

## The Stereochemical Basis of Anticonvulsant Drug Action.

### I. The Crystal and Molecular Structure of Diphenylhydantoin, a Noncentrosymmetric Structure Solved by Centric Symbolic Addition

BY ARTHUR CAMERMAN\*

*Department of Biological Structure, University of Washington, School of Medicine, Seattle, Washington, U.S.A.*

AND NORMAN CAMERMAN

*Department of Biochemistry, University of Toronto, Toronto, Canada*

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To investigate relationships between the molecular shape and biological activity of anticonvulsant drugs we have determined the molecular structure of diphenylhydantoin. The compound crystallizes in the orthorhombic system with cell dimensions  $a=6.230$ ,  $b=13.581$ ,  $c=15.532$  Å, space group  $Pn2_1a$ . A total of 1210 independent reflections to  $2\theta=50^\circ$  for Mo  $K\alpha$  radiation was measured on a four-circle diffractometer. The structure was solved by centrosymmetric phasing techniques, utilizing Sayre's equation for direct sign determination in space group  $Pnma$ . This technique proved successful because the 7-atom hydantoin group lies in a plane only  $2.40^\circ$  from (010) with the two phenyl rings on each side of the plane. Thus, the structure approximates the situation that would exist for special position ( $c$ ) of  $Pnma$ , and many reflections have phases close to 0 or  $\pi$ . The plane of the hydantoin ring forms angles of  $113$  and  $114^\circ$  with the planes through the two phenyl rings. The phenyl-phenyl angle is  $90^\circ$ . Final  $R$  index is 0.052.

#### Introduction

Various barbiturates and hydantoins exhibit markedly different hypnotic and anticonvulsant properties, depending on the nature of the substituents at the C(5) position of the heterocyclic ring. Compounds with aliphatic side groups at this position are commonly used as sedatives, whereas phenyl substitution is necessary to obtain effective activity against *grand mal* epilepsy. These facts indicate to us a possible steric mode of behavior for this type of drug – the spatial properties of the C(5) substituent relative to the rest of the molecule may be an important factor in determining the drug's pharmacological site of action.

Accordingly, in order to investigate relationships between the molecular shape and biological activity, we have studied the molecular structures of a number of chemically different compounds that are used as anticonvulsants in treating *grand mal* epilepsy. The first of these is diphenylhydantoin.

Since its introduction into medicine (Merritt & Putnam, 1938), diphenylhydantoin (DPH) has been an extremely effective and widely used drug for treating *grand mal* and psychomotor epilepsies. Unlike barbiturates, which are also used in seizure therapy, DPH is not a sedative, thus proving that antiepileptics need not impair consciousness.

#### Experimental

DPH was obtained as the sodium salt, and colorless lath-shaped crystals of the free acid were grown from

aqueous solution adjusted to pH 11.0 with NaOH. The crystals are orthorhombic and systematic absences indicated space groups  $Pnma$  or  $Pn2_1a$ . Unit-cell dimensions were determined by least-squares minimization of the difference between calculated and observed  $\theta$  values for 12 reflections measured at both  $+2\theta$  and  $-2\theta$  with Mo  $K\alpha$  radiation ( $\lambda=0.71069$  Å) on a four-circle diffractometer. The crystal density was measured by flotation in a mixture of methylene chloride and methyl alcohol. The crystallographic data are:

Diphenylhydantoin,  $C_{15}H_{12}N_2O_2$   
 $a = 6.230 \pm 0.001$  Å  $F(000) = 528$   
 $b = 13.581 \pm 0.001$   $\mu(\text{Mo } K\alpha) = 0.9 \text{ cm}^{-1}$   
 $c = 15.532 \pm 0.002$  Systematic absences:  
 $Z = 4$   $0kl \rightarrow k+l \text{ odd}$   
 $D_m = 1.29 \text{ g.cm}^{-3}$   $hk0 \rightarrow h \text{ odd}$   
 $D_x = 1.28$  Space group:  $Pnma$  or  $Pn2_1a$ ;  
 M.W., 252.3  $Pn2_1a$  indicated by structure analysis.

Intensities were measured to  $2\theta=50^\circ$ , corresponding to an interplanar spacing of 0.84 Å; the crystal used had dimensions  $0.3 \times 0.2 \times 0.1$  mm along  $a$ ,  $b$ , and  $c$  respectively, and was mounted with  $a$  parallel to the  $\phi$  axis of the diffractometer. The  $\omega-2\theta$  scan technique with Nb-filtered Mo  $K\alpha$  radiation was employed, with a scan rate of  $2^\circ/\text{min}$  and stationary background counts for half the scan time on each side of the reflection. A total of 1210 independent reflections was measured, of which 876 had intensities greater than  $2\sigma_c$ , where  $\sigma_c = (N_{B1} + N_{PK} + N_{B2})^\dagger$ ;  $N_{B1}$  and  $N_{B2}$  are stationary background counts on each side of the peak over a total time equal to the scan time, and  $N_{PK}$  is the scan count. Reflections with intensities less than  $2\sigma_c$  were

\* Present address: Department of Neurology, University of Washington School of Medicine, Seattle, Wash., U.S.A.

Table 1. *Intensity statistics*

		Centrosymmetric space group	Noncentric space group	Diphenylhydantoin
Average	$E$	0.798	0.886	0.814
Average	$E^2-1$	0.968	0.736	0.858
Fraction	$E > 1$	0.3173	0.3679	0.2946
	$E > 2$	0.0455	0.0183	0.0432
	$E > 3$	0.0027	0.0001	0.0043

classified as unobserved and were not used in the structure refinement. Frequently measured standard reflections indicated the diffractometer reliability to be  $\pm 1\%$ ; hence, the estimated error in the intensity of each reflection was taken to be  $\sigma_I = [\sigma_c^2 + (0.01\sigma_I^2)^2]^{\frac{1}{2}}$ . Structure amplitudes were obtained from the intensities in the usual fashion and weights were taken as  $\sqrt{w} = 1/\sigma_F$ . No absorption corrections were applied. The linear absorption coefficient for Mo  $K\alpha$  is  $0.9 \text{ cm}^{-1}$ .

### Solution of the structure

Systematic extinctions indicated the space group to be  $Pn2_1a$  or  $Pnma$ . Since density measurements show  $Z=4$ ,  $Pnma$  would restrict the hydantoin ring to lie in a mirror plane at  $y=\frac{1}{2}$  and the two phenyl groups to be related through the mirror. Statistical analysis of the normalized structure amplitudes (Table 1) suggested the centrosymmetric space group to be more appropriate; accordingly, the reiterative application of Sayre's equation (Sayre, 1952) was used to determine the phases of 142 reflections having  $E > 1.5$ . A computer program written by Long (1965) was employed in the phase determination. The features of this program are: (1) the origin-determining reflections may be chosen arbitrarily or they may be specified automatically by the program based on the magnitude of  $\sum \times E_h$ , where  $\sum$  is the sum in Sayre's equation,  $\sum_k (E_h E_{h-k})$ ; (2) two methods of iteration

are possible: (a) newly predicted signs may be used immediately in determining signs of reflections that are still unknown, or (b) newly determined signs are not used to predict additional signs until the next cycle; (3) once the origin-determining reflections are specified,  $n$  other reflections are alternately assigned phases of 0 or  $\pi$  to yield  $2^n$  different solutions.

In the first attempt at structure solution, the reflections that were to have phases assigned were allowed to be specified by the program routine; 32 solutions were obtained by using both iteration procedures. None of these solutions was satisfactory, however, as all solutions predicted some signs of the seven specified input reflections to be different from those which were originally assigned to these reflections. One criterion for the acceptability of any solution is that the signs finally predicted for the input reflections are the same as those initially assigned.

For a second attempt at solving the structure, three origin-determining reflections and four other reflec-

tions whose phases were allowed to assume the values of 0 and  $\pi$  were arbitrarily chosen based on high  $E$  values only; this time a number of solutions satisfied the criterion discussed above. Table 2 lists the reflections used in both trials.  $E$  maps were computed for two acceptable sets of signs, one from each iterative procedure, the sets having the highest consistency index in their respective groups. The map obtained from the set of signs derived by procedure 2(b) was not interpretable, but that from the signs obtained by method 2(a) showed the 7 atoms of the hydantoin group in the mirror at  $y=\frac{1}{2}$ . No phenyl ring atoms could be located.

Table 2. *Reflections to which phases were assigned to implement Sayre's equation.*

First three reflections were used to specify the origin. Final phases are in millicycles.

$hkl$	Trial 1		$hkl$	Trial 2	
	$E$	Final phase		$E$	Final phase
1 2 2	2.26	954	5 1 1	2.69	980
1 1 15	3.53	984	1 4 14	3.66	904
1 2 3	1.52	142	4 6 9	2.15	878
1 1 1	1.93	966	3 7 7	2.59	839
1 6 2	2.31	841	1 2 2	2.26	954
2 1 5	2.01	990	2 1 5	2.01	990
3 5 7	2.23	869	1 1 15	3.53	984

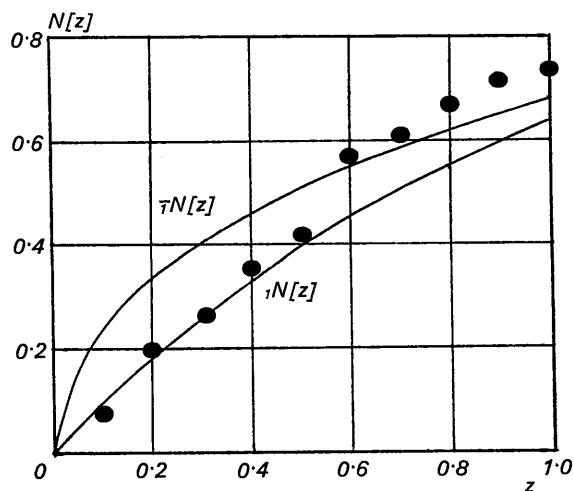


Fig. 1. Distribution of normalized intensities for diphenylhydantoin.  $N(z)$  is the fraction of the reciprocal lattice points where the normalized intensity is less than  $z$ .

These 7 atom positions were used to calculate structure factors ( $R=0.50$ ) and a three-dimensional Fourier map which showed the positions of the 6 phenyl ring atoms. However, a cycle of full-matrix least-squares refinement of the 13 atomic positions and isotropic temperature parameters dropped  $R$  only to 0.33. Clearly, something was wrong with the structure.

At this point, it was decided to change to the acentric space group  $Pn2_1a$ . The 13 atomic positions were left unchanged, the multiplicities of the 7 hydantoin atoms were adjusted, and a cycle of full-matrix least-squares refinement was performed in  $Pn2_1a$  ( $R=0.30$ ). It is emphasized here that meaningful refinement can be performed in space group  $Pn2_1a$  by leaving the atoms positions derived in space group  $Pnma$  unchanged. The starting structure is, of course, different in the two space groups: the action of the mirror plane in  $Pnma$  requires only one phenyl ring to be located, the mirror symmetry automatically fixing the second ring. In  $Pn2_1a$  the two phenyl rings are independent of each other and, hence, 6 additional atoms must be

located in addition to the 13 which completely specified the structure in  $Pnma$ . A difference Fourier map was then calculated and it yielded the positions of the atoms in the second phenyl ring. Two cycles of full-matrix isotropic least-squares refinement followed by two cycles of anisotropic refinement dropped  $R$  to 0.081. All hydrogen atoms were located in a difference Fourier map. Further refinement of all atoms reduced  $R$  to 0.052. In all least-squares refinements the quantity minimized was  $\sum w(F_o - F_c)^2$ . The average shift/error ratio in the last least-squares cycle was 0.23; the final goodness-of-fit parameter was 1.23.

Inspection of the  $E$  values used in the two attempts at structure solution (Table 2) suggests that the more important criterion in selecting origin-determining reflections is the magnitude of  $E$ . Choosing the 123 plane with  $E$  of only 1.52 as an origin-determining reflection may have been one of the causes of failure in the first attempt to solve the structure.

Another possible reason for the failure of the first set of starting reflections to yield a solution and the

Table 3. Fractional coordinates and anisotropic temperature parameters ( $\text{\AA}^2$ ) for the nonhydrogen atoms.

Estimated standard deviations are given in parentheses. The anisotropic thermal parameters are in the form  $\exp[-0.25(h^2B_{11}a^{*2} + \dots + 2klB_{23}b^*c^*)]$ .

	$x$	$y$	$z$	$B_{11}$	$B_{22}$	$B_{33}$	$B_{12}$	$B_{13}$	$B_{23}$
N(1)	0.4027 (9)	0.2424 (7)	0.4425 (4)	1.5 (2)	5.6 (4)	2.8 (2)	-0.0 (3)	0.2 (2)	0.6 (3)
C(2)	0.3271 (10)	0.2479 (8)	0.3623 (4)	3.1 (3)	3.4 (3)	2.3 (2)	-0.5 (6)	0.4 (2)	0.1 (3)
N(3)	0.1043 (9)	0.2502 (9)	0.3689 (4)	3.0 (2)	5.1 (4)	2.1 (2)	0.4 (4)	-0.9 (2)	0.2 (3)
C(4)	0.0365 (10)	0.2538 (10)	0.4509 (4)	2.3 (2)	3.5 (3)	2.6 (3)	-0.5 (5)	-0.5 (2)	0.2 (4)
C(5)	0.2381 (9)	0.2500	0.5091 (3)	1.5 (2)	4.3 (3)	2.3 (2)	-0.1 (4)	0.1 (2)	0.6 (5)
O(6)	0.4267 (9)	0.2498 (9)	0.2956 (3)	4.8 (3)	8.0 (4)	2.5 (2)	0.2 (4)	1.2 (2)	0.2 (3)
O(7)	-0.1494 (7)	0.2548 (9)	0.4761 (3)	1.8 (2)	6.7 (3)	4.3 (2)	-0.2 (4)	-0.1 (2)	0.2 (3)
C(8)	0.2246 (13)	0.1560 (9)	0.5619 (4)	3.5 (3)	4.1 (4)	2.2 (3)	-0.3 (3)	-1.1 (3)	0.2 (3)
C(9)	0.0696 (41)	0.1457 (19)	0.6263 (13)	5.0 (7)	11.7 (1.4)	6.4 (7)	-0.1 (9)	1.5 (5)	5.1 (9)
C(10)	0.0532 (36)	0.0642 (20)	0.6764 (11)	9.3 (1.0)	13.7 (1.5)	7.9 (8)	-4.2 (9)	0.7 (7)	6.5 (9)
C(11)	0.1901 (45)	-0.0185 (16)	0.6604 (11)	15.5 (1.6)	7.4 (1.0)	5.9 (7)	-6.7 (9)	-5.3 (9)	3.1 (7)
C(12)	0.3356 (38)	-0.0113 (13)	0.6016 (10)	16.7 (1.4)	4.5 (6)	5.9 (6)	-0.1 (8)	-4.2 (9)	0.3 (6)
C(13)	0.3543 (25)	0.0773 (12)	0.5503 (7)	9.2 (8)	5.0 (6)	3.4 (4)	0.2 (6)	-0.3 (5)	0.1 (4)
C(14)	0.2657 (12)	0.3412 (10)	0.5649 (4)	2.6 (3)	5.5 (5)	2.4 (3)	-1.0 (3)	0.3 (3)	-0.5 (3)
C(15)	0.1299 (22)	0.4183 (10)	0.5613 (6)	7.9 (6)	4.0 (5)	4.8 (4)	0.8 (5)	-0.4 (5)	0.3 (4)
C(16)	0.1774 (62)	0.5010 (18)	0.6101 (11)	14.8 (1.7)	4.3 (6)	5.5 (6)	0.6 (8)	-0.3 (8)	0.1 (5)
C(17)	0.3548 (29)	0.5029 (13)	0.6640 (7)	9.9 (9)	6.3 (7)	4.8 (5)	-2.6 (7)	1.9 (6)	-2.5 (5)
C(18)	0.4840 (27)	0.4272 (20)	0.6645 (9)	5.8 (7)	14.8 (1.6)	7.4 (8)	-2.9 (8)	0.2 (6)	-6.8 (9)
C(19)	0.4424 (19)	0.3395 (15)	0.6172 (7)	4.0 (4)	10.6 (9)	5.9 (5)	-0.7 (6)	-0.8 (4)	-4.3 (6)

Table 4. Fractional coordinates, isotropic temperature parameters ( $\text{\AA}^2$ ), and bond distances ( $\text{\AA}$ ) for the hydrogen atoms.

Estimated standard deviations are given in parentheses.

	$x$	$y$	$z$	$B$	H-C (or N)
H(1)	0.548 (13)	0.246 (9)	0.456 (5)	4.2 (1.9)	0.93 (8)
H(3)	0.043 (10)	0.250 (8)	0.323 (4)	2.7 (1.5)	0.80 (7)
H(9)	0.037 (30)	0.176 (11)	0.627 (9)	8.7 (3.4)	0.46 (16)
H(10)	-0.117 (42)	0.069 (23)	0.714 (16)	15.5 (8.7)	1.22 (26)
H(11)	0.110 (36)	-0.059 (17)	0.701 (11)	12.9 (5.7)	0.97 (21)
H(12)	0.477 (40)	-0.076 (23)	0.585 (14)	13.6 (8.3)	1.28 (28)
H(13)	0.458 (18)	0.089 (11)	0.512 (7)	6.6 (3.1)	0.89 (12)
H(15)	-0.029 (24)	0.417 (12)	0.522 (8)	9.3 (3.7)	1.17 (15)
H(16)	0.102 (58)	0.526 (27)	0.622 (21)	23.2 (10.0)	0.61 (36)
H(17)	0.321 (18)	0.588 (12)	0.693 (7)	6.4 (2.9)	1.26 (15)
H(18)	0.582 (24)	0.426 (14)	0.706 (9)	11.1 (4.3)	0.89 (15)
H(19)	0.559 (20)	0.300 (10)	0.618 (8)	9.3 (3.3)	0.91 (13)

success of the second set may lie in the fact that the reflections in the first set are, in total, less centric than those in the second set. Inspection of the final phases of each of the reflections (Table 2) reveals that in trial 1, 3 of the 7 reflections assigned centric phases have phase angles differing from 0 or 180° by 45° or more; whereas in trial 2, only one reflection is that different in phase from centricity. Programs used in the structure determination and refinement were from the X-ray 67 system (Stewart *et al.*, 1967). Scattering factors used were the following: O, N and C (Berghuis, Haanappel, Potters, Loopstra, MacGillivray & Vee-

nendaal, 1955) and H (Stewart, Davidson & Simpson, 1965).

Results and discussion

Fractional coordinates and temperature parameters for the non-hydrogen atoms are listed in Table 3. As can be seen from the y coordinates, the seven atoms comprising the hydantoin group lie in a plane which is almost perpendicular to C. When the y coordinate of C(5) is set at 0.25 to fix the origin in the space group, the maximum deviation of any of the other 6 atoms from the plane at y=1/4 is 0.1 Å and the average

Table 5. Comparison of observed and calculated structure amplitudes for diphenylhydantoin

The data are listed in groups of constant *h* and *k*. The four columns within each group are *l*, |*10F<sub>o</sub>*|, |*10F<sub>c</sub>*| and phase (milli-cycles). The sign in front of |*10F<sub>c</sub>*| is that of the *A* part of the structure factor. Reflections whose measured intensities were less than 2σ<sub>c</sub> are indicated with an asterisk and were treated as unobserved reflections and left out of the refinement procedure.

Table with multiple columns containing diffraction data such as h, k, l, 10Fo, 10Fc, and phase. The table is organized in groups by h and k values, with multiple columns for different l values.

deviation is 0.044 Å. The dihedral angle between the best plane through the 7 hydantoin atoms and (010) is 2.40°. Thus, it is readily apparent why the centrosymmetric symbolic addition procedure yielded the atomic positions of the hydantoin group even though the true space group for diphenylhydantoin is non-centrosymmetric; the proximity of the hydantoin-group plane to (010) results in all of the phases, calculated from the positions of those atoms only, to be very close to 0 or  $\pi$ .

Analysis of the distribution of normalized intensities by the zero moment,  $N(Z)$ , test is shown in Fig. 1. For normalized intensities from 0 to 0.5 the distribution for diphenylhydantoin follows that of an acentric structure, but for normalized intensities of 0.6 or greater the distribution is that of a centric space group. It may be that whenever such a mixed distribution of intensities occurs, a sufficiently large part of a structure in a non-centrosymmetric space group approximates a centrosymmetric arrangement in the unit cell, and use of centric sign-determining methods may provide a partial structure as a starting point in the crystallographic determination.

Table 4 lists the hydrogen-atom coordinates, tem-

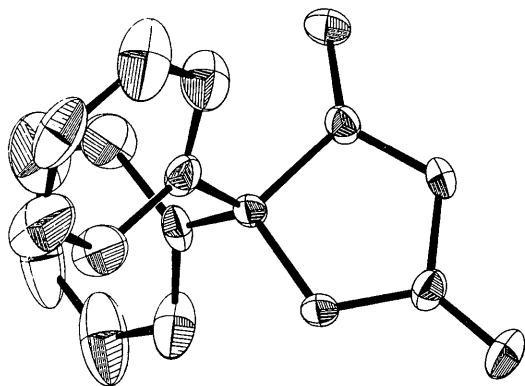


Fig. 2. Perspective drawing of the diphenylhydantoin molecule, illustrating relative thermal motions of the atoms.

perature parameters, and bond lengths. Observed and calculated structure amplitudes are listed in Table 5.

Fig. 2 shows the conformation of the molecule and the magnitudes and shapes of the atomic thermal ellipsoids. The two phenyl rings are planar (maximum deviation of the ring atoms from the best plane through each ring is 0.02 Å), as is the 5-atom hydantoin ring (maximum deviation of a ring atom from the plane is 0.03 Å with O(6) and O(7) situated -0.09 and +0.05 Å respectively from the plane through the five ring atoms). The obtuse angles between the normals to the respective planes are: hydantoin-phenyl [C(8)-C(13)], 114°; hydantoin-phenyl [C(14)-C(19)], 113°; phenyl-phenyl, 90°.

Bond lengths for the non-hydrogen atoms are illustrated in Fig. 3, and bond angles are listed in Table 6. Large standard deviations and fairly large differences between chemically equivalent bonds in the phenyl rings are primarily due to the large, extremely anisotropic thermal motion of these groups (Fig. 2). Analysis of the individual atomic thermal ellipsoids in terms of rigid-body tensors was performed using the method of Schomaker & Trueblood (1968). Calculations were carried out for a molecule consisting of three connected rigid bodies: (a) hydantoin group plus C(8) and C(14); (b) C(8)-C(13)+C(5); and (c) C(14)-C(19)+C(5). The differences between the  $U(I, J)$  derived from the input  $B(I, J)$  and those calculated from the rigid-body parameters indicate that the rigid-body treatment of the thermal motion is acceptable. Root-mean-square  $\Delta U(I, J)$ 's for the three rigid bodies, (a), (b) and (c) are 0.0048, 0.0049 and 0.0066 Å<sup>2</sup> respectively. Table 7 lists the r.m.s. amplitudes of libration and translation along the principal axes of the libration and translation tensors and the direction cosines of the respective axes referred to the cell axes  $a$ ,  $b$  and  $c$ . Rotational corrections derived from the rigid-body analyses were applied to the molecule. These corrected bond lengths are shown in parentheses in Figure 3. Before thermal correction the averaged bond lengths for the two phenyl groups were 1.370 and 1.379 Å, and after correction they were

Table 6. Bond angles (°) in diphenylhydantoin

Estimated standard deviations in parentheses.

C(2)-N(1)-C(5)	114.2 (5)	C(5)-C(14)-C(15)	122.5 (0.8)
N(1)-C(5)-C(4)	99.1 (4)	C(5)-C(14)-C(19)	114.6 (1.1)
N(1)-C(5)-C(8)	111.2 (9)	C(15)-C(14)-C(19)	122.9 (1.3)
N(1)-C(5)-C(14)	112.4 (8)	C(14)-C(15)-C(16)	118.2 (1.7)
C(4)-C(5)-C(8)	107.4 (8)	C(15)-C(16)-C(17)	121.0 (2.3)
C(4)-C(5)-C(14)	113.4 (9)	C(16)-C(17)-C(18)	118.7 (1.7)
C(8)-C(5)-C(14)	112.5 (6)	C(17)-C(18)-C(19)	123.0 (1.5)
C(5)-C(4)-N(3)	107.3 (5)	C(18)-C(19)-C(14)	116.0 (1.5)
C(5)-C(4)-O(7)	125.6 (5)	C(5)-C(8)-C(13)	124.0 (0.8)
N(3)-C(4)-O(7)	127.0 (6)	C(5)-C(8)-C(9)	120.5 (1.3)
C(4)-N(3)-C(2)	112.6 (5)	C(9)-C(8)-C(13)	115.4 (1.3)
N(3)-C(2)-N(1)	106.6 (5)	C(8)-C(9)-C(10)	123.0 (2.1)
N(3)-C(2)-O(6)	125.0 (6)	C(9)-C(10)-C(11)	119.7 (1.9)
N(1)-C(2)-O(6)	128.4 (6)	C(10)-C(11)-C(12)	118.8 (1.9)
		C(11)-C(12)-C(13)	120.6 (1.9)
		C(12)-C(13)-C(8)	122.4 (1.3)

Table 7. Principal-axis r.m.s. amplitudes of libration *L* and translation *T* and direction cosines referred to cell axes *a*, *b* and *c*

	Rigid body (a): atoms 1-8+14				Rigid body (b): atoms 5+8-13			
<i>L</i> and direction cosines	5.70° 3.93 3.41	0.013 0.514 0.858	-0.147 0.849 -0.507	-0.989 -0.120 0.087	13.42° 6.20 2.53	-0.058 -0.514 -0.856	0.709 -0.625 0.327	-0.703 -0.588 0.400
<i>T</i> and direction cosines	0.218 Å 0.163 0.145	0.088 0.388 0.918	-0.981 0.193 0.012	-0.173 -0.901 0.398	0.331 Å 0.207 0.167	0.682 0.586 0.437	-0.636 0.771 -0.042	-0.362 -0.250 0.898
	Rigid body (c): atoms 5+14-19							
<i>L</i> and direction cosines	13.32° 3.42 2.55	0.047 0.188 0.981	0.649 -0.752 0.113	0.759 0.632 -0.157				
<i>T</i> and direction cosines	0.304 Å 0.215 0.181	-0.606 -0.507 -0.613	0.741 -0.641 -0.202	-0.291 -0.576 0.764				

1.396 and 1.407 Å. Bond lengths for the hydantoin group are all normal and compare well with those found for the hydantoin atoms in allantoin (Mootz, 1965).

A second model which could also adequately describe the apparent phenyl anisotropy is one featuring disorder. If we were to choose two orientations for each phenyl ring with atom positions at the extremes of the thermal ellipsoids (Fig. 2), we might obtain more acceptable individual bond lengths for the aromatic bonds. However, the two orientations for each ring would be so close to one another that analytical refinement of the atom positions would not be rewarding. As the anisotropic thermal model is also satisfactory (the relationship between dynamic and static disorder in this case is one too close to distinguish without re-examining the structure at low temperature), it was unnecessary to investigate a disordered model more closely.

Whichever is the correct model, the effect upon the hydrogen-atom positions is unfortunate. As shown in Table 4, the estimated standard deviations in the hydrogen-atom positions and thermal parameters are extremely large and some of the bond lengths involving hydrogen are peculiar to say the least. It appears that the errors introduced by the dynamic or static disorder of the phenyl rings are large enough to make the hydrogen parameters unreliable.

The question of whether or not certain conformational features are necessary for antiepileptic efficacy can best be answered by further structural studies on other useful anticonvulsants and comparison with diphenylhydantoin. Such studies are in progress in these laboratories, and preliminary results (Camerman & Camerman, 1970) indicate that structural features of this molecule which may be pertinent to its anticonvulsant properties are the two phenyl rings at C(5) and the two carbonyl oxygen atoms. Distances between the centroids of the phenyl rings and the oxygen positions have been calculated and are shown in Table 8.

Table 8. Distances (Å) between phenyl-ring centroids and oxygen atoms

C(8)—C(13)—C(14)—C(19)	4.835
C(8)—C(13)—O(6)	5.677
C(8)—C(13)—O(7)	3.968
C(14)—C(19)—O(6)	5.514
C(14)—C(19)—O(7)	4.227
O(6)—O(7)	4.555

### Intermolecular distances

The molecules are laced together through hydrogen bonds between hydrogens bonded to the nitrogen atoms and the two carbonyl oxygen atoms. Distances and angles between the atoms involved are listed in Table 9.

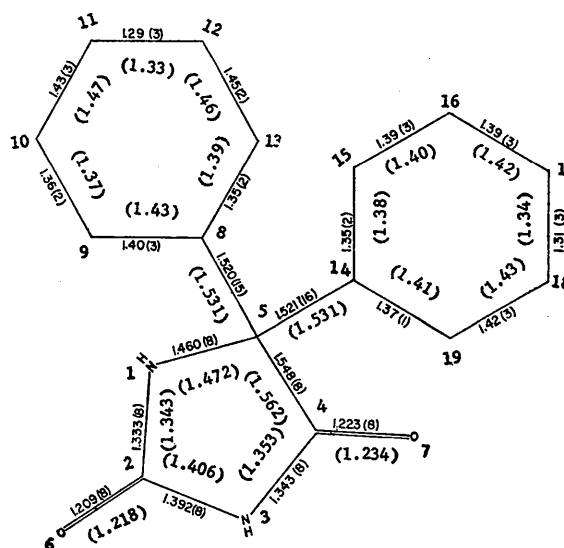


Fig. 3. Bond lengths with e.s.d.'s in parentheses. The bond lengths in parentheses are the thermally corrected ones. Estimated standard deviations are the same as for the uncorrected distances.

Table 9. *Intermolecular hydrogen bonding scheme*

O(6') is at symmetry position $[-\frac{1}{2} + x, y, \frac{1}{2} + z]$ .			
O(7') is at symmetry position $[1 + x, y, z]$ .			
H(1)···O(7')	1.92 Å	H(3)···O(6')	1.98 Å
N(1)···O(7')	2.84	N(3)···O(6')	2.78
N(1)–H(1)–O(7')	176.3°	N(3)–H(3)–O(6')	173.3°

Undoubtedly, it is this hydrogen-bonding scheme that restrains the hydantoin atoms from exhibiting the large thermal motion exhibited by the unfettered phenyl groups.

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## Crystal and Molecular Structure of Nitratobis-(2,2'-dipyridyl)cobalt(III) Hydroxide Nitrate Tetrahydrate, $[\text{Co}(\text{C}_{10}\text{H}_8\text{N}_2)_2(\text{NO}_3)](\text{NO}_3)(\text{OH}) \cdot 4\text{H}_2\text{O}$

BY C. W. REIMANN, M. ZOCCHI\*, A. D. MIGHELL AND A. SANTORO

*Institute for Materials Research, National Bureau of Standards, Washington, D. C. 20234, U.S.A.*

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The structure of nitratobis-(2,2'-dipyridyl)-cobalt(III) hydroxide nitrate tetrahydrate,  $[\text{Co}(\text{C}_{10}\text{H}_8\text{N}_2)_2(\text{NO}_3)](\text{NO}_3)(\text{OH}) \cdot 4\text{H}_2\text{O}$ , has been determined by single-crystal X-ray diffraction techniques. Crystals of this complex are monoclinic with  $a = 10.923(2)$ ,  $b = 15.998(4)$ ,  $c = 14.442(2)$  Å,  $\beta = 101.93(2)^\circ$ , space group  $C2/c$ ,  $\rho_c = 1.57 \text{ g.cm}^{-3}$ ,  $\rho_o = 1.54 \text{ g.cm}^{-3}$ , and  $Z = 4$ . The structure was solved by Patterson and Fourier methods. The cobalt atom is octahedrally coordinated by two molecules of 2,2'-dipyridyl and by a bidentate nitrate group. Water molecules, nitrate groups, and the hydroxide ions are involved in hydrogen bonds which extend continuously in the *a* and *c* directions. The final refinement of the structure by full-matrix anisotropic least-squares analysis resulted in an *R* value of 6.2%, based on 2995 observed reflections.

### Introduction

Most of the information on the stereochemistry of first-row transition metal ion complexes that contain coordinated nitrate groups and nitrogen donor ligands is derived from spectroscopic data (Addison & Sutton, 1967). From the analysis of the spectroscopic data it is inferred that the nitrate groups may act as monodentate, bidentate, or bridging ligands. But very few crystal-structure data are available to confirm the spectroscopic interpretations and to provide accurate bond distances and angles for coordinated nitrate groups.

As part of a series of studies of amine complexes of

transition metal nitrates, a crystalline hydrate containing two molecules of 2,2'-dipyridyl, two nitrate groups, and one hydroxide ion per cobalt(III) ion was selected for an X-ray diffraction analysis. In this complex the 2,2'-dipyridyl molecules may assume either a *cis* or *trans* configuration, each permitting several possibilities for the overall coordination, including coordination by one or both of the nitrate groups. The presence of water molecules and hydroxide ions, moreover, indicates that hydrogen bonding would occur in the structure. Therefore, determination of the structure was undertaken, to determine the role of the nitrate groups in the structure, to provide accurate values of the bond distances and angles for the nitrate groups and the 2,2'-dipyridyl molecule, and to obtain information on the hydrogen-bonding network.

\* Present address: Istituto Politecnico di Milano, Milano, Italy.