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A Refinement of the Crystal Structure of Diketopiperazine (2,5-Piperazinedione)*

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The crystal structure of 2,5-diketopiperazine, 'glycine anhydride', which was first determined by Corey in 1938, has been refined on the basis of complete three-dimensional intensity data obtained from molybdenum *X*-radiation. The structural parameters for the heavy atoms, including individual anisotropic temperature factors, were refined by difference maps and least-squares methods; the positions of the hydrogen atoms were located from a difference map. The final *R* factor is 0·072 for 1144 observed reflections and the standard deviations in the positional parameters of the heavy atoms are about 0·0013 Å.

The structure is essentially that found by Corey with the exception of the observed length of the C–C bond which has changed from 1·47 to 1·499 Å and of the $C(H_2)$–N bond which has changed from 1·41 to 1·449 Å. Both of these distances are still significantly shorter than normal single-bond distances.

The apparent N–H distances is 0·86 Å and the apparent C–H distances are 0·93 and 0·95 Å.

Introduction

The crystal structure of diketopiperazine (2,5-piperazinedione; the cyclic anhydride of glycylglycine) was first determined by Corey (1938); it was the first compound containing a peptide bond to be studied by X-ray diffraction. Later, Vainshtein (1955) undertook an electron diffraction investigation of the crystal structure of diketopiperazine; his results confirmed the structure deduced by Corey, although he reported significantly different values for some of the bond distances.

Both earlier investigators found the diketopiperazine molecule to be planar (except for the hydrogen atoms of the methylene group). Corey reported a value of 1·33 Å for the C_1–N bond distance, essentially identical with the presently accepted value for the peptide bond length; Vainshtein (1955), on the other hand, reported a value of 1·38 Å. In addition, both Corey and Vainshtein reported values for the C_2–N and C_1–C_2 distances considerably smaller than the normal single-bond distances. In order to check on these distances, as well as to obtain more accurate values for all the distances and angles within this interesting molecule, the structure of diketopiperazine has been reinvestigated.

Experimental

Diketopiperazine tends to crystallize in the form of needles elongated along the *c* direction, and considerable difficulty was experienced in obtaining a crystal large enough in all dimensions for efficient photography with molybdenum radiation. A number of samples of different origin were dissolved in many different solvents, including alcohols and solutions of organic dyes in water, without success; finally, however, a sample was found which gave a few large, tabular crystals directly from its water solution. One of these crystals was reduced to an approximate sphere one millimeter in diameter by carefully dissolving away the edges with a damp brush; this crystal was used in collecting all the intensity data. Multiple-film equi-inclination Weissenberg photographs were prepared, with molybdenum radiation and zirconium oxide filter, for layer lines 0 through 6 about the *c* axis and 0 through 7 about the *a* axis; thin copper foils were sandwiched between the layers of film to increase the effective film factor to about 3·5. By this means most of the reflections within the sphere of molybdenum radiation were covered; of these, approximately 1160 were strong enough to be observed. Intensities were estimated visually and were corrected for Lorentz and polarization factors; no correction for absorption was applied. Finally, the F^2 values from the various sets of photographs were correlated by an averaging process.

Unit-cell dimensions were obtained from a Straumanis-type powder photograph taken with chromium radiation. The low-angle lines were indexed on the basis of the unit-cell dimensions given by Vainshtein (1955) and were used as input to a preliminary least-squares treatment. The adjusted values for the cell dimensions were then used to index the back-reflection lines, of which six well-resolved ones were chosen for a final least-squares treatment. The resulting unit-cell dimensions are given in Table 1, together with the values reported by Corey and by Vainshtein (corrected from kX. to Ångström units).

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Table 1. *Unit-cell dimensions of diketopiperazine*

	Corey	Vainshtein	This investigation
a	5·20 Å	5·20 (0·004) Å	5·228 (0·002) Å
b	11·53	11·45 (0·03)	11·554 (0·002)
c	3·97	3·971(0·003)	3·980 (0·004)
β	83° (1°)	81° 55′ (10′)	97° 59′ (1′)

The values in parentheses are reported but undefined uncertainties for the earlier investigations; in the present investigation they are estimated standard deviations.

The density calculated on the basis of two molecules in the unit cell is 1·592 g.cm.$^{-3}$; that observed by flotation in mixed solvents is 1·593 g.cm.$^{-3}$, with an estimated probable error of about 0·002 g.cm.$^{-3}$. No reflection of the types $h0l$ with h odd or $0k0$ with k odd was observed, and the space group is confirmed to be $P2_1/a$; accordingly, the diketopiperazine molecule must possess a center of symmetry as reported by the earlier investigators.

Refinement of the parameters

(i) *The heavy atoms*

Refinement of the atomic positional and temperature-factor parameters was carried out through three stages of structure-factor and difference-map calculations with data of the type $0kl$ and four stages with data of the type $hk0$; through eight structure-factor and difference-map calculations on complete three-dimensional data; and, finally, through four stages of structure-factor and least-squares calculations, again based on the complete set of data. The two-dimensional calculations as well as the first three-dimensional structure-factor and difference-map calculations were carried out on an IBM 604 calculating punch and associated equipment; the remaining calculations were carried out on a Burroughs 205 computer with the exception of the second three-dimensional difference map which was calculated by Dr John Bryden on an IBM 704 computer at China Lake, California.

It perhaps should be pointed out that the computational facilities at our disposal were in a state of flux during much of the period of this investigation, and often the choice of a refinement method was dictated not so much by logic as by the availability of adequate computing equipment and programs. The complete least-squares program, which allows (for centrosymmetric monoclinic structures) the optimization of the individual temperature factors as well as the positional parameters, was not available until the investigation was nearly completed.

The starting parameters were those of Corey. (The positive direction of the a axis has been reversed to correspond to an obtuse angle β.) After three cycles of structure-factor difference-map calculations, during which a single anisotropic temperature factor of the type $\exp(-\beta k^2-\gamma l^2)$ was introduced, the R factor for the $0kl$ reflections was 0·15. Four structure-factor difference-map calculations based on the $hk0$ data, for which the R factor became 0·11, completed the two-dimensional calculations. The parameters at this stage of the refinement are given in Table 2.

The first three-dimensional structure-factor calculation led to an R factor of 0·23; two least-squares cycles in which only the positional parameters were optimized, and the weighting system of Hughes (1941) was used, reduced it to 0·18. Values for the individual anisotropic temperature factors were introduced and adjusted in two structure-factor difference-map cycles, the changes in the temperature-factor parameters being determined by the method of Leung *et al.* (1957). The R factor was then 0·10.

At this stage the intensity photographs were rechecked, and it was found that for about 20 reflections errors had been made either in indexing or transcribing the data. In addition, an estimate of the observational error in estimating intensities was made by comparing

Table 2. *Parameters of the heavy atoms*

(The temperature parameter for each atom is of the form

$$T_i=\exp(-\alpha_i h^2-\beta_i k^2-\gamma_i l^2-\delta_i hk-\varepsilon_i hl-\eta_i kl))$$

		x	y	z	$10^3\alpha$	$10^3\beta$	$10^3\gamma$	$10^3\delta$	$10^3\varepsilon$	$10^3\eta$
C_1	a	0·180	0·070	0·705						
	b	0·186	0·071	0·713	11	2·5	32·2	0	0	0
	c	0·1820	0·0697	0·7170	13·7	3·0	32·3	0·16	−5·4	1·01
C_2	a	0·955	0·120	0·495						
	b	0·951	0·123	0·507	11	2·5	32·2	0	0	0
	c	0·9485	0·1233	0·5150	19·2	2·70	35·9	2·20	−15·2	−0·68
N	a	0·780	0·044	0·305						
	b	0·778	0·042	0·294	11	2·5	32·2	0	0	0
	c	0·7802	0·0432	0·3098	14·8	3·02	43·7	1·78	−16·6	0·09
O	a	0·340	0·132	0·885						
	b	0·335	0·133	0·889	11	2·5	32·2	0	0	0
	c	0·3311	0·1328	0·9044	20·9	3·50	56·7	−1·02	−29·3	−1·64

a: parameters derived by Corey (1938); the form factors were empirical, and no temperature factor was used.
b: parameters obtained from two-dimensional refinements.
c: final parameters.

the values F_a and F_c obtained from the photographs taken about the a and c axes, respectively. It was found that the errors were approximately constant for small values of F_o and proportional to F_o for the larger values. In order to estimate the standard deviations in the F_o values, the approximate expression developed by Tippett (1925) and discussed by Ibers (1956) was used. The reflections were grouped in classes depending upon the size of F_o and within each class the standard deviation of a single observation was calculated according to the expression

$$\sigma(F_o)=0{\cdot}89|\overline{F_a-F_c}|$$

where $|F_a-F_c|$ is the difference between the two observations, F_a and F_c, of a single reflection; these differences were averaged for all reflections within the class. The resulting standard deviations, in electrons per unit cell, could be represented by the expressions

$$\sigma(F_o)=0{\cdot}21 \quad \text{if} \quad F_o \leq 2{\cdot}9$$
$$\sigma(F_o)=0{\cdot}071F_o \quad \text{if} \quad F_o \geq 2{\cdot}9\,.$$

The weighting function used in the final least-squares calculations was taken as the inverse of the square of these standard deviations multiplied by the multiplicity (1 or 2) expressing the number of independent observations of a given reflection. In addition, a few reflections were given zero weight when extinction or contamination with white radiation seemed to be important; all unobserved reflections were also given zero weight.

Six structure-factor difference-map cycles were then carried out, during which the R factor decreased to 0·084 and the sum of squares of the weighted residuals ($\Sigma w\Delta F^2$) dropped from 8300 to 3115. The contributions of the hydrogen atoms were included beginning with the fourth of these structure-factor calculations; positions for the hydrogen atoms as indicated by the preceding difference map and temperature factors the same as those found for the adjacent atom (N or C_2) were used. Atomic form factors were those of Berghuis *et al.* (1955) for the heavy atoms and of McWeeny (1951) for hydrogen.

At this point in the investigation the structure-factor least-squares program for the Burroughs 205 computer was extended by Mr A. Hybl so that, for centrosymmetric monoclinic structures, it became possible to optimize by the least-squares procedure the individual anisotropic temperature factors as well as the positional parameters. Four structure-factor least-squares cycles were calculated, the R factor dropping to 0·072 and the sum of squares of the weighted residuals to 2418. During these refinements the positional parameters remained essentially constant (the maximum shift was 0·001 Å), whereas some of the temperature-factor parameters changed appreciably. The parameters of the hydrogen atoms were not optimized.

The final parameters for the heavy atoms are listed in Table 2, and the electron density in the plane of the molecule, calculated on the basis of the final set of signs, is shown in Fig. 1.

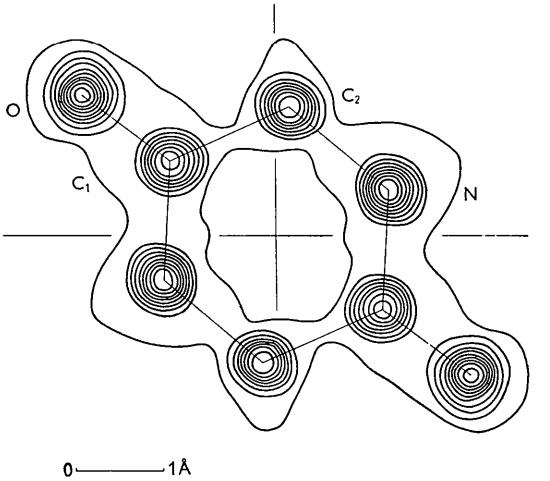

Fig. 1. The final electron-density map, drawn in the plane of the molecule. The contours are at intervals of 2 e.Å^{-3} beginning with 1 e.Å^{-3}. The b axis is vertical.

(ii) *The hydrogen atoms*

Before the last least-squares adjustment of the heavy atoms parameters, a difference map was calculated from structure factors from which the contri-

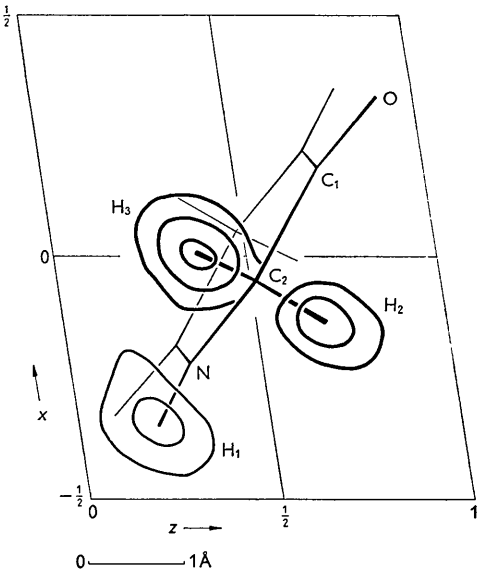

Fig. 2. A composite drawing of the electron density associated with the hydrogen atoms. The contours are at ¼, ½, and ¾ e.Å^{-3}.

Table 3. *The final hydrogen-atom parameters and their peak electron densities*

Atom	x	y	z	ϱ (e.Å^{-3})
H_1(N)	0·649	0·078	0·203	0·60
H_2(C_2)	0·868	0·161	0·678	0·65
H_3(C_2)	0·009	0·179	0·369	0·85

Table 4. *Observed and calculated structure factors*

The three columns in each group contain the values, reading from left to right, of k, 10 F_o, and 10 F_c. Reflections indicated by an asterisk (*) were given zero weight in the least-squares calculations

0,k,0

0	---	1200
2	---	303
4	277*	-340
6	55	-46
8	51	47
10	99	-108
12	107	-112
14	26	23
16	53	56
18	<13	-8
20	32	-25
22	<14	7
24	19	16

0,k,1

0	102	-108
1	131	129
2	89	-90
3	93	84
4	61	-48
5	149	-139
6	41	45
7	119	-114
8	42	42
9	28	-29
10	< 8	-8
11	35	-42
12	20	20
13	26	-32
14	26	28
15	28	29
16	< 11	-12
17	52	55
18	22	-18
19	32	29

0,k,2

0	53	-51
1	99	96
2	131	-134
3	73	71
4	142	-139
5	50	44
6	62	63
7	22	22
8	146	151
9	79	86
10	42	43
11	21	25
12	36	-39
13	26	-28
14	<10	-8
15	15	-13
16	19	20
17	<11	-6
18	<12	-2
19	22	-20
20	13	-14
21	16	-14

0,k,3

0	35	28
1	50	52
2	69	70
3	35	29
4	82	81
5	66	-68
6	32	-24
7	12	-16
8	88	-94
9	71	74
10	32	-35
11	39	43
12	13	15
13	18	-19
14	<11	-4
15	20	-18
16	18	-17
17	<13	4
18	<13	3
19	13	-11
20	17	13
21	17	-11

0,k,4

0	36	37
1	11	12
2	24	24
3	<11	6
4	<11	-13
5	17	-20
6	30	-30
7	24	-25
8	<12	-9
9	22	-23
10	< 8	4
11	25	-24
12	< 8	-4
13	9	-8
14	< 9	2
15	19	18
16	15	14
17	22	23
18	<13	6
19	13	11
20	10	-10

0,k,5

0	75	-84
1	20	17
2	31	-31
3	27	27
4	31	31
5	<13	8
6	16	14
7	< 8	-3
8	< 8	-3
9	< 9	2
10	25	22
11	<10	0
12	26	25
13	<11	-8
14	<11	-6
15	<12	-6
16	17	-16

0,k,6

0	<14	8
1	14	-13
2	<15	4
3	17	-16
4	<17	0
5	10	4
6	<11	2
7	15	12
8	8	5
9	7	7

0,k,7

0	<16	5
1	<16	-1
2	<16	9
3	<16	-3
4	<16	8
5	<16	-6
6	<16	-8
7	<16	-6
8	20	-15

1,k,0

1	111	166
2	146	-150
3	3	-7
4	77	71
5	37	-38
6	177	172
7	36	-38
8	56	56
9	< 8	-3
10	30	30
11	< 9	-7
12	50	55
13	24	-20
14	<11	-2
15	<12	10
16	60	-59
17	28	24
18	44	-43

1,k,1

1	175	166
2	222	-224
3	220	221
4	54	45
5	40	29
6	109	111
7	121	-130
8	76	-84
9	104	-112
10	102	-112
11	18	-16
12	< 9	6
13	24	23
14	41	44
15	<11	-8
16	<11	7
17	18	-16
18	13	5
19	<13	8
20	22	21
21	17	12

1,k,2

1	23	-18
2	91	-83
3	207	-198
4	13	15
5	77	-74
6	40	38
7	138	140
8	61	-64
9	104	108
10	67	-71
11	19	-21
12	< 9	0
13	21	-22
14	21	22
15	27	26
16	<15	10
17	<11	11
18	16	16
19	16	-19
20	21	19

1,k,3

1	32	-32
2	32	-30
3	42	-37
4	< 6	4
5	13	22
6	42	45
7	40	41
8	44	44
9	< 8	0
10	32	32
11	< 9	4
12	21	20
13	16	14
14	<13	4
15	<14	-1
16	29	-29
17	17	-17
18	29	-30
19	<15	0
20	15	-12
21	16	13

1,k,4

1	112	121
2	< 5	-2
3	19	-17
4	21	-18
5	54	-54
6	18	-16
7	10	6
8	5	7
9	7	-8
10	<10	11
11	53	-53
12	< 9	1
13	19	-21
14	< 9	0
15	26	26
16	<10	2
17	15	14
18	<11	-2
19	9	-12

1,k,5

1	19	-18
2	28	29
3	< 7	1
4	< 7	5
5	7	7
6	21	-22
7	< 8	-5
8	18	-16
9	7	-5
10	12	-12
11	11	12
12	18	-16
13	19	16
14	<12	-3
15	<12	1
16	16	17
17	<13	-7
18	18	16

1,k,6

1	<14	-12
2	<14	10
3	20	-20
4	<11	5
5	<12	4
6	<12	3
7	27	24
8	12	10
9	24	22

1,k,7

1	29	30
2	27	-25
3	<14	-1
4	13	-14
5	13	-12

2,k,0

0	238	-247
1	172	168
2	188	-187
3	92	89
4	53	-45
5	152	-164
6	32	36
7	42	-42
8	74	80
9	117	127
10	76	79
11	66	68
12	<10	13
13	39	-37
14	<11	-10
15	36	-32
16	9	10
17	<12	1
18	<13	8
19	<13	-8
20	<14	-10
21	20	-17

2,k,1

0	113	-96
1	< 5	4
2	167	155
3	32	23
4	237	231
5	39	31
6	86	-91
7	53	56
8	167	-186
9	60	59
10	21	-23
11	15	16
12	50	53
13	<13	-6
14	<13	8
15	9	-9
16	27	-26
17	25	-23
18	15	14
19	28	-26
20	19	17

2,k,2

0	21	20
1	22	21
2	55	57
3	23	25
4	53	47
5	21	-18
6	36	-37
7	58	-63
8	36	-39
9	57	-60
10	< 8	5
11	25	-26
12	11	-9
13	<11	-6
14	23	-23
15	15	13
16	<11	4
17	36	35
18	16	14
19	33	32
20	<20	-5
21	<17	7

2,k,3

0	278	281
1	112	-118
2	119	120
3	143	-144
4	74	-73
5	25	29
6	50	-44
7	37	33
8	< 7	-8
9	46	-52
10	55	-57
11	19	-16
12	46	-52
13	40	43
14	17	13
15	21	18
16	28	29
17	18	-20
18	<13	-3
19	<13	-8
20	14	-12
21	12	12

2,k,4

0	44	44
1	28	-27
2	16	14
3	24	-24
4	22	-22
5	26	26
6	< 7	-8
7	28	31
8	15	14
9	17	17
10	< 8	-6
11	28	27
12	23	-23
13	19	17
14	<10	4
15	22	-19
16	16	12
17	27	-30
18	<14	4
19	13	-12

2,k,5

0	26	26
1	19	-18
2	30	28
3	17	-17
4	21	20
5	8	10
6	15	-14
7	<12	0
8	39	-40
9	25	-24
10	22	-21
11	10	-11
12	<12	8
13	12	10
14	8	9

2,k,6

0	23	22
1	13	10
2	17	17
3	< 6	-3
4	6	8
5	32	-34
6	< 8	-2
7	16	-14
8	16	-12
9	29	26
10	17	-14
11	25	24

2,k,7

0	10	-12
1	10	10
2	<14	-6
3	14	14

3,k,0

1	< 7	4
2	51	52
3	188	-191
4	56	-48
5	58	-61
6	113	-111
7	146	154
8	60	-61
9	88	96
10	< 9	6
11	40	-37
12	<10	-3
13	30	-27
14	7	-9
15	21	20
16	24	20
17	<13	0
18	31	34
19	19	-19
20	16	14

3,k,1

1	37	-32
2	15	-18
3	80	-74
4	16	-19
5	32	-23
6	26	26
7	44	42
8	74	77
9	26	21
10	46	49
11	<11	6
12	<11	5
13	28	27
14	7	-3
15	22	19
16	20	-18
17	<12	-7
18	37	-38
19	<13	-7
20	27	-25

3,k,2

1	177	174
2	69	67
3	27	23
4	55	-53
5	18	-19
6	99	-102
7	8	-10
8	30	30
9	52	-54
10	86	94
11	48	-55
12	15	18
13	7	-10
14	35	-35
15	<11	6
16	17	-15
17	<12	-6

3,k,3

1	57	-58
2	33	33
3	32	29
4	12	-12
5	35	37
6	42	-42
7	19	-16
8	26	-26
9	< 9	-8
10	32	-32
11	27	26
12	36	-34
13	<11	9
14	<11	9
15	21	-20
16	38	39
17	<12	-11
18	25	24

3,k,4

1	82	-84
2	104	108
3	25	-19
4	43	41
5	25	23
6	31	-30
7	25	25
8	11	11
9	28	30
10	29	31
11	25	27
12	20	-18
13	<12	4
14	31	-32
15	13	-12
16	<13	4
17	<12	-6
18	18	16

3,k,5

1	< 9	3
2	17	-15
3	44	45
4	< 9	4
5	19	19
6	13	14
7	43	-45
8	20	15
9	35	-35
10	11	10

3,k,6

1	16	16
2	<13	3
3	<13	3
4	<13	2
5	<13	-8
6	<14	-7
7	<14	-7
8	16	14

3,k,7

1	20	-22
2	<13	4
3	<13	0
4	<13	4
5	13*	10

4,k,0

0	30	20
1	8	-7
2	50	42
3	16	19
4	61	46
5	33	25
6	< 9	2
7	48	44
8	22	-23
9	64	-62
10	12	-18
11	17	-17
12	24	-22
13	<12	4
14	26	-24
15	<13	3
16	9	-10
17	26	23
18	<11	3
19	31	33
20	<12	6

4,k,1

0	145	-130
1	124	-116
2	104	-89
3	123	-119
4	19	-8
5	61	54
6	46	47
7	29	31
8	51	52
9	71	-70
10	44	41
11	29	-28
12	25	24
13	47	49
14	<13	-1
15	24	24
16	14	-14
17	22	-22
18	<13	-4
19	<13	-7
20	<13	5
21	13	16

Table 4 (*cont.*)

5,k,1

0	11	8
1	50	44
2	71	65
3	17	19
4	66	63
5	96	-99
6	60	-60
7	82	-86
8	88	-92
9	< 7	12
10	< 8	-9
11	18	18
12	31	29
13	19	-18
14	<10	4
15	<10	0
16	<10	0
17	30	31
18	16	12
19	20	21

4,k,2

0	96	96
1	< 6	-6
2	7	9
3	< 6	3
4	64	-69
5	28	28
6	< 7	-9
7	32	32
8	25	24
9	38	38
10	20	-19
11	42	43
12	19	-18
13	<10	8
14	28	26
15	33	-36
16	25	25
17	30	-34

5,k,2

0	114	-110
1	14	-8
2	49	-48
3	13	14
4	19	19
5	59	61
6	< 6	3
7	30	31
8	< 7	4
9	38	-43
10	37	39
11	43	-46
12	31	34
13	<10	4
14	<10	3
15	19	20

4,k,3

0	94	97
1	28	-25
2	48	49
3	18	-17
4	< 8	-9
5	38	35
6	8	-12
7	19	19
8	23	-24
9	37	-38
10	40	-44
11	36	-37
12	19	-21
13	9	10
14	<11	9
15	21	23

5,k,3

0	46	-42
1	< 6	9
2	5	-8
3	20	17
4	30	30
5	12	8
6	18	18
7	7	8
8	< 8	6
9	21	26
10	< 9	8
11	23	25
12	10	-8
13	<10	-3
14	24	-26
15	22	-21
16	15	-15
17	15	-12

4,k,4

0	7	2
1	25	25
2	35	-35
3	23	21
4	48	-48
5	32	-33
6	26	27
7	35	-37
8	60	63
9	< 9	-3
10	10	11
11	<10	-1
12	18	-19
13	12	-13
14	<10	3
15	<10	3
16	<11	9
17	18	21
18	8	-7
19	15	14

5,k,4

0	22	27
1	37	-38
2	23	24
3	48	-52
4	< 8	9
5	< 8	-5
6	15	-14
7	< 8	5
8	23	-23
9	14	-13
10	14	-14
11	< 9	-1
12	< 9	-1
13	21	20
14	< 9	4
15	11	8
16	<10	2
17	15	-9

4,k,5

0	22	-22
1	<10	-2
2	14	-15
3	7	-7
4	<10	0
5	<10	-1
6	<11	9
7	20	18
8	<11	6
9	24	22

5,k,5

0	6	5
1	10	9
2	< 8	-2
3	15	14
4	12	-11
5	< 9	3
6	6	-8
7	11	-8

4,k,6

0	30	37
1	11	14
2	19	20
3	<16	12
4	<16	-6
5	13	-14
6	11	-12
7	<16	-8
8	<17	-7
9	17*	14

5,k,6

0	14	-11
1	< 12	-2
2	8	-8
3	< 12	4
4	< 13	2
5	18	15
6	< 13	9
7	14	10

5,k,0

1	66	58
2	120	123
3	74	64
4	46	43
5	< 10	2
6	40	-35
7	67	-65
8	29	22
9	51	-52
10	50	46
11	< 9	-8
12	24	-19
13	<10	1
14	41	-41

15	<10	-1
16	<11	2
17	<12	4
18	18	17

5,k,1

1	62	-56
2	26	-24
3	47	44
4	17	-15
5	46	43
6	12	-9
7	16	-13
8	35	-34
9	< 8	2
10	48	-50
11	20	20
12	20	-18
13	20	-18
14	24	25
15	36	-36
16	31	30
17	<12	-5
18	16	14
19	14	14

5,k,2

1	35	-35
2	34	-33
3	25	-24
4	40	38
5	20	18
6	76	78
7	41	45
8	13	16
9	21	22
10	23	-27
11	6	-6
12	7	1
13	10	-10
14	9	12
15	8	-9
16	15	-14
17	8	-10
18	20	-20

5,k,3

1	22	23
2	54	-53
3	47	45
4	21	21
5	< 9	3
6	72	74
7	53	-56
8	17	18
9	37	-39
10	17	-18
11	9	9
12	12	11
13	8	10
14	15	15

15	<12	-4
16	17	-20
17	<12	3
18	22	-27

5,k,3

1	40	43
2	14	-11
3	< 7	0
4	29	-31
5	7	-9
6	27	-31
7	< 8	7
8	< 9	2
9	< 9	-6
10	25	28
11	24	-26
12	16	16
13	14	-17

5,k,4

1	22	25
2	< 9	4
3	7	10
4	10	11
5	< 9	-1
6	< 9	-7
7	<10	4
8	29	-31
9	9	-10
10	21	-20
11	12	-13
12	<10	1
13	<10	-8
14	<11	3
15	<11	-2
16	<11	5
17	<11	-2
18	15	17
19	<10	-1
20	14	13

5,k,4

1	13	13
2	16	-14
3	< 8	4
4	< 8	-6
5	13	-13
6	< 8	1
7	10	-12
8	6	-9
9	6	-9
10	15	-15
11	< 9	3
12	<10	-3
13	17	16
14	10	10
15	14	14
16	8	7

5,k,5

1	31	-34
2	35	-35
3	18	-18
4	<11	-4
5	<11	8
6	22	22
7	22	22
8	<12	-8
9	18	17
10	26	-24
11	8	9
12	<12	3
13	<13	5
14	15	16

5,k,5

1	< 9	-6
2	22	26
3	<10	-11
4	16	18
5	<10	-2
6	<10	2
7	14	12
8	<11	2
9	13	11

5,k,6

1	12	13
2	< 12	3
3	<12	-10
4	<12	1
5	<12	-9
6	<12	1
7	<12	7
8	11	10
9	12	2
10	12	15

6,k,0

0	46	43
1	30	24
2	< 11	1
3	28	29
4	36	-38
5	< 11	-3
6	7*	-13
7	7	8
8	< 12	-2
9	44	43
10	< 12	-12
11	31	28
12	< 13	10
13	< 13	-14
14	36	34
15	29	-24
16	19	17
17	14	-10

6,k,1

0	99	97
1	< 6	12
2	45	43
3	27	25
4	23	-22
5	31	26
6	< 8	-9
7	20	17
8	< 8	0
9	18	-13
10	30	-32
11	30	-31
12	36	-37
13	<10	-8
14	<11	-5
15	17	16

6,k,1

0	13	-13
1	44	45
2	38	-38
3	69	67
4	40	-40
5	13	14
6	25	26
7	< 7	1
8	54	57
9	21	21
10	17	16
11	< 9	3
12	<10	-12
13	25	-26
14	<11	0
15	16	-13
16	<11	5
17	12	9

6,k,2

0	40	-40
1	42	41
2	35	-32
3	23	21
4	< 8	-3
5	71	-74
6	33	30
7	56	-59
8	35	35
9	18	18
10	15	12
11	13	12
12	<11	-6
13	22	-22
14	<11	-8
15	<12	2
16	<12	-8
17	28	30
18	<12	-6
19	16	15

6,k,2

0	< 5	6
1	7	-7
2	6	9
3	19	-19
4	19	18
5	< 8	-12
6	16	17
7	10	11
8	8	-1
9	19	18
10	18	-17
11	<10	9
12	17	-16
13	<10	3
14	14	-12
15	<11	-2
16	<12	-11
17	8	-10
18	<12	-3
19	12	-12

6,k,3

0	32	-31
1	< 9	-3
2	19	-18
3	14	-12
4	< 9	-5
5	<10	-8
6	<10	-6
7	20	19
8	<10	4
9	28	29
10	22	20
11	13	9
12	16	16
13	<12	-4
14	<12	4
15	<12	-3
16	<12	5
17	14	-12
18	<12	5
19	17	-17

6,k,3

0	37	32
1	9	10
2	16	15
3	<13	-6
4	15	-12
5	40	-41
6	20	-20
7	24	-27
8	11	-11
9	14	10
10	<10	-3
11	10	11

6,k,4

0	24	24
1	31	30
2	34	32
3	35	36
4	24	22
5	<12	-9
6	23	-22
7	<10	-9
8	36	-38
9	24	24
10	17	-13
11	18	14
12	<11	1
13	16	-16
14	<11	-3
15	13	-12

6,k,4

0	20	-20
1	<12	6
2	11	-8
3	17	17
4	< 9	6
5	19	19
6	< 9	-2
7	7	8
8	7	-6
9	7	-8
10	8	7
11	11	-12
12	14	14

6,k,5

0	23	-22
1	8	-9
2	<12	0
3	8	-9
4	19	18
5	<12	4
6	<12	1
7	<12	-5
8	<12	-7
9	22	-22
10	<12	7
11	16	-16
12	<13	6
13	<13	5
14	12	-10

6,k,6

0	25	-24
1	<12	2
2	15	-13

7,k,0

1	60	-50
2	30	-30
3	< 12	4
4	29	-27
5	12	14
6	18	-16
7	<13	-2
8	<13	-5
9	<13	6
10	20	14

11	28	28
12	20	18
13	22	22

7,k,1

1	44	43
2	30	-28
3	< 7	-3
4	35	33
5	31	-28
6	71	69
7	20	-17
8	13	13
9	10	-10
10	24	-21
11	< 11	-8
12	< 11	5
13	< 12	5
14	< 12	10
15	12	16
16	19	-17
17	13	10
18	19	-20

7,k,1

1	8	-10
2	27	28
3	< 11	9
4	< 11	7
5	14	15
6	< 8	-6
7	13	13
8	21	20
9	< 12	11
10	28	26
11	< 10	-6
12	< 11	-2
13	25	-25
14	18	-17
15	19	-19
16	12	-7

7,k,2

1	23	25
2	10*	11
3	7	8
4	16	14
5	< 11	9
6	< 10	-3
7	7	9
8	21	-20
9	15	-14
10	18	-16
11	24	-25
12	< 12	-3
13	< 12	-10
14	< 12	2
15	< 13	-4
16	< 13	8
17	< 13	-9
18	15	14

7,k,2

1	4	5
2	30	-34
3	26	28
4	29	-32
5	7	9
6	11	-14
7	26	-30
8	< 9	-7
9	24	-24
10	< 10	-1
11	< 11	5
12	9	10
13	< 12	7
14	9	11

7,k,3

1	16	-15
2	37	-38
3	41	-41
4	21	-23
5	11	-10
6	< 11	1
7	42	44
8	< 12	-9
9	30	33
10	10	-17
11	< 12	-4
12	< 12	4
13	< 12	-5
14	18	17

7,k,3

1	< 10	2
2	9	10
3	6	-7
4	12	10
5	16	-14

7,k,4

1	14	12
2	22	23
3	8	-13
4	< 11	2
5	15	-12
6	8	-8
7	< 11	3
8	19	19
9	< 11	-2
10	26	28
11	< 11	-6
12	< 11	1
13	8	9
14	13	-15
15	14	14

7,k,4

1	15	-15
2	< 9	3
3	< 9	4
4	15	16
5	11	12
6	16	17

7,k,5

1	27	28

7,k,6

1	< 13	-11
2	12	15
3	13	-3
4	< 13	-5
5	< 13	4
6	19	-20

8,k,0

0	48	-44
1	< 13	7
2	13	-12
3	< 13	-8
4	26	27
5	46	-41
6	19	16
7	29	-28

8,k,1

0	19	-18
1	< 12	-8
2	< 12	-11
3	12	-15
4	9	-8
5	< 12	-5
6	12	-14
7	< 13	7
8	< 13	0
9	9	10
10	20	20
11	13	8
12	16	17

8,k,1

0	30	28
1	14	-16
2	12	15
3	25	-28
4	< 12	-4
5	18	-17
6	< 12	-2
7	< 12	-7
8	< 12	2
9	< 13	1
10	< 13	-9
11	< 13	11
12	22	-18

8,k,2

0	< 12	-1
1	14	14
2	24	23
3	28	29
4	32	32
5	19	23
6	19	-17
7	< 12	11
8	41	-43

8,k,2

0	< 12	2
1	9	-10
2	< 12	1
3	11	-12
4	< 12	-3
5	< 12	1
6	12	-12
7	< 12	-4
8	15	-13
9	18	-13

8,k,3

0	< 12	-5
1	17	-19
2	< 12	2
3	19	-19
4	< 12	9
5	10	10
6	< 12	7
7	< 12	-4
8	< 12	5
9	28	-29
10	< 12	2
11	10	-13
12	< 12	-9
13	12	14
14	15	-16
15	12	11

8,k,3

0	< 11	3
1	< 11	8
2	< 11	-7
3	16	19
4	11	-12
5	16	18
6	< 12	5
7	< 12	8
8	17	15

8,k,4

0	27	-30
1	8	-9
2	18	-18
3	13	-14

8,k,5

0	20	23
1	10	-10
2	9	8
3	< 13	-5
4	< 13	-10
5	20	21
6	< 13	-7
7	18	18

9,k,1

1	< 13	-3
2	9	-12
3	22	-22
4	27	-26
5	9	-8
6	24	-24
7	31	25
8	< 13	-5
9	21	20

9,k,1

1	16	20
2	< 13	-8
3	< 13	-11
4	18	-19
5	16	-18
6	20	-20

9,k,2

1	< 13	-4
2	18	21
3	< 13	0
4	< 13	3
5	< 13	-5
6	< 13	-6
7	< 13	-12
8	18	16
9	12	-6
10	15	19
11	< 13	10
12	< 12	-5
13	12	16
14	11	-12

9,k,2

1	< 12	-8
2	16	17
3	< 12	-2
4	15	16

9,k,3

1	18	21
2	18	19

9,k,4

1	18	-21
2	< 10	5
3	7	9
4	11	-12
5	16	15
6	20	-22

butions of the hydrogen atoms had been omitted. A composite drawing of this difference map is shown in Fig. 2, and the hydrogen-atom parameters, obtained by a 27-point Gaussian analysis of the peaks (Shoemaker *et al.*, 1950), are listed in Table 3. These parameters were used in calculating the bond distances and angles in Table 6. Aside from the hydrogen atoms, whose peak electron densities are given in Table 3, the only regions on the difference map with electron densities greater than 0·2 e.Å^{-3} are a positive region of about 0·4 e.Å^{-3} between atoms C_1 and N on the section $y=0$ and a negative region of about 0·35 e.Å^{-3} near C_1. The electron density between atoms C_1 and O is essentially zero.

In a parallel attempt to obtain reliable values for the hydrogen-atom parameters, a number of least-squares calculations were made in which only the positional parameters of the hydrogen atoms were adjusted. Two weighting schemes were used: (1) The basic weighting scheme discussed previously was modified to give zero weight to all reflections with $\sin\theta$ greater than a certain value (three calculations were made, with $\sin\theta_{\max.}$ equal to 0·46, 0·40, and 0·30, respectively); (2) The basic weighting scheme was modified by the factor f_H/f_N—the ratio of the form factor of hydrogen to that of nitrogen for each reflection—so that $\sqrt{w'}=[w(f_H/f_N)]^{\frac{1}{2}}$. Although the hydrogen positions resulting from all of these calculations were similar, they differed by considerable amounts from those indicated by the difference map. Furthermore, the resulting bond distances and angles were not sensible, the distances ranging from 0·75 to 1·15 Å and the angles departing by as much as 20° from the expected values. Accordingly, the parameters obtained from the difference map were accepted as final values for the hydrogen atoms. An extensive study of the weighting function most appropriate for the refinement of light atoms in the presence of heavy atoms is clearly warranted.

Accuracy of the results

The observed and calculated structure factors are listed in Table 4. The R factor for 1144 observed reflections with non-zero weight is 0·072. The standard deviation of an observation of unit weight can be calculated from the expression

$$\left(\Sigma\frac{w(\Delta F)^2}{m-n}\right)^{\frac{1}{2}},$$

where m and n are the number of observations and parameters, respectively (Peterson & Levy, 1957). The resulting value is 1·5. Deviation of this number from the ideal value of unity implies either that the structural parameters have not been properly optimized or that the weighting system does not reflect the true errors in the observations; in all probability the former effect is predominant. A comparison of the individual ΔF values with the calculated standard deviations shows that for 14 out of 1144 reflections ΔF is more than four times as large as the standard deviation, whereas the probability for such an occurrence is only 1 in 16,000. In all 14 cases the structure factors are small in magnitude, as would be expected if the errors are primarily due to F_c. (For a given region of $\sin\theta$, the absolute errors in F_c should be essentially independent of the magnitude of F and hence could lead to large relative errors for small structure factors.)

As in the case of the refinement of glycine (Marsh, 1958), a major source of error in the calculated structure factors is probably the use of inappropriate form factors, due to bond effects and to the method of interpolating form factors in the least-squares program. In this respect it is interesting to note that of the 14 weak reflections with discrepancies over four times the standard deviations, 12 have relatively small Bragg angles and, hence, lie in the region where bond effects and interpolation errors are important.

The standard deviations in the positional parameters of the heavy atoms, calculated from the residuals and diagonal terms of the normal equations in the least-squares treatment, range from 0·0011 Å to 0·0014 Å, being smaller for the nitrogen and oxygen atoms and in the direction of the b axis (which lies nearly in the plane of the molecule). It seems appropriate, then, to quote a limit of error of about 0·005 Å in the apparent positions; this corresponds to a limit of error of about 0·007 Å in the bond distances and 0·3° in the bond angles. The estimated limit of error in the apparent hydrogen-atom parameters is about 0·1 Å.

Discussions of the results

(i) *The bond distances and angles*

The bond distances and angles calculated from the heavy-atom parameters of Table 3 are listed in Table 5 and shown in Fig. 3; for comparison, the values reported by Corey (1938) and by Vainshtein (1955) are

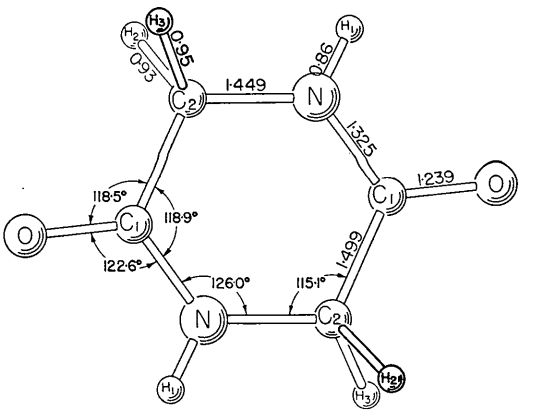

Fig. 3. The bond distances and angles in diketopiperazine calculated from the final set of parameters.

also listed in Table 5. A consideration of the libration effects implied by the relative temperature factors of atoms C_1 and O indicates that the length of the C–O bond should be increased by about 0·015 Å, leading to a value of 1·254 Å; no such correction has been applied to the other bond distances in the molecule.

Table 5. *Bond distances and angles*

Bond	This Investigation	Corey	Vainshtein
C_1–C_2	1·499 Å	1·47 Å	1·44 Å
C_1–N	1·325	1·33	1·38
C_1–O	1·239	1·25	1·22
C_2–N	1·449	1·41	1·40
Angle			
C_2–C_1–O	118·5°	120°	121½°
N–C_1–O	122·6	120	121
C_2–C_1–N	118·9	120	117½
C_1–N–C_2	126·0	120	121½
N–C_2–C_1	115·1	120	121

The best plane of the molecule centered at (0, 0, ½), calculated by the least-squares method of Schomaker *et al.* (1959) with all eight heavy atoms weighted equally, is defined by the equation

$$-3{\cdot}3022x-1{\cdot}8636y+3{\cdot}3380z=1{\cdot}6690\,,$$

the distance from this plane to the origin being 1·669 Å. The atoms in one half molecule

$$\left(\begin{matrix}\mathrm{N}\\ \mathrm{C_2}\end{matrix}\!\!>\!\mathrm{C_1}\text{—O group}\right)$$

are almost exactly coplanar, but there is a slight twist of one of these groups with respect to the other half of the molecule which leads to the following small but significant deviations of the atoms from the best molecular plane: C_1, −0·007 Å; C_2, −0·009 Å; N, +0·010 Å; O, +0·009 Å.

The C–O and C_1–N bond distances are normal for a peptide group (Corey & Pauling, 1953); the C—C and C_2–N distances are shorter by about 0·02 Å than the normal values for a peptide group and by about 0·04 Å than normal single-bond values, presumably indicating a conjugative effect throughout the ring. The bond-angle strain required by the planar configuration is quite evenly distributed, all of the interior angles of the ring being between 3° and 5° greater than the normal values for a peptide. Concordantly, the external angles C–C–O and N–C–O are both about 2½ degrees smaller than normal. The slight non-planarity of the ring does little to relieve the bond-angle strain, as the interior angles would be increased by an average of only 0·004° if the ring were exactly planar.

The apparent bond distances and angles involving the hydrogen atoms, calculated from the parameters of Table 3, are given in Table 6. The distances are considerably shorter than the normal single-bond internuclear separations but are essentially the same as

Table 6. *Bond distances and angles involving the hydrogen atoms*

N–H_1	0·86 Å	C_1–N–H_1	123°
C_2–H_2	0·93	C_2–N–H_1	111
C_2–H_3	0·95		
		C_1–C_2–H_2	104
		C_1–C_2–H_3	107
		N–C_2–H_2	113
		N–C_2–H_3	108
		H_2–C_2–H_3	109

those found in glycine (Marsh, 1958) and in diformylhydrazine (Tomiie *et al.*, 1958). Recently Tomiie (1958) has presented an explanation of this apparent shortening in terms of the ionic character of the bonds and the temperature motions of the hydrogen atoms.

The bond angles involving the hydrogen atoms are all within 5° of normal. H_1 is 0·02 Å from the molecular plane and exactly in the plane of the C_1–N–C_2 group; H_2 is 0·73 Å to one side of the molecular plane and H_3 is 0·80 Å to the other side.

(ii) *The temperature factors*

The temperature-factor parameters for the five heavy atoms were transformed into parameters related to the principal axes of the ellipsoids of vibration

Table 7. *Magnitudes and direction cosines of the principal axes of the vibration ellipsoids*

Atom	Axis i	B_i	g_i^1	g_i^2	g_i^3
C_1	1	2·356	−0·433	0·095	0·836
	2	1·604	0·190	0·982	0·014
	3	1·252	0·881	−0·165	0·565
C_2	1	3·248	−0·624	−0·134	0·683
	2	1·520	0·410	0·783	0·525
	3	1·224	0·665	−0·607	0·526
N	1	3·444	−0·443	−0·062	0·832
	2	1·668	0·265	0·944	0·234
	3	1·080	0·856	−0·324	0·521
O	1	4·856	−0·502	−0·018	0·795
	2	1·920	−0·262	0·956	−0·168
	3	1·304	0·824	0·293	0·598

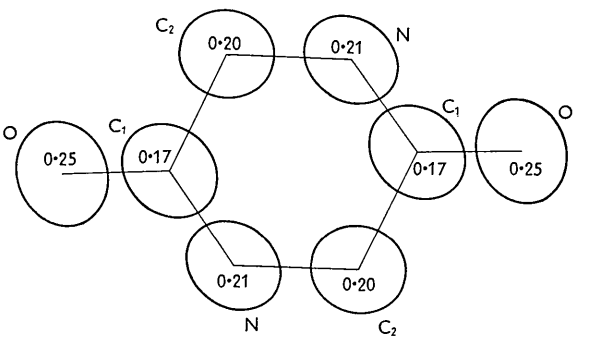

Fig. 4. A schematic drawing of the relative magnitudes of thermal anisotropy, in units of B, projected onto the plane of the molecule. The numbers are the calculated root mean square amplitudes of vibrations, in Ångströms, normal to the plane of the molecule.

(Rollett & Davies, 1955); the magnitudes of these principal axes and their direction cosines relative to the unit-cell axes are listed in Table 7. A schematic drawing of these ellipsoids projected onto the plane of the molecule is shown in Fig. 4.

For all atoms except C_1 the direction of the principal axis of vibration (B_1) lies within 8° to the normal of the molecular plane; for C_1 the angle is 16°. Probably none of these deviations is greater than the experimental error. The in-plane vibrations (Fig. 4) can be approximately described in terms of rigid-body motions consisting of rotation about the center of the molecule coupled with a translation in a direction normal to the N–H · · · O hydrogen bond; the out-of-plane vibrations can be explained on the basis of a libration about the long axis of the molecule coupled with a somewhat smaller libration about an axis normal to the long axis.

(iii) *Packing of the molecules*

The packing is that described extensively by Corey (1938). Hydrogen bonds hold the molecules together to form ribbons parallel to the [101] direction; adjacent ribbons are held together only by van der Waals interactions. The distances and angles involving the hydrogen bonds, which occur in pairs about centers of symmetry, are given in Table 8. A given oxygen atom is 0·027 Å out of the best plane of the adjacent molecule to which it is hydrogen bonded.

Table 8. *Hydrogen bond distances and angles*

N · · · O	2·853 Å	N–H · · · O	170°
H · · · O	2·01	H–N · · · O	7
		C_1–N · · · O	115·6
		C_2–N · · · O	118·3
		C–O · · · N	121·8
		C–O · · · H	125

The closest van der Waals contacts are: H–H, 2·69, 2·75, 2·79, 3·00 and 3·09 Å; O–H, 2·56, 2·72, 2·92 and 3·08 Å; N–H, 2·95 Å. It should be noted that all these distances involve hydrogen atoms whose apparent positions, as given in Table 3, obviously do not correspond to the positions of the nucleii. The shortest intermolecular distances involving heavy atoms only are: O–C_2, 3·31 and 3·36 Å; O–C_1, 3·51 Å; N–C_1, 3·38 Å; N–C_2, 3·52 Å; C_1–C_2, 3·61 Å; and C_2–C_2, 3·92 Å.

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