A Procedure toward the Fully Automatic Method for Solving Crystal Structures

Kentaro YAMAGUCHI

School of Pharmaceutical Sciences, Showa University, 1–5–8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan.
Received July 29, 1992

A fully automatic procedure has been devised for crystal structure analysis by X-ray crystallography. Automatic decisions at each critical point of the analysis, at which user intervention used to be required, are provided based on empirical considerations. The new procedure, named FASE (Fully Automatic Structure Elucidation), simply refines the intense peaks using two-step weighted Fourier (WTF) calculations following phase determination. The molecular recognition based on the interpretation of electron-density maps is not necessary in this procedure. It is able to solve structures without any user intervention; the user simply inputs "FASE" to carry out this procedure. The complete structure is solved and displayed in most cases. This procedure has been applied to 137 crystals of organic compounds and 112 chemically significant structures were derived. The *R* values refined without any missing atom using isotropic refinement normally lie in the range of 0.15—0.30, which are acceptable values in such a rough stage (all non-hydrogen atoms are assigned as carbon). These results usually reached to the final structure, including hydrogen atoms with *R* values around 0.05, by further anisotropic refinement using appropriate methods.

Keywords crystallography; X-ray; crystal structure; phase determination; molecular structure; automatic solution

Introduction

Recent progress in X-ray crystallography has made it possible to accomplish the immediate solution of the molecular structure of organic compounds in most cases. However, the solution procedure still requires user decisions at critical points of the analysis. This often makes X-ray analysis seem difficult to researchers with no expertise in the field of crystallography. In this report, a fully automatic procedure for crystal structure solution without any user intervention is described.

The computer programs for molecular structure analysis in X-ray crystallography are available as packages which include solution, refinement and other useful programs. UNICSIII,[1] SHELXS,[2] XTAL,[3] TEXAN,[4] CRYSTALS,[5] SRI88[6] and CRYSTAN[7] are popular program packages available worldwide. The automatic procedure has recently been implemented into the package UNIQUE (CRYSTALS+SIR88).[8a] In the new package named FASE (Fully Automatic Structure Elucidation) presented here, quick and reliable structure elucidation is conducted completely automatically.

Although the automatic procedure involves several critical points at which user intervention is required, there are two major problems: (a) the estimation of the chemical significance of the trial solution and (b) the refinement of the solution for recovery of the complete structure. In general, molecular recognition is necessary to solve these problems. Concerning problem (a), a typical procedure for the interpretation of electron-density maps involves four steps: (1) peak search; (2) separation of peaks into clusters; (3) application of stereochemical criteria to produce molecular fragments; (4) comparison of the fragments with the expected molecular model (discussed by Main and Hull in 1978[8b]) or (4′) labelling of atomic peaks in terms of atomic species (discussed by Cascarano *et al.* in 1991[8a]). Steps (1) and (2) are well established. However, steps (3) and (4) or (4′) involving the assignment of the atomic species and interatomic relationships are still rather complicated and difficult. As regards problem (b), the recovery of the complete structure is done by several cycles of least-squares calculations together with Fourier calculations, taking account of the chemical significance. In the procedure presented here, molecular recognition and peak interpretation as mentioned above are not necessary. This new procedure simply refines the intense peaks using two-step weighted Fourier (WTF) calcula-

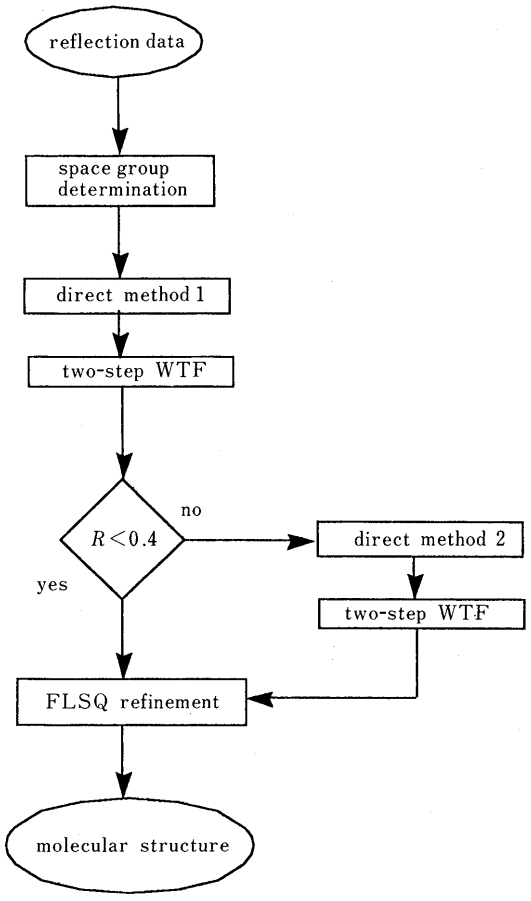

Chart 1

tions following phase determination. This simple method achieved effective structure elucidation in most cases, overcoming both problems (a) and (b).

In consequence, even the researchers with no expertise of crystallography, such as chemists, will be able to solve the crystal structure directly and easily.

Methods

An outline of this procedure, FASE, is shown in the scheme. After the reflection data measured by the diffractometer are reduced, the space-group is determined based on the reflection conditions. The phase determination is done by the direct method using SAPI85[9] (direct method 1) and the two-step WTF calculation is applied. If the structure has not been solved, the other direct method MULTAN78[10] (direct method 2) is activated. Then, the procedure executes full-matrix least-squares refinement (FLSQ)[11] with isotropic thermal parameters[12] when the structure has been solved. Hydrogen atoms are not taken into account in this procedure and all non-hydrogen atoms are assigned as carbon. The final result is shown on the graphic display using PLUTO.[13] In this procedure, three critical points are involved: (1) space-group determination; (2) assessing the reliability of trial solutions in the direct method; (3) evaluation of the determined phase.

The space-group determination and the refinement are basically done with the programs included in the package RCRYSTAN.[14] In order to avoid interrupting this procedure, the most frequently appearing space-group in the articles involving X-ray analysis was selected among the possibilities, if a unique space-group was not obtained. The reliability of the trial solutions is estimated using the combined figure of merit (CFOM) calculated in the program SAPI85. The judgement as to whether the structure is solved or not at the point just after the phase determination is the most important step in this procedure. In this procedure, the two-step WTF calculation is applied instead of molecular recognition and peak interpretation, as mentioned in the introduction.

The two-step WTF calculation begins with the first WTF using the most intense $NP1$ peaks from the E map supplied with phase determination, then the second WTF follows using $NP2$ intense peaks obtained from the previous step. The number of peaks for the first WTF ($NP1$) and second WTF ($NP2$) are chosen according to

$$NP1 = 0.8NA \quad (1)$$

$$NP2 = NA \quad (2)$$

NA is the number of atoms to be determined, which should be supplied at an early stage. The most effective two-step WFT calculation has been derived from various trials using other possible combinations of number of steps and value of coefficient. The coefficient 0.8 is an empirical result suited for this system. If the R value which is calculated before the second WFT is less than 0.40,[15] then the phase determination is estimated to be successful and the refinement (FLSQ) follows. When the R value is above 0.40, the other direct method MULTAN78 is executed to create another solution. However, no other trials are executed if this fails. This empirical decision without molecular recognition usually brings quick success in molecular structure determination.

The program package FASE is composed of 104 sub-program units written in FORTRAN77 and 41 control command procedures written in shell script (C-shell) on the UNIX operating system. A PANAFACON A70 computer was used for this experiment. All the reflection data were collected on a Rigaku AFC-5 diffractometer with standard parameters.

The procedure starts with input "FASE" after the necessary crystal parameters (title, formula, cell dimensions and Laue symmetry) and the reflection data [H, K, L, F_O and $\sigma(F_O)$] are provided.

Results and Discussion

This procedure has been applied to crystals of 137 organic compounds. The structure of 80 crystals were solved by direct method 1 using SAPI85 and those of 32 crystals by direct method 2 with MULTAN78. Table I lists the 112 successfully determined structures. Entry number (No.), reference (Ref.), formula of the molecule, molecular weight (MW), space group (SPG), number of planes (NOP), number of molecules in the unit cell (Z), number of atoms to be determined (NA), number of incorrectly located atoms (NU), time required for elucidation (T) (min), and R factors ($\times 1000$) calculated before final WFT ($R1$), after final isotropic refinement ($R2$) and after manually refined final step including hydrogen atoms with anisotropic thermal parameters ($R3$) are shown in Table I.

The highest MW was 848 throughout these analyses, which confirmed the applicability of this method to general organic molecules. The shortest computing time of 3 min for the whole calculation suggests that a quick solution would be obtained even with a slower, older computer. This procedure was also tested on a fast new computer (Kubota TITAN 1500) equipped with the vector processor. It was 8 to 12 times faster in executing some of these analyses. The accuracy of the solution using this procedure is acceptable because NU was 0 in most cases. A chemically significant structure was determined even in a case in which 4 atoms were incorrectly located out of 27 atoms (No. 33). Refined $R2$ values without a missing atom were usually in the range of 0.15—0.30, estimated to be good values in such a rough stage (all non-hydrogen atoms are assigned as carbon),[16] which also implies that the results using 2-cycle FLSQ refinement with isotropic thermal parameters are acceptable. Further refinement using appropriate methods usually yielded the complete structure. Although the primitive lattice appeared so often, it is concluded to be applicable to general organic crystals because the structures of various crystal systems including symmetric and asymmetric space groups were successfully determined. The 25 unsolved crystals were further analyzed manually. The problems in these cases involve the failure of atomic species assignment for the most part. A few examples in which the phase determination failed were observed. Nevertheless, the two-step complementary phase determination, using two types of direct methods, SAPI85 and MULTAN78, is able to solve structures in a great majority of cases.

Some results using this procedure are shown in Figs. 1 to 6. A methylchlorothricolide derivative (No. 79) was determined without any missing atom (Fig. 1). Though the structure is exhibited as a ball and stick model without discrimination of the atomic species, it should be possible to draw its constitutional formula. An ORTEP stereo view of this compound which was further refined manually to the final stage ($R=0.054$) is shown in Fig. 2. It is almost identical with a previous PLUTO view which was refined using this procedure ($R=0.213$). Figure 3 shows the result for another methylchlorothricolide derivative (No. 80) with three incorrect atoms. The incorrectly located atoms, indicated by closed circles, could be placed at the proper positions (shown by dotted lines) on the basis of other analytical results and chemical considerations. Figure 4 is the result for a relatively large natural product molecule (No. 15) with two incorrect atoms (absolute configuration is reversed). The analytical result for a synthetic highly symmetrical trianilide (No. 3) is presented in Fig. 5. All atoms are located correctly in this case. Figure 6 shows an example in which the determination failed. Though the phase seems to be determined correctly, it is sometimes difficult to determine the structure even in the case of a small, simple compound. The failure was probably

TABLE I. Analytical Results

No.	Ref.	Formula	MW	SPG	*NOP*	*Z*	*NA* (*NU*)	*T*	*R*1	*R*2	*R*3
1	32	$C_{12}H_{10}N_2O_2$	214	$Pca2_1$	955	4	16 (0)	15	244	144	50
2	35	$C_{22}H_{20}N_2O_2$	344	$P2_1/a$	1624	2	13 (0)	12	353	296	72
3	35	$C_{30}H_{27}N_3O_3$	477	$P2_1/n$	4416	4	36 (0)	47	298	198	57
4	42	$C_{14}H_{21}N_3O_2$	263	$P2_1/a$	2690	4	19 (0)	19	258	174	45
5	35	$C_{42}H_{46}N_8O_4$	726	$P2_1/c$	3191	2	27 (0)	41	277	178	57
6	38	$C_{24}H_{21}N_3O$	367	$P\bar{1}$	1697	1	28 (2)	45	359	351	42
7	42	$C_9H_{11}N_3O_3$	209	$P42_1c$	1823	8	15 (2)	15	213	155	52
8	44	$C_{12}H_8N_4O$	224	$P2_1/n$	1030	4	17 (0)	11	340	156	63
9	up[b]	$C_{12}H_{16}N_2O_5$	268	$P2_12_12_1$	1142	4	19 (1)	39	340	361	90[a]
10	up	$C_{15}H_{18}O_4$	262	$P2_1/n$	2277	4	19 (0)	16	323	260	68
11	up	$C_{27}H_{18}O_6$	438	$P2_1/c$	3728	4	33 (0)	35	302	194	68
12	up	$C_{12}H_{16}N_2O_5$	268	$P2_12_12_1$	1149	4	19 (0)	41	233	163	44
13	up	$C_{27}H_{18}O_6$	438	$Pbca$	3836	8	33 (1)	42	379	304	66
14	up	$C_{33}H_{33}N_3O_3$	519	$Pbca$	4542	8	39 (0)	71	261	219	58
15	up	$C_{45}H_{68}O_{15}$	848	$P2_12_12_1$	3846	4	60 (2)	87	321	217	76
16	up	$C_{22}H_{18}Cl_2N_2O_2$	413	$P2_1/c$	3414	4	28 (0)	44	301	193	83[a]
17	up	$C_{15}H_{11}NO_3$	253	$P2_1/a$	3725	4	19 (0)	53	201	172	46
18	up	$C_{12}H_{12}N_2O_4$	248	$P2_12_12_1$	1070	4	18 (0)	15	240	162	46
19	up	$C_{16}H_{14}N_6$	290	$P2_1/n$	1035	2	11 (0)	10	279	196	146[a]
20	up	$C_{14}H_{12}N_4$	236	$Pcab$	1756	8	18 (0)	23	224	144	49
21	up	$C_{17}H_{13}N_3O_2$	291	$P\bar{1}$	1969	2	22 (0)	18	334	219	87
22	21	$C_8H_5N_5$	171	$P2_1/a$	1253	4	13 (0)	13	248	156	48
23	19	$C_9H_9N_3$	159	$P2_1/n$	2805	8	24 (0)	24	258	204	53
24	19	$C_{10}H_{11}N_3$	173	$Pcab$	1524	8	13 (0)	30	175	168	60
25	33	$C_{15}H_{20}N_2O_3$	276	$P2_1/c$	2076	4	20 (1)	30	370	285	70
26	24	$C_{10}H_7N_5$	197	$P2_1nb$	795	4	15 (1)	12	301	237	44
27	18	$C_8H_5N_7$	199	$P2_1/a$	1205	4	15 (0)	11	356	239	146[a]
28	up	$C_2H_2N_6S$	142	$P2_1/a$	805	4	9 (0)	19	286	193	74
29	25	$C_{13}H_{12}N_4$	224	$P2_1/a$	1662	4	17 (0)	15	271	176	55
30	20	$C_8H_7N_5O$	189	$P2_1/n$	1271	4	14 (0)	22	282	199	45
31	17	$C_{15}H_{13}NO_2$	239	$P\bar{1}$	1768	2	18 (0)	16	276	190	60
32	43	$C_6H_4N_4O_2$	164	$Pcab$	692	8	12 (0)	3	283	158	49
33	42	$C_{22}H_{21}N_3O_2$	359	$P2_1$	1496	2	27 (4)	36	381	352	43
34	22	$C_8H_5N_5$	171	$P2_1/a$	1229	4	13 (0)	12	324	186	60
35	27	$C_6H_{10}N_4$	138	$P2_1/a$	1083	4	10 (0)	20	257	169	58
36	27	$C_5H_7N_3O$	125	$P2_12_12_1$	670	4	9 (1)	9	393	477	57
37	27	$C_{10}H_9N_3O$	187	$P2_1/n$	1527	4	14 (0)	13	297	278	50
38	27	$C_{13}H_{13}N_3$	211	$Pcab$	1633	8	16 (0)	21	286	182	47
39	27	$C_{10}H_9N_3$	171	$P2_1/c$	1293	4	13 (0)	11	307	196	55
40	34	$C_{30}H_{21}N$	395	$P\bar{1}$	3485	2	31 (0)	21	355	282	48
41	31	$C_8H_5N_7$	171	$P2_1/n$	1250	4	15 (0)	14	257	163	69
42	39	$C_{11}H_{10}N_4O$	214	$P2_12_12_1$	928	4	16 (1)	29	318	304	49
43	29	$C_{12}H_6N_2O$	194	$P\bar{1}$	1332	1	30 (1)	28	350	289	49
44	27	$C_{11}H_{10}N_4O$	214	$P2_1/n$	1617	4	16 (0)	16	265	197	48
45	27	$C_{11}H_{10}N_4O$	214	$P2_12_12_1$	930	4	16 (1)	26	338	242	50
46	38	$C_{10}H_9N_3O$	187	Pc	664	2	14 (1)	23	381	418	36
47	up	$C_{14}H_{16}N_2O_4S$	308	$P\bar{1}$	2172	2	21 (1)	25	399	369	57
48	up	$C_{17}H_{15}FN_2O_4$	330	$P2_12_12_1$	1578	4	24 (0)	35	330	249	111
49	23	$C_{15}H_{18}N_4O_5$	334	$P2_12_12_1$	1372	4	24 (0)	23	292	200	43
50	up	$C_{23}H_{16}N_4S_3$	444	$P2_1/a$	3775	4	30 (2)	32	391	281	62
51	28	$C_{12}H_8N_2O$	196	$C2/c$	1716	8	15 (0)	29	325	270	60
52	32	$C_{12}H_{11}N_3O$	213	$P2_1/a$	1171	4	16 (0)	15	352	398	48
53	up	$C_{13}H_{12}N_2O$	212	$Pc2_1n$	881	4	16 (1)	19	336	303	58
54	41	$C_{12}H_7F_4N_3O$	285	$P2_1/n$	1725	4	20 (0)	16	342	250	55
55	32	$C_{13}H_{13}N_3O$	227	$P\bar{1}$	2960	2	34 (0)	37	270	170	59
56	40	$C_{14}H_2F_{10}N_2O_2$	420	$P2_1/n$	1079	2	14 (0)	12	322	355	40
57	up	$C_{16}H_{20}N_2O_3$	288	$C2/c$	4041	24	63 (0)	78	301	156	44
58	up	$C_{17}H_{18}N_2O_3$	298	$P2_12_12_1$	1296	4	22 (0)	25	219	146	39
59	32	$C_{22}H_{20}N_2O_2$	344	$Pcab$	1597	4	13 (0)	18	280	247	60
60	up	$C_{22}H_{20}N_2O_2$	344	$P2_1/n$	3155	4	26 (0)	42	282	270	64
61	up	$C_{22}H_{20}N_2O_2$	344	$P2_1/a$	3355	4	26 (0)	49	277	231	58
62	up	$C_{20}H_{20}N_2O_2$	344	$P\bar{1}$	5532	4	52 (0)	89	307	201	60
63	up	$C_{38}H_{34}N_4O_4$	610	$P2_1/n$	2448	2	23 (0)	22	296	225	58
64	35	$C_{22}H_{20}N_2O_2$	344	$P2_1/n$	2768	4	26 (0)	26	270	220	64
65	35	$C_{22}H_{20}N_2O_2$	344	$P2_1/a$	1378	4	13 (0)	14	353	296	72
66	35	$C_{30}H_{27}N_3O_3$	477	$P2_1/n$	3864	4	36 (0)	51	298	198	57
67	up	$C_{17}H_{18}N_2O_3$	298	$P2_12_12_1$	1309	4	22 (0)	17	213	156	44
68	up	$C_{16}H_{18}N_2O_2$	270	$P2_1$	2118	4	40 (0)	35	258	144	64

TABLE I. (continued)

No.	Ref.	Formula	MW	SPG	*NOP*	*Z*	*NA* (*NU*)	*T*	*R*1	*R*2	*R*3
69	up	$C_{12}H_{11}N_3O$	213	$P2_1nb$	845	4	16 (2)	21	351	344	63
70	30	$C_{13}H_{10}N_4O$	238	$C2/c$	1654	8	18 (0)	22	311	177	63
71	37	$C_{17}H_{23}ClN_2O_2$	338	$P\bar{1}$	2746	2	22 (3)	40	415	418	81[a]
72	up	$C_{12}H_{12}N_2OS$	232	$Pcab$	1714	8	16 (0)	36	401	464	66
73	up	$C_{15}H_{16}O_7$	308	$P2_1/n$	2109	4	22 (0)	21	287	212	51
74	up	$C_9H_8O_2$	148	$P2_1/n$	1158	4	11 (0)	9	308	222	56
75	up	$C_{12}H_{17}NO$	191	$P\bar{1}$	1675	2	28 (1)	35	308	323	55
76	up	$C_{20}H_{30}O_2$	302	$P2_12_12_1$	1502	4	22 (1)	33	325	232	69
77	up	$C_{17}H_{18}N_2O_2$	282	$P\bar{1}$	4665	4	84 (2)	97	351	298	74
78	26	$C_{34}H_{48}O_9$	600	$P\bar{1}$	4774	2	43 (1)	74	393	258	68
79	26	$C_{30}H_{40}O_7$	512	$P2_1/a$	4044	4	37 (0)	50	282	213	54
80	26	$C_{34}H_{48}O_9$	600	$P2_12_12_1$	2775	4	43 (3)	122	358	247	63
81	26	$C_{31}H_{40}O_8$	540	$P2_1/n$	2851	4	39 (2)	59	399	310	104
82	36	$C_{17}H_{15}FN_2O$	282	$P2_1$	1115	4	22 (0)	18	320	191	49
83	up	$C_{23}H_{27}NO_4$	381	$P2_1/c$	3068	4	28 (1)	45	399	383	76
84	up	$C_{22}H_{26}N_2O_3$	366	$P2_1/c$	2901	4	27 (0)	27	327	217	64
85	up	$C_{24}H_{30}N_2O_3$	394	$P2_1/a$	3297	4	29 (0)	33	324	219	68
86	up	$C_{24}H_{30}N_2O_3$	394	$P2_1/a$	3323	4	29 (0)	53	315	220	60
87	up	$C_{36}H_{32}N_4O_2$	552	$P2_1/a$	2133	2	21 (0)	32	312	211	65
88	up	$C_{42}H_{46}N_8O_4$	726	$P2_1/c$	2831	2	27 (0)	43	277	178	57
89	up	$C_{24}H_{26}N_4O_2$	402	$P2_1/a$	1607	2	15 (0)	14	272	220	63
90	up	$C_{23}H_{20}N_2O$	340	$P2_1$	1495	2	26 (0)	44	227	131	41
91	up	$C_{33}H_{36}N_6O_3$	564	$P\bar{1}$	4472	2	42 (0)	73	305	195	55
92	up	$C_{42}H_{46}N_8O_4$	726	Pa	2922	2	54 (1)	65	383	297	55
93	up	$C_{28}H_{28}N_4O_2$	452	$P2_1/a$	1736	4	17 (0)	26	246	168	46
94	up	$C_{15}H_{16}N_2O$	240	$P2_1/a$	1861	4	18 (0)	16	285	189	62
95	up	$C_{13}H_{17}NO_2S$	267	$P2_1/c$	2017	4	17 (1)	29	450	487	56
96	up	$C_{15}H_{13}NO$	223	$P\bar{1}$	7410	8	68 (1)	260	478	257	230[a]
97	up	$C_{24}H_{26}N_4O_2$	402	Cc	1927	4	30 (0)	25	376	285	42
98	up	$C_{33}H_{36}N_6O_3$	564	Cc	2208	4	42 (1)	43	373	295	45
99	up	$C_{14}H_{13}NO$	211	$P2_1/c$	1687	4	16 (0)	26	270	174	52
100	up	$C_{14}H_{13}NO$	211	$Pbca$	1728	4	16 (0)	38	311	200	57
101	up	$C_{15}H_{15}NO$	225	$Pbac$	1872	4	17 (0)	39	326	204	59
102	up	$C_{15}H_{15}NO$	225	$Pnca$	924	4	8 (1)	11	390	394	64
103	up	$C_{17}H_{19}NO$	253	Cc	2178	4	38 (2)	55	332	274	77
104	up	$C_{16}H_{17}NO$	239	$P2_1/a$	2061	4	18 (0)	17	297	245	58
105	up	$C_{15}H_{15}NO$	225	$Pbn2_1$	1000	4	17 (0)	13	391	251	42
106	up	$C_{16}H_{17}NO$	239	$P2_1/n$	2000	4	18 (0)	27	274	185	47
107	up	$C_{16}H_{17}NO$	239	$P\bar{1}$	2002	4	18 (0)	16	284	178	51
108	up	$C_{18}H_{21}NO$	267	$P\bar{1}$	2237	2	20 (0)	31	237	165	47
109	up	$C_{13}H_{14}N_2O_4S$	294	$P2_1/c$	2029	4	20 (0)	31	399	312	130[a]
110	up	$C_{12}H_{14}N_2O_2$	250	$P2_12_12_1$	1063	4	16 (1)	16	334	309	61
111	up	$C_{18}H_{23}O_{10}$	399	$P2_12_12_1$	1863	4	35 (2)	52	334	294	48
112	up	$C_{20}H_{20}N_2O_3S$	368	$P2_1/n$	2808	4	26 (0)	52	399	353	38

Symbols appearing in the first column are explained in the text. *a*) H-atoms were not refined. *b*) up: unpublished data.

caused by the problems of peak selection after the WFT calculation.

The limitations of this procedure basically arise from the failure of the phase determination and peak selection. The nature of the difficulties may be summarized as follows. (1) High molecular weight; while no large molecule over MW 1000 was tested, the structures of larger molecules are generally more difficult to elucidate. (2) High complexity; molecules of moderate complexity were elucidated successfully, and simple, small molecules or plane structure required only a short calculation time. (3) Presence of heavy atoms; because the atomic species have not been discriminated at this point, determination of some structures including extremely heavy atoms compared to carbon was unsuccessful. This can be mainly ascribed to the discrepancy of the estimated thermal parameters. An atomic species identification routine will be added to this procedure to overcome this problem. (4) Use of low quality reflection data; low quality reflection data caused by relatively poor crystal quality, including thermal vibration of the atoms, result in unsatisfactory precision of the analysis.

In conclusion, this procedure FASE [(SAPI85, or MULTAN78, *etc.*)+2WTF+FLSQ] is useful for the structure determination of organic compounds. Fully automatic computerized structure determination based on X-ray crystallography seems to be difficult because of the necessity for decisions at certain critical points at which sophisticated crystallographic and chemical consideration might be required. However, in this procedure, a solution can be derived in most cases without any chemical structural consideration to recognize the molecule on the *E* map afforded each Fourier calculation following phase determination. This simply suggests that if correct phase angles are determined, the intense peaks on the *E* map are always correct. The problem is, whether all the intense peaks should be taken as valid. This procedure adopts 80% as an empirical value to optimize the elucidation

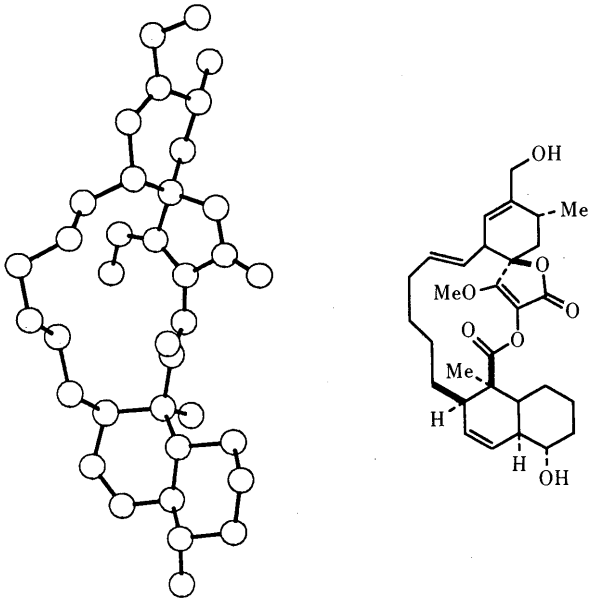

Fig. 1. Synthesized Methylchlorothricolide Derivative (No. 79)

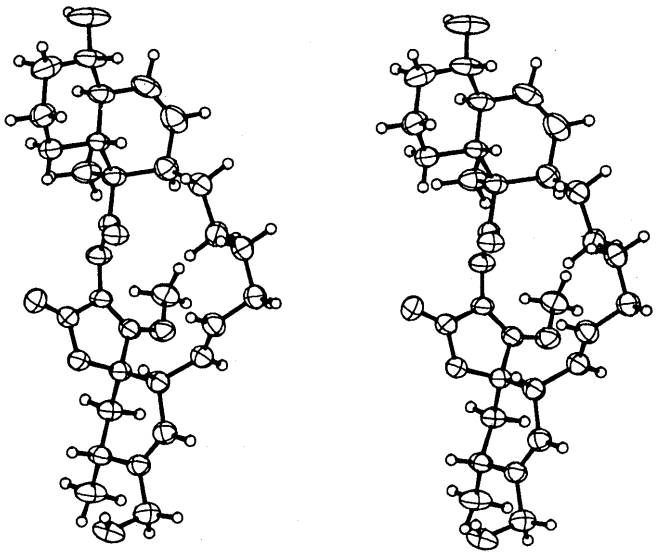

Fig. 2. ORTEP Drawing of Further Refined No. 79 (stereo view)

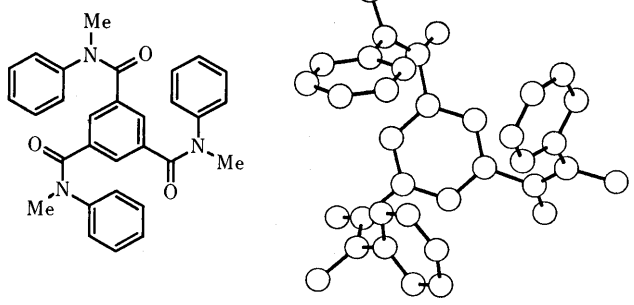

Fig. 5. Synthetic *N*-Methylamide Derivative (No. 3)

system. Although it is expected that the procedure would be even more useful if a quick molecular recognition routine is added to this program, this method already provides acceptable results.

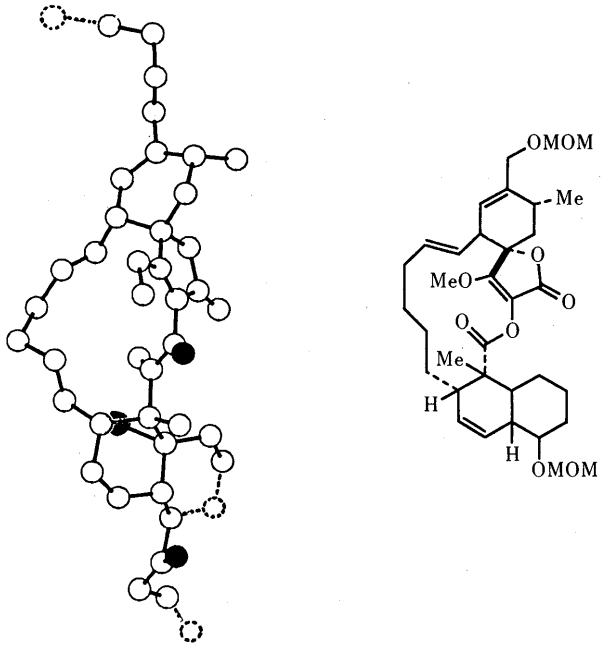

Fig. 3. Synthesized Methylchlorothricolide Derivative (No. 80)

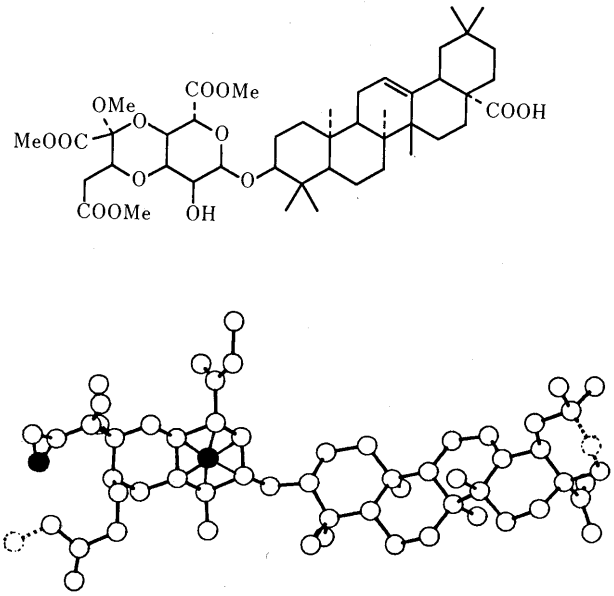

Fig. 4. The Example of Natural Product (No. 15)

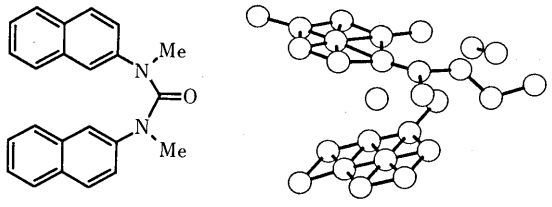

Fig. 6. Example of Unsuccessful Elucidation

Acknowledgement Professor Koichi Shudo, Tokyo University, is thanked for sharing his ideas during discussions, as well as for his critical comments and suggestions on the manuscript. Professor Go Matsumura, Showa University, is appreciated for useful discussions. Thanks are also due to Ms. Emi Yasudome, Showa University, for her technical assistance in testing various crystals using this procedure.

References and Notes

1) T. Sakurai and K. Kobayashi, *Rep. Ins. Phys., Chem. Res.*, **55**, 69 (1979).
2) G. M. Sheldric, Univ. of Cambridge, England, 1976.
3) S. R. Hall, J. M. Stewart and R. J. Munn, *Acta Crystallogr., Sect. A*, **36**, 979 (1980).
4) Rigaku Corp. Tokyo, 1988.
5) D. J. Watkin, J. R. Carruthers and P. V. Betteridge, Univ. of Oxford, 1985.
6) G. Cascarano, C. Giacovazzo, M. C. Burla, A. Nunzi, G. Polidori, M. Camalli, R. Spagna and D. Viterbo, Proc. Ninth Eur. Crystallogr. Meet., Torino, 1985, Abstr., pp. 1-46.
7) H. Burzlaff, R. Bohme and M. Gomm, Univ. of Erlangen, Germany, 1977.
8) *a*) G. Cascarano, C. Giacovazzo, G. Camalli, R. Spanga and D. J. Watkin, *Acta Crystallogr., Sect. A*, **47**, 373 (1991); *b*) P. Main and S. E. Hull, *Acta Crystallogr., Sect. A*, **34**, 353 (1978).
9) J.-X. Yao, C.-D. Zheng, J.-Z. Qian, F.-S. Han, Y.-X. Gu and H.-F. Fan, SAPI85, a Computer Program for Automatic Solution of Crystal Structure from X-Ray Diffraction Data, Institute of Physics, Chinese Academy of Sciences, Beijing, China, 1985.
10) P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, MULTAN78, a System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data, Univs. of York, England, and Louvain, Belgium, 1978.
11) Though the block-diagonal least-squares (BLS) method was tested, FLSQ was effective and even faster in such a rough stage.
12) Since atomic species were not discriminate in this procedure, an isotropic refinement was suitable compared to an anisotropic one.
13) W. D. S. Motherwell and W. Clegg, PLUTO, Program for Plotting Molecular and Crystal Structures, Univ. of Cambridge, England.
14) Rigaku Corporation, RCRYSTAN: X-Ray Analysis Program System, Rigaku Corporation, Tokyo, Japan, 1985.
15) Though other values were tested, 0.40 was the most reliable one.
16) Higher R values were recorded when the crystal included heteloritic atom(s).
17) K. Yamaguchi, A. Ohsawa, T. Itoh and C. Kawabata, *Yakugaku Zasshi*, **108**, 1040 (1988).
18) T. Kaihoh, T. Itoh, K. Yamaguchi and A. Ohsawa, *J. Chem. Soc., Chem. Commun.*, **1988**, 1608.
19) K. Yamaguchi, A. Ohsawa, T. Kaihoh, T. Itoh, M. Okada, C. Kawabata and H. Igeta, *Acta Crystallogr., Sect. C*, **45**, 1902 (1989).
20) K. Yamaguchi, A. Ohsawa, T. Itoh and C. Kawabata, *Acta Crystallogr.*, Sect. C, **46**, 261 (1990).
21) K. Yamaguchi, A. Ohsawa, T. Kaihoh, T. Itoh and C. Kawabata, *Acta Crystallogr., Sect. C*, **46**, 821 (1990).
22) K. Yamaguchi, A. Ohsawa, T. Kaihoh and T. Itoh, *Acta Crystallogr., Sect. C*, **46**, 1161 (1990).
23) K. Yamaguchi, H. Hayakawa, H. Ashizawa, H. Tanaka and T. Miyashita, *Acta Crystallogr., Sect. C*, **46**, 1065 (1990).
24) K. Yamaguchi, A. Ohsawa and C. Kawabata, *Acta Crystallogr., Sect. C*, **46**, 1751 (1990).
25) T. Itoh, M. Okada, K. Nagata, K. Yamaguchi and A. Ohsawa, *Chem. Pharm. Bull.*, **38**, 2108 (1990).
26) K. Takeda, Y. Igarashi, K. Okazaki, E. Yoshii and K. Yamaguchi, *J. Org. Chem.*, **55**, 3431 (1990).
27) K. Yamaguchi, A. Ohsawa and T. Itoh, *Acta Crystallogr., Sect. C*, **46**, 2177 (1990).
28) K. Yamaguchi, Y. Itoh, A. Ohsawa and H. Igeta, *Acta Crystallogr., Sect. C*, **46**, 2260 (1990).
29) K. Yamaguchi, Y. Itoh, A. Ohsawa and H. Igeta, *Acta Crystallogr., Sect. C*, **46**, 2263 (1990).
30) S. Kamiya, K. Yamaguchi, M. Miyahara and N. Miyata, *Chem. Pharm. Bull.*, **38**, 3226 (1990).
31) K. Yamaguchi, T. Kaihoh, T. Itoh and A. Ohsawa, *Acta Crystallogr., Sect. C*, **47**, 590 (1990).
32) K. Yamaguchi and K. Shudo, *J. Agric. Food Chem.*, **39**, 793 (1991).
33) K. Yamaguchi, T. Itoh, K. Nagata, M. Okada and A. Ohsawa, *Acta Crystallogr., Sect. C*, **47**, 1763 (1991).
34) K. Yamaguchi, T. Itoh, M. Okada and A. Ohsawa, *Acta Crystallogr., Sect. C*, **47**, 1764 (1991).
35) K. Yamaguchi, G. Matsumura, H. Kagechika, I. Azumaya, Y. Ito, A. Itai and K. Shudo, *J. Am. Chem. Soc.*, **113**, 5474 (1991).
36) Y. Takeuchi, N. Itoh, H. Note, T. Koizumi and K. Yamaguchi, *J. Am. Chem. Soc.*, **113**, 6318 (1991).
37) M. Ogawa, H. Matsuda, H. Eto, T. Kuraishi, A. Iwasa, T. Nakashima and K. Yamaguchi, *Chem. Pharm. Bull.*, **39**, 2301 (1991).
38) K. Yamaguchi, T. Itoh, T. Kaihoh and A. Ohsawa, *Acta Crystallogr., Sect. C*, **47**, 2193 (1991).
39) K. Yamaguchi, T. Itoh, M. Ohsawa and G. Matsumura, *Acta Crystallogr., Sect. C*, **47**, 2256 (1991).
40) K. Yamaguchi, G. Matsumura, N. Haga and K. Shudo, *Acta Crystallogr., Sect. C*, **48**, 556 (1992).
41) K. Yamaguchi, G. Matsumura, N. Haga and K. Shudo, *Acta Crystallogr., Sect. C*, **48**, 558 (1992).
42) K. Yamaguchi, G. Matsumura, M. Tanno, S. Sueyoshi and N. Miyata, *Acta Crystallogr., Sect. C*, **48**, 1051 (1992).
43) K. Yamaguchi, H. Takahashi, T. Kaihoh, T. Itoh, M. Okada, K. Nagata, G. Matsumura and A. Ohsawa, *Acta Crystallogr., Sect. C*, **48**, 964 (1992).
44) K. Yamaguchi, Y. Takahashi, T. Itoh and A. Ohsawa, *Acta Crystallogr., Sect. C*, **48**, 1152 (1992).