	0·001 (2)	- (-)	0·15 (13)
I[c]	0·013 (22)	0·002 (2)	1·09 (115)	0·14 (14)
I[d]	0·015 (26)	0·005 (10)	0·94 (164)	0·33 (63)
II	0·010 (35)	0·009 (13)	0·56 (199)	0·38 (78)
III	0·025 (39)	0·009 (15)	1·17 (250)	0·50 (91)
IV	0·069 (52)	0·010 (15)	4·88 (323)	1·00 (93)
V	0·043 (41)	0·016 (9)	0·87 (251)	0·38 (62)

Koten, Smeets & Spek, 1990) crystallizes in the centrosymmetric space group $P2_1/c$, $a = 20·044$, $b = 9·8127$, $c = 20·857$ Å, $\beta = 110·52°$, and contains two diethyl ether molecules per unit cell, disordered over two inversion centres. A diethyl ether disorder model with distance constraints was used. Despite relatively high temperature factors of the ether atoms, the reasonable R value and the absence of high residual peaks in a difference Fourier map of this region validate this model. An empirical absorption correction (*DIFABS*; Walker & Stuart, 1983) was applied. For the results of Tables 1 and 2 the BYPASS method was applied before empirical absorption correction, because the BYPASS method can differentiate better between discrepancies of F_h^o and F_h^c, resulting from the omission of solvent or absorption artefacts, than the empirical absorption correction method (van der Sluis, 1989). The lower R value obtained by the BYPASS method indicates that the constrained model does not represent the electron density completely. Two MAIN cycles with two FS cycles were needed to reach convergence. Grid used = 0·213 Å.

Compound IV

Trichlorobis(dimethyl sulfoxide)(1-methylbenzimidazole)rhodium(III) dimethyl sulfoxide solvate (Smeets, Spek, Niele, Martens & Nolte, 1987) crystallizes in the centrosymmetric space group *Pbca*, $a = 14·088$, $b = 15·774$, $c = 20·623$ Å and contains 24 dimethyl sulfoxide molecules. Two of the unique dimethyl sulfoxide molecules are coordinated to the Rh atom and the third unique dimethyl sulfoxide molecule was found as a solvate molecule. The latter was omitted during the calculations for the purpose of this test. Grid used = 0·210 Å. One MAIN cycle with four FS cycles and one MAIN cycle with two FS cycles were needed to reach convergence.

Compound V

$(Mesityl)_4Li_2CrTHF_2.THF$ (Edema, Gambarotta, van Bolhuis, Smeets & Spek, 1989) crystallizes in space group $I222$, $a = 8·703$, $b = 14·130$, $c = 17·993$ Å. One ordered THF molecule is coordinated to the Li atom and one rigid THF molecule was refined on the 222 site with a disorder model. The latter was omitted during the test calculations. Because THF is a flexible molecule it is not surprising that the R value found by the BYPASS method is lower than the original. One MAIN cycle with two FS cycles and one MAIN cycle with one FS cycle were needed to reach convergence. Grid used = 0·207 Å.

Applications

In this section we discuss four applications of the BYPASS procedure to structures with severely disordered solvent.

Compound VI

2-Hydroxy-(5-{[4-(2-pyridinylamino)sulfonyl]-phenyl}azo)benzoic acid dimethylformamide solvate

hydrate (van der Sluis & Spek, 1990). The crystals are triclinic, space group $P\bar{1}$, $a = 7{\cdot}204$, $b = 11{\cdot}286$, $c = 28{\cdot}203$ Å, $\alpha = 87{\cdot}77$, $\beta = 87{\cdot}91$, $\gamma = 82{\cdot}81°$. Least-squares refinement of the ordered part of the structure converged at $R = 0{\cdot}096$. H atoms involved in hydrogen bonding could be located from a difference electron-density map but had to be refined with distance restraints. The difference map also showed a large infinite elliptically shaped channel along x, 0·85, 0·25 filled with nearly continuous residual density. No pronounced peaks are present and no definite *a priori* clues were available as to the nature of the contents of the solvent region, thus precluding refinement with a discrete-atom model. Subsequent refinement with the BYPASS procedure converged with one MAIN cycle with three FS cycles and one MAIN cycle with one FS cycle to $R = 0{\cdot}044$. Grid used = 0·24 Å. Distance restraints on the above mentioned hydrogen bonds were no longer necessary. Residual density $-0{\cdot}26 < \Delta\rho < 0{\cdot}24$ e Å^{-3}. Three different solvents are candidates for the interpretation of the density found in the channel: ethanol was used for the isolation of the compound and water and dimethylformamide (DMF) are used in the crystallization. Ethanol could be ruled out on the basis of NMR data that also indicated the presence of only one DMF molecule in the asymmetric unit. This DMF molecule is found in the ordered part of the structure. This indicates that the channel must be filled with disordered water. The electron count in the solvent channel yields 90·4 electrons equivalent with 4·5 water molecules in the asymmetric unit. The corresponding calculated density of 1·377 Mg m^{-3} is in good agreement with the experimental value 1·37 (1) Mg m^{-3}. The hydrophobic nature of the channel wall seems to be the cause of the disorder of the water molecules. A section at $y = 0{\cdot}175$ of the solvent Fourier map is presented in Fig. 3.

Compound VII

[(4-Nitrophenyl)triphenylphosphonium] bromide methanol solvate (van der Sluis, van der Vlist & Krabbendam, 1990). The crystals are monoclinic, space group $C2/c$, $a = 20{\cdot}794$, $b = 18{\cdot}900$, $c = 14{\cdot}547$ Å, $\beta = 107{\cdot}55°$. The crystals collapse vehemently when removed from the mother liquor. After solving the ordered part of the structure we found an irregular tubular electron density around $x = \frac{1}{2}$, $y = \frac{1}{2}$, $0 \le z \le 1$ in a difference Fourier map. Attempts to interpret this electron density in terms of methanol failed because of severe disorder. Simply attributing the scattering factor of C atoms with partial occupancies to peaks in a difference Fourier map resulted in an R value of 0·058, high standard deviations in the positional parameters of the atoms of the ordered part of the structure, slight but unexpected deviations from planarity of the phenyl rings and a high residual electron density (0·9 e Å^{-3}, not near the bromide ion). We therefore decided to apply the BYPASS method. After two MAIN cycles (with three and one FS cycles respectively) convergence was reached at $R = 0{\cdot}048$. The methanol was found to be inhomogeneously distributed in continuous channels formed by the hydrophobic phenyl groups of the ordered part of the structure around $x = \frac{1}{2}$, $y = \frac{1}{2}$ and symmetry-related positions. It can now be understood that the hydrophilic methanol molecules are disordered in the hydrophobic pocket and that they can easily escape from the crystals apparently resulting in the observed complete disrupture of the crystals. Summation over all grid points in the solvent Fourier map yielded just over two methanol molecules per asymmetric unit. The maximum residual densities found after the procedure are close to the bromide ion, and are interpreted as absorption artefacts. The standard deviations in positional parameters for the ordered part of the structure are halved compared with the results obtained with the discrete-atom approach, and the phenyl rings are now planar within 0·03 Å. Fig. 4 shows a section of the solvent Fourier map at $y = \frac{1}{2}$.

Compound VIII

Dichromium(II) bis(tetramethyldibenzotetraaza-[14]annulene)-toluene (1/2) (Edema, Gambarotta, van der Sluis, Smeets & Spek, 1989). Space group $P\bar{1}$, $a = 11{\cdot}610$, $b = 14{\cdot}843$, $c = 15{\cdot}554$ Å, $\alpha = 96{\cdot}93$,

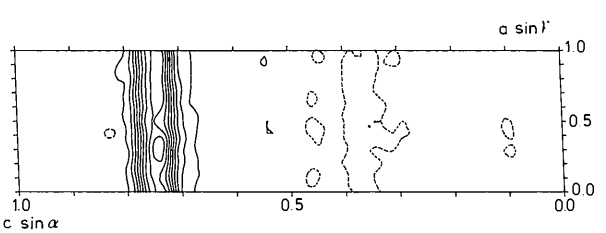

Fig. 3. A section at $y = 0{\cdot}175$ of the solvent Fourier map of compound VI. Contour levels starting at 0·00, increments 0·15, maximum 1·35 e Å^{-3}. Zero level dashed.

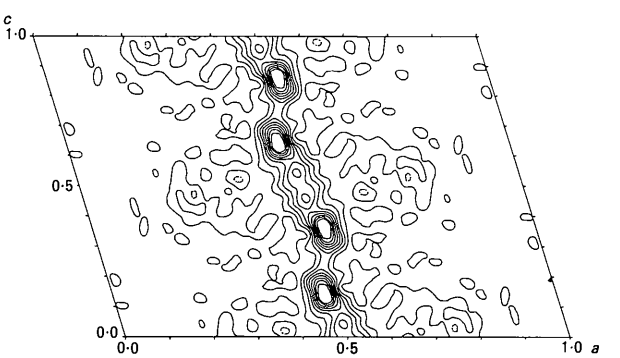

Fig. 4. A section at $y = 0{\cdot}5$ of the solvent Fourier map of compound VII. Contour levels starting at −0·30, increments 0·30, maximum 2·40 e Å^{-3}. Negative contour dashed.

$\beta = 102{\cdot}13$, $\gamma = 107{\cdot}50°$. Two solvent areas were identified, one clearly indicating a toluene molecule disordered over two orientations. Least-squares refinement with a disorder model converged at $R = 0{\cdot}079$. A large globular electron density was left near $(\frac{1}{2}, \frac{1}{2}, 0)$. Attempts to refine a disorder model in this region failed. Therefore the BYPASS method was applied. Convergence was reached after two MAIN cycles (with two and one FS cycles respectively) at $R = 0{\cdot}059$. Grid used = 0·187 Å. The standard deviations in structural parameters are now halved. Fig. 5 shows a section of the solvent Fourier map around $(\frac{1}{2}, \frac{1}{2}, 0)$ at $x = 0{\cdot}525$. It shows no recognizable features.

Compound IX

3α-Acetoxy-17β-butyroxy-2β,16β-dipiperidino-5α-androstane-16β-*N*-monoallyl bromide hydrate pentane solvate (Kooijman, Kanters, Kroon & Kelder, 1990). The compound crystallizes from methylene dichloride/pentane in the orthorhombic space group $P2_12_12_1$, $a = 38{\cdot}641$, $b = 15{\cdot}584$, $c = 6{\cdot}978$ Å. Convergence was reached at $R = 0{\cdot}113$. By means of the solvent determination method (according to Fig. 2) one water molecule with partial occupancy was found. Its presence was obscured by the detrimental influence of a disordered pentane molecule. Including this water molecule in the structural model resulted in an R value of 0·110. The pentane molecule was found severely disordered on a twofold axis. Although the electron density shows some features it was found impossible to refine a (rigid) pentane molecule. After the BYPASS method was applied using two MAIN with three FS cycles convergence was reached at $R = 0{\cdot}063$. Grid used = 0·205 Å. All unusual geometrical features present before the procedure was applied (large unexpected scatter in bond distances and angles and large anisotropy of the thermal motion ellipsoids of some atoms) were removed. Fig. 6 shows the solvent Fourier map at $z = 0{\cdot}375$ along the twofold axis at $x = \frac{1}{2}$, $y = \frac{1}{2}$.

Discussion

Test calculation I[a] shows that no electron density leaks into the solvent region from the surrounding structural model. Also this structural model is virtually unaffected. This result makes it possible to use the BYPASS method for solvent identification purposes.

In test calculation I[b] the number of electrons is reproduced within 1·5% (see Table 1). The hydroxyl H atom is hydrogen bonded. Therefore part of its electron density falls inside the van der Waals volume of the accepting O atom and therefore cannot be completely recovered. A somewhat lower value is therefore expected, as in all cases with hydrogen bonding. These effects are not likely to be found with severely disordered solvent molecules. In test calculation II it is found that better results were obtained with a solvent radius of 1·2 Å. This is used in order to describe the very small solvent area (*i.e.* a solvent area with a high curvature) adequately. The water H atoms could not be determined during the structure determination study, but were recovered by the

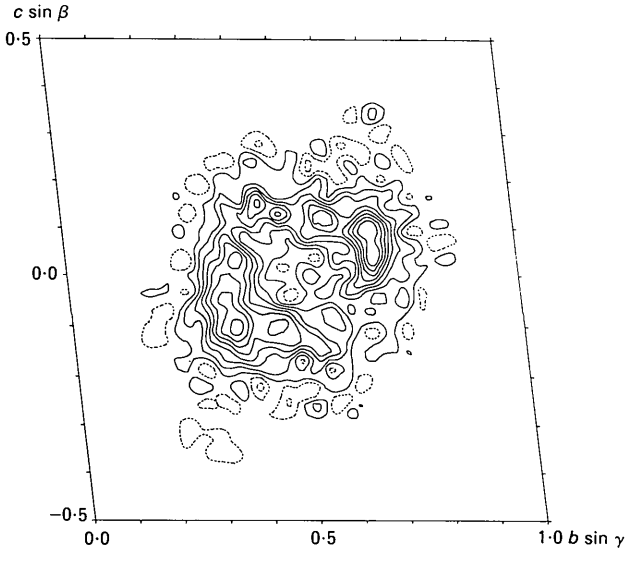

Fig. 5. A section at $x = 0{\cdot}525$ of the solvent Fourier map of compound VIII. Contour levels starting at −0·30, increments 0·20, maximum 1·50 e Å^{-3}. Negative levels dashed.

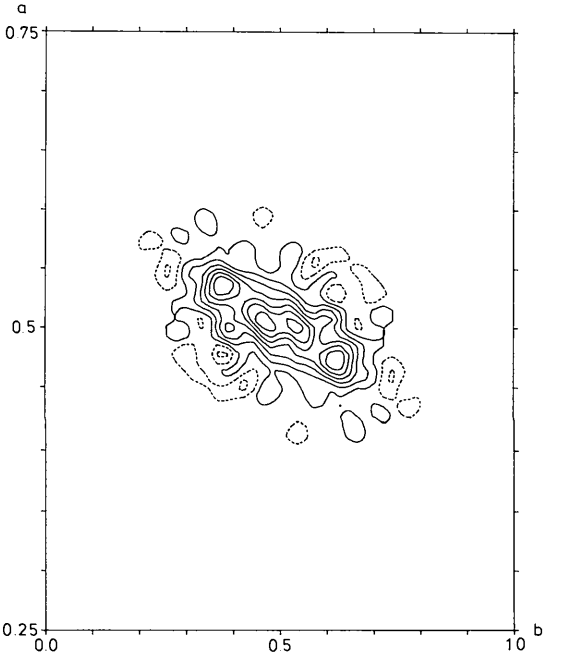

Fig. 6. A section at $z = 0{\cdot}357$ of the solvent Fourier map of compound IX. Contour levels starting at −0·40, increments 0·30, maximum 2·30 e Å^{-3}. Negative levels dashed.

BYPASS procedure. The hydroxyl H atoms are probably disordered. Test calculation III shows an overestimate of 6%. This is possibly due to interfering absorption artefacts. Calculations for compounds IV and V show excellent estimates for the number of electrons. All the applications show electron counts near integral or hemi-integral numbers, which is not surprising although there is no clear structural demand. For compound IX it is possible that part of the pentane is replaced by a more electron dense solvent (methylene dichloride). It can be concluded that taking into account the above mentioned effect the number of electrons can be reproduced well within 5%. Test calculations with all van der Waals radii increased or decreased 10% show changes less than 1% in the electron count. Also changes of the structural model were found to be insignificant (van der Sluis, 1989). This clearly shows that the boundary between solvent and ordered part of the structure is well chosen.

Furthermore a correspondence better than 30% is found between the volume of the solvent molecule in the crystal, as calculated by the program, and the molecular volume in liquid solvent at room temperature. The addition of 20% to the value of the liquid solvent volume gives a correspondence of better than 10% for the severely disordered solvent molecules of all applications. This increases the potential of the method in the identification of severely disordered solvent molecules.

From Table 2 it can be seen that in all cases all structural parameters improve considerably upon the application of the procedure. E.s.d.'s and deviations from the starting model introduced by refinement without the solvent model decrease by a factor 2–5.

The rate of convergence can be speeded up if a model of the solvent without structure (for instance assign the scattering factors of a C atom with $U = 0{\cdot}08$ Å^2 to all peaks found in a difference Fourier map, refining the population parameter) is used. This effect was tested with test runs with compounds IV and V (van der Sluis, 1989).

For the four applications it can be concluded that the structural model improves considerably upon application of the procedure. Unusual geometrical features disappeared and e.s.d.'s decreased by a factor 2–5. Furthermore, information was obtained about the number of electrons in the solvent area and its volume, as a guide to the identification of the solvent.

Refinement of disordered structures is often very time consuming, both in human time and in machine time, owing to poor convergence of the refinement. The present procedure eliminates most of the human intervention at the cost of some additional computing time.

We thank Dr H. Krabbendam for stimulating discussions and reading the manuscript.

Note added in proof: After acceptance of this paper, our attention was drawn to an Abstract [Rae & Baker (1984). *Acta Cryst.* A**40**, C428] that addresses the disordered solvent problem in a closely related manner.

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