8 times with 25 ml of methylene chloride; treatment with 25 ml of 0.3 *M* pyridine–HCl solution in methylene chloride; washing 5 times with 25 ml of methylene chloride; washing 6 times with 25 ml of DMF until free of chloride; treatment 2 times with 25 ml of 10% triethylamine in DMF; washing 6 times with DMF; potentiometric titration of the neutralization solution and washings (remaining amino groups); washing with 25 ml of the following solvents; 4 times ethanol, 2 times acetic acid. The fully protected peptide, esterified to the resin, was transesterified in a mixture of triethylamine, methanol, and hexamethylphosphoric acid triamide (1:1:6, v/v) for a period of 48 hr.[11] After a filtration and concentration 2.05 g of product (60% yield, with respect to Gly) was obtained. After gel filtration on Sephadex LH 20 in DMF (3 × 230 cm column) 735 mg of peptide (21%) resulted. Amino acid analyses were as follows: Gly, 1.06; Ala, 1.0; Val; 2.1; Leu, 1.85; Thr, 1.72 (not corrected).

The R_f values for the tlc on silica gel were: 0.6 (1-butanol–acetic acid–water, 3:1:1), 0.55 (2-butanol–pyridine–water, 2:2:1); nonuniform spots, ninhydrin negative, Cl_2/tolidine positive.

For identification by mass spectrometry[12] 31.7 mg of the product was treated for 1 hr with 1 ml of TFA, precipitated with ether, dissolved in methyl alcohol, and again precipitated with ether. The dried precipitate was acetylated for 1 hr with 3 ml of 50% acetic acid–acetic anhydride; 8.7 mg of the acetylated peptide mixture obtained after evaporation to dryness was permethylated according to the method described by Hakamori.[13] The mass spectrum of the permethylated peptide mixture was measured on the LKB 9000 (LKB Produkter Stockholm). Under the conditions employed, the peptide bond is preferentially cleaved, and the fragmentation series corresponding to cleavage of amino acids from the peptide with retention of the positive charge on the acyl fragment (*i.e.*, Ac-(CH_3) Val-(CH_3) Thr(Bzl)-(CH_3)Val- etc. for V and Ac-(CH_3) Thr(Bzl)-(CH_3)Val- etc. for VI were found.

For end group determination, 1 mg of the peptide mixture was deblocked with TFA, dansylated according to the method described by Hartley and Massey,[14] and hydrolyzed with 6 *N* HCl at 110° for 20 hr. Tlc with benzene–pyridine–acetic acid (80:20:5, v/v) on silica gel showed the presence of the derivatives of valine and threonine (R_f: 0.83 and 0.27). Estimation of the fluorescence of both spots gave a ratio of about 1:2.

The trifluoroacetylation was carried out with methyl-TFA after cleavage of the BOC group by treatment with 1 *N* HCl in acetic acid for 30 min.

Acknowledgment. We gratefully acknowledge the support of this work by the Deutsche Forschungsgemeinschaft.

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Stereochemical Basis of Anticonvulsant Drug Action. II. Molecular Structure of Diazepam[1]

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Abstract: The crystal structure of diazepam has been determined as part of an investigation into relationships between molecular shape and pharmacological activity of anticonvulsant drugs. The compound crystallizes in the monoclinic system with cell dimensions $a = 12.928$, $b = 13.354$, $c = 7.976$ Å, $\beta = 90.01°$, space group $P2_1/a$. The structure was determined by direct centrosymmetric phasing procedures using data collected on a four-circle diffractometer. Refinement was by anisotropic full-matrix least squares to a final *R* value of 0.039. The two phenyl rings are planar and the obtuse angle between the normals to the two planes is 125°. There are conformational features very similar to certain features found in another anticonvulsant drug, diphenylhydantoin.

Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) (I) and other derivatives of 1,4-benzodiazepine were first successfully employed in medicine as tranquilizing agents. More recently, however, these drugs have displayed pharmacological properties that indicated clinical potential for the treatment of various types of epilepsy. Diazepam, in particular, has been shown to possess specific anticonvulsant activity to varying degrees against grand mal, psychomotor, and petit mal epilepsies.[3,4] Indeed, after dramatic results were obtained from clinical tests, diazepam was praised as the "drug of choice for the emergency treatment of all cases of status epilepticus."[5] The role of diazepam as a most important antianxiety agent and at the same time as a useful anticonvulsant seemingly contradicts the general rule that desynchronizing drugs are also good antiepileptics while synchronizing drugs may have a facilitating effect on seizure discharge.[6] In the light of diazepam's range of therapeutic properties we have decided to determine the three-dimensional molecular structure of this compound and compare its steric configuration to that of other chemically different anticonvulsant drugs. A preliminary account of the similarities in configuration between diphenylhydantoin and diazepam has been reported.[7]

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(1) Part I of this series: A. Camerman and N. Camerman, *Acta Crystallogr., Sect. B*, in press.
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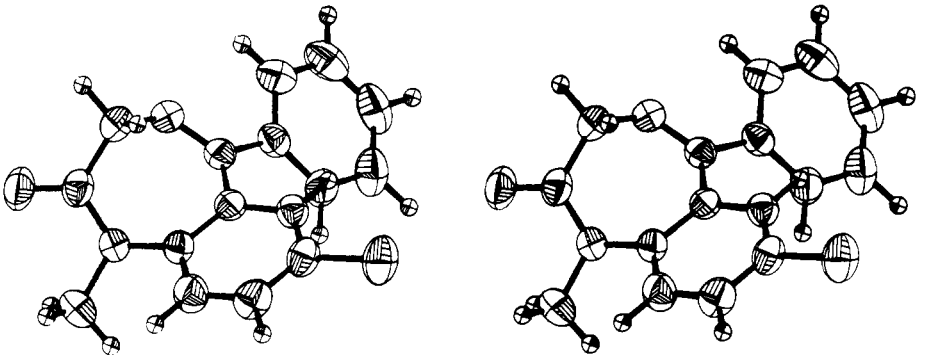
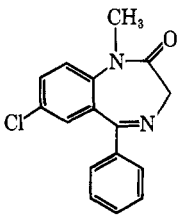


Figure 1. Stereoscopic drawing of diazepam illustrating the molecular conformation and the thermal motion ellipsoids for the nonhydrogen atoms. Hydrogen atoms are represented by isotropic spheres.



I

Experimental Section

Diazepam powder was dissolved in a mixture of water and acetone and colorless, lath-shaped crystals were obtained by solvent evaporation. Unit cell parameters were determined at 65°F by least-squares minimization of the difference between calculated and observed values for reflections measured at both $+2\theta$ and -2θ using a four-circle diffractometer (λ Mo Kα = 0.71069 Å). Density was measured by flotation in a potassium iodide solution. Crystal data are given in Table I. X-Ray intensities were measured on

Table I. Diazepam Crystal Data

Formula	$C_{16}H_{13}N_2OCl$
Mol wt	284.73
Crystal system	Monoclinic
a, Å	12.9284 ± 0.0041
b, Å	13.3537 ± 0.0068
c, A	7.9763 ± 0.0017
β, deg	90.010 ± 0.025
V, Å^3	1377.04
D_m, g cm^{-3}	1.39
Z	4
D_x, g cm^{-3}	1.37
F(000)	592
Absent reflections:	$0k0$ when k odd; $h0l$ when h odd
Space group	$P2_1/a$
μ (for Mo Kα), cm^{-1}	3.0

a manually operated four-circle diffractometer on a crystal approximately 0.33 × 0.20 × 0.12 mm to 2θ = 55°, corresponding to an interplanar spacing of 0.77 Å. The $\omega/2\theta$ scan technique using Nb-filtered Mo radiation was employed. A total of 3171 independent reflections was measured, of which 2438 had intensity greater than $2\sigma_c$, where $\sigma_c = (N_{B1} + N_{PK} + N_{B2})^{1/2}$, N_{B1} and N_{B2} are the background counts on each side of the peak, and the N_{PK} is the scan count. Those reflections whose intensities were less than $2\sigma_c$ were classified "unobserved" and not used in structure refinement. Frequently measured standard reflections indicated the diffractometer stability to be ±1%; hence the estimated error in the intensity of each reflection is $\sigma_I = [\sigma_c^2 + (0.01\sigma_c^2)^2]^{1/2}$. Structure factors were obtained from the intensities in the usual fashion; weights were taken as $w^{1/2} = 1/\sigma_F$. No absorption corrections were applied.

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Structure Determination. The structure factor data were converted to normalized values, E, and the symbolic addition procedure[8] was used to determine phases of the reflections with $E > 1.80$. The 50 reflections with the largest magnitudes of E ($|E| > 2.34$) were chosen as generators in a computer program[9] used to obtain phases. Three origin-specifying reflections (Table II)

Table II. Phases Assigned to Origin Specifying Reflections

$\vec{h}$	$E(\vec{h})$	$\phi(\vec{h})$
2 7 9	3.76	π
7 8 1	3.35	π
3 8 2	2.75	0

were assigned phases and iterative application of the Σ_2 formula

$$SE_h \sim S\Sigma E_k E_{h-k}$$

(where S mean sign of), with minimum acceptable probability of 0.90, led to signs for the other 47 planes. These reflections were then used in the Σ_2 formula to generate signs for planes with $2.34 > |E| > 1.80$. Using this procedure 154 of the total of 193 reflections with $|E| > 1.80$ had signs determined.

A three-dimensional E map was computed from the 154 data; this map could be interpreted to yield the positions of 15 of the 20 nonhydrogen atoms. A three-dimensional Fourier synthesis calculated with phases based on the partial structure revealed the positions of the other five atoms.

Refinement of the Structure. The first postulated structure gave a discrepancy factor of 0.25 which decreased to 0.16 in two cycles of

$$R = \frac{\sum||F_o| - |F_c||}{\sum|F_o|}$$

full-matrix, least-squares refinement of atomic coordinates and isotropic thermal parameters. The quantity minimized in the least-squares calculations was $\Sigma w(F_o - F_c)^2$. Two more cycles of refinement using anisotropic thermal parameters reduced R to 0.071. A difference electron density map calculated at this stage revealed the 13 hydrogen atom positions.

Further full-matrix, least-squares refinement of all atomic coordinates and anisotropic thermal parameters reduced R to 0.039.

Atomic scattering factors used were the following: O, N, and C: Berghuis, *et al.*,[10] H: Stewart, *et al.*,[11] Cl: Viervoll and Øgrim.[12] Programs in the X-ray 67 system[13] were used for most of the calculations.

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Table III. Fractional Coordinates and Anisotropic Thermal Parameters (Å²) for Diazepam[a]

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl(1)	0.3117(0)	0.6647(0)	0.9153(1)	6.11	3.72	3.50	0.03	−0.55	−1.49
C(2)	0.2770(1)	0.6014(1)	0.7336(2)	4.10	2.59	2.66	−0.22	0.02	−0.28
C(3)	0.1889(1)	0.6294(1)	0.6477(2)	4.22	3.21	3.54	0.93	0.24	−0.08
C(4)	0.1649(1)	0.5807(1)	0.5002(2)	3.57	3.61	3.28	0.92	−0.38	0.08
C(5)	0.2774(1)	0.5044(1)	0.4373(2)	2.77	2.97	2.43	−0.04	−0.13	0.20
C(6)	0.3167(1)	0.4759(1)	0.5262(2)	2.53	2.52	2.48	−0.14	0.06	0.27
C(7)	0.3396(1)	0.5262(1)	0.6750(2)	2.88	2.75	2.76	−0.25	−0.19	−0.02
N(8)	0.1966(1)	0.4555(1)	0.2870(1)	2.61	3.78	2.58	−0.14	−0.31	−0.11
C(9)	0.0860(1)	0.4377(2)	0.2567(3)	2.87	5.44	4.04	−0.39	−0.74	−0.33
C(10)	0.2615(1)	0.4416(1)	0.1539(2)	3.71	3.08	2.47	−0.27	−0.13	0.37
O(11)	0.2296(1)	0.4141(1)	0.0178(1)	4.86	4.92	2.43	−0.71	−0.42	−0.35
C(12)	0.3743(1)	0.4598(2)	0.1894(2)	3.37	4.64	2.52	−0.36	0.25	0.44
N(13)	0.4133(1)	0.3866(1)	0.3099(2)	2.74	4.15	2.71	0.09	0.24	−0.02
C(14)	0.3875(1)	0.3969(1)	0.4647(2)	2.27	2.88	2.76	−0.29	−0.03	−0.17
C(15)	0.4369(1)	0.3271(1)	0.5870(2)	2.59	2.76	3.04	−0.05	−0.38	−0.35
C(16)	0.3932(1)	0.3052(1)	0.7423(2)	3.57	3.83	2.85	0.39	−0.23	0.05
C(17)	0.4432(1)	0.2411(1)	0.8530(2)	5.65	4.54	3.21	0.63	−1.06	0.27
C(18)	0.5374(2)	0.1988(1)	0.8105(2)	4.97	4.10	4.48	0.75	−2.06	−0.07
C(19)	0.5804(2)	0.2196(1)	0.6555(3)	3.04	3.69	6.11	0.74	−1.04	−0.43
C(20)	0.5308(1)	0.2829(1)	0.5443(2)	2.75	3.16	4.36	0.11	0.02	−0.16
H(3)	0.1426(14)	0.6835(14)	0.6952(23)	3.88	4.45	5.98	2.14	−0.66	−2.44
H(4)	0.1011(14)	0.6017(13)	0.4391(21)	4.30	4.57	4.21	2.38	−2.23	−1.11
H(7)	0.4036(12)	0.5082(12)	0.7347(19)	2.31	3.48	3.82	1.08	−1.94	−0.27
H(9.1)	0.0499(13)	0.4344(17)	0.3666(23)	3.42	9.63	2.71	−1.41	1.22	−1.89
H(9.2)	0.0567(17)	0.4912(19)	0.1846(32)	5.46	7.96	9.39	−1.34	−3.80	4.08
H(9.3)	0.0760(14)	0.3738(17)	0.1954(27)	3.67	4.74	8.05	−2.16	0.15	−3.20
H(12.1)	0.3835(13)	0.5342(14)	0.2328(20)	4.17	3.70	3.78	−0.78	−1.04	1.06
H(12.2)	0.4127(12)	0.4517(14)	0.0781(18)	3.27	8.46	1.11	−0.50	2.28	−0.39
H(16)	0.3224(14)	0.3339(14)	0.7754(21)	3.09	5.98	4.54	2.28	0.77	1.07
H(17)	0.4124(17)	0.2301(18)	0.9735(19)	10.91	11.33	10.20	0.63	1.20	1.41
H(18)	0.5753(16)	0.1546(16)	0.8964(23)	7.09	9.43	5.34	4.84	−3.71	2.38
H(19)	0.6480(14)	0.1934(15)	0.6220(25)	2.48	6.51	9.68	1.92	1.81	1.66
H(20)	0.5591(12)	0.2985(12)	0.4338(18)	4.68	4.78	3.30	0.75	2.46	0.74

[a] Estimated standard deviations are given in parentheses.

The final atomic positional and thermal parameters for all the atoms are listed in Table III. The B_{ij}'s are coefficients in the expression

$$\exp[-0.25(h^2B_{11}a^{*2} + \ldots + 2klB_{23}b^*c^*)]$$

The table of final observed and calculated structure factors may be found in the microfilm edition of this journal.[14]

Discussion

Molecular Structure. Figure 1 is a stereoscopic drawing illustrating both the conformation of the diazepam molecule and the magnitudes and shapes of the atomic thermal ellipsoids. The compound may be regarded as a nonplanar, seven-atom heterocyclic ketone fused to a planar chlorophenyl ring and substituted with another planar phenyl group. Least-squares planes were calculated through the atoms comprising the two phenyl rings; deviations of the atoms from these planes are given in Table IV. The obtuse angle between the normals to the best planes through the two groups is 125.3°.

Bond lengths and angles in diazepam are illustrated in Figures 2 and 3, respectively. Estimated standard deviations are 0.002 Å and 0.12–0.18° for bonds and angles between nonhydrogen atoms and 0.02 Å and 1.0–2.0° for bonds and angles involving hydrogen. Both nitrogen atoms appear to be essentially trigonal in configuration and the shortening of the C(5)–N(8) bond (see Figure 2 for numbering scheme) from the trigonal carbon–trigonal nitrogen single bond length of 1.47 Å[15] suggests that there is some electron delocalization between the chlorophenyl ring and the adjacent amide group. That is, resonance structures drawn with a double bond between C(5) and N(8) do play a minor role in the electronic description of the diazepam molecule. Other bond lengths are what one would expect for such a molecule and require no special comment.

The configuration of the seven-membered ring can be seen best in Figure 1. It can be described approximately as a boat-shaped structure with a fold between atoms C(6) and C(12).

The structure of another derivative of 1,4-benzodiazepine has been reported.[16] In that molecule the seven-membered ring is also boat-shaped but the two

Table IV. Deviations of Atoms from Least-Squares Planes

Plane I		Plane II	
Atom	Δ, Å	Atom	Δ, Å
C(15)	−0.006	C(2)	−0.003
C(16)	0.001	C(3)	0.002
C(17)	0.005	C(4)	0.001
C(18)	−0.006	C(5)	−0.002
C(19)	0.001	C(6)	0.001
C(20)	0.005	C(7)	0.001
C(14)[a]	−0.036	N(8)[a]	0.034
		Cl(1)[a]	−0.067
		C(14)[a]	−0.029

[a] These atoms not used in calculating the plane.

(14) This table will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

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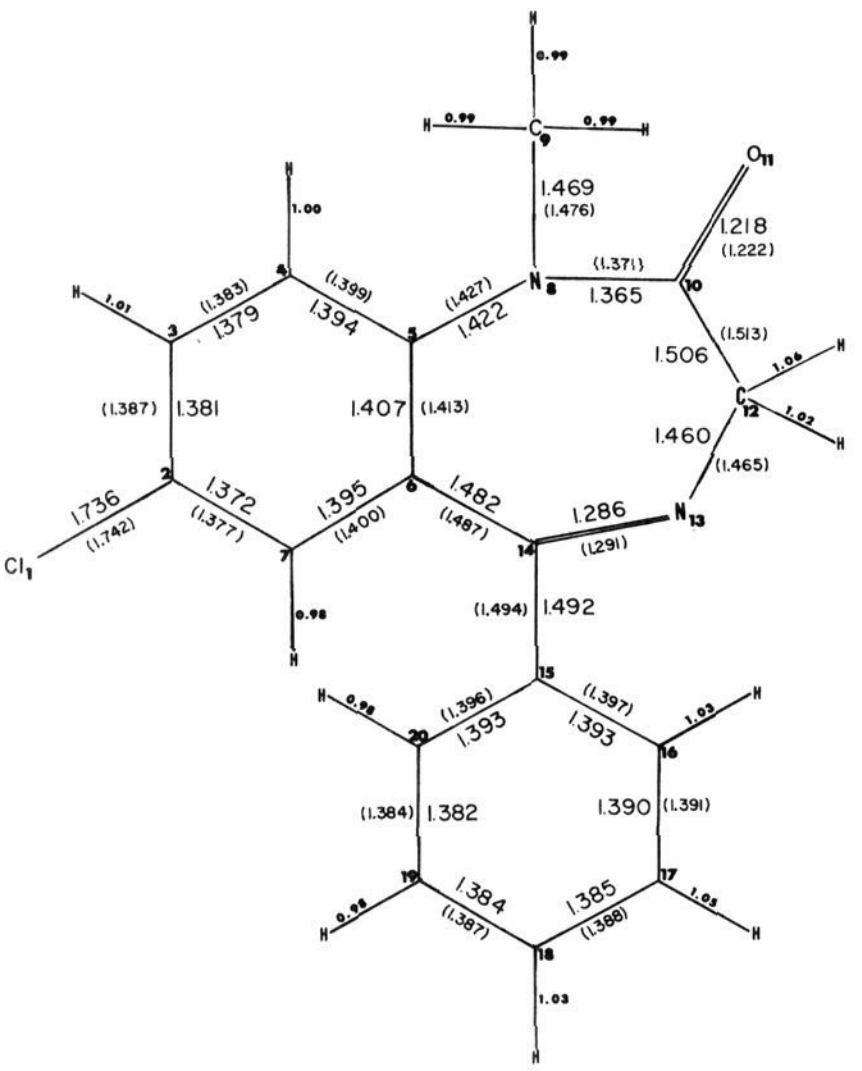

Figure 2. Bond lengths in diazepam before correction for thermal motion of the atoms, and after correction (in parentheses).

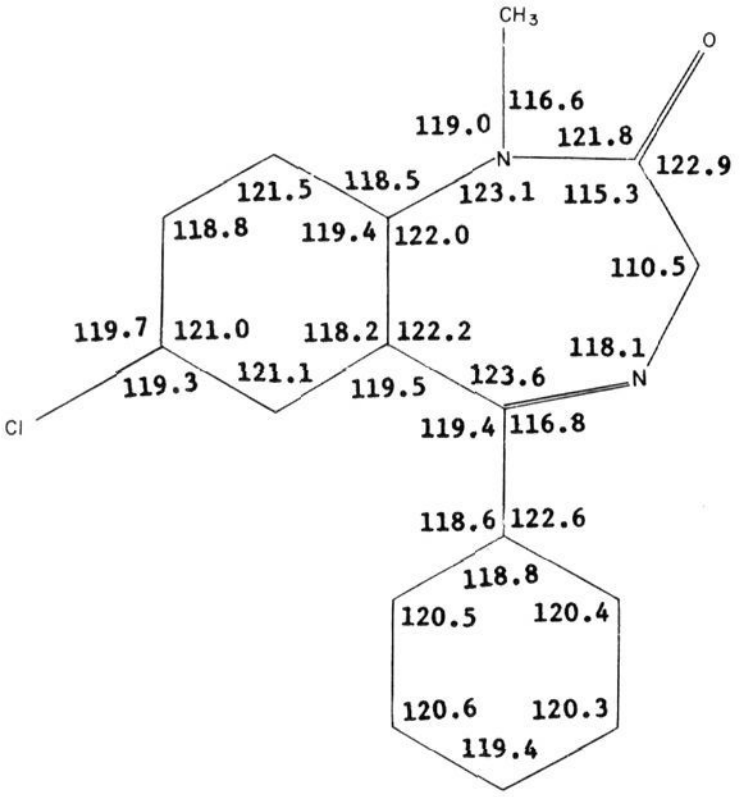

Figure 3. Bond angles in diazepam.

nitrogen-atom ends of the boat are twisted with respect to each other. However, in that molecule the nitrogen corresponding to N(13) has a methyl group attached to it, forms only a single bond to C(14), and displays a tetrahedral rather than trigonal (as in diazepam) configuration.

Figure 1 shows the magnitudes and shapes of the nonhydrogen atom thermal ellipsoids. Analysis of the thermal motion in terms of rigid-body tensors[17] was

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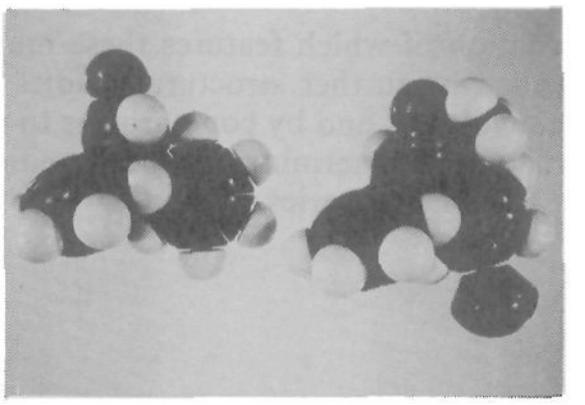

Figure 4. Molecular models of the stereochemical conformations in the crystal of diphenylhydantoin (left) and diazepam.

performed with calculations carried out for a molecule consisting of two connected rigid bodies: atoms 1–14 and atoms 14–20. The small differences between the U_{ij} derived from the input B_{ij} and those calculated from the rigid-body parameters indicate that this treatment of the thermal motion is acceptable. Root-mean-square ΔU_{ij}'s for the two rigid bodies are 0.0024 and 0.0013 Å^2, respectively. Rotational corrections to the bond lengths derived from the rigid-body treatment were applied to the molecule; the corrected bond lengths are shown in parentheses in Figure 2. As can be seen from a comparison of the two sets of bond lengths in Figure 2, the corrections to the bonds are not large; before correction the average bond length in phenyl 15–20 was 1.388 Å, after correction it was 1.391 Å.

Conformational Similarities to Diphenylhydantoin. A space-filling model of diazepam has been constructed from the results of the structure determination. Figure 4 shows a comparison of that model with a similar model constructed for diphenylhydantoin,[1] the anticonvulsant drug most widely employed against grand mal epilepsy. Although the two drugs are chemically very different, it is evident that the relative positioning and space-filling characteristics of the two phenyl groups in each compound are very similar, lending a striking conformational resemblance to the two molecules. In addition, when the two molecules are superimposed such that the two phenyl rings of each best overlap, a ketonic oxygen of each drug also overlaps. To a lesser degree N(13) of diazepam also superposes onto the second ketonic oxygen of diphenylhydantoin. Hence the groups which may be pertinent to diazepam's effectiveness against epilepsy are the phenyl and chlorophenyl rings and O(11) and N(13). Distances between the centroids of the two rings and the oxygen and nitrogen positions have been calculated and are shown in Table V, along with comparable distances in diphenylhydantoin.

Table V. Distances (Å) between Aromatic Ring Centroids and O(11) and N(13) in Diazepam and Comparable Distances in Diphenylhydantoin (DPH).

Distance		DAZ	DPH
Group (15)–(20)	Group (1)–(7)	5.056	4.835
Group (15)–(20)	O(11)	6.684	5.677
Group (15)–(20)	N(13)	3.644	3.968
Group (1)–(7)	O(11)	5.345	5.514
Group (1)–(7)	N(13)	4.059	4.227
O(11)	N(13)	3.346	4.555

The question of whether specific conformational features are necessary for antiepileptic effectiveness, and

the determination of which features these may be, can best be clarified by further structural studies on other useful anticonvulsants and by comparisons to the drugs already structurally determined. Such studies are in progress in these laboratories.

Acknowledgment. We thank Professor L. H. Jensen for the use of his facilities and for encouragement and advice. Supported in part by U.S. Public Health Service Grant GM-10828 from the National Institutes of Health.

Communications to the Editor

On the Completely Stereospecific Exchange of Carbon Monoxide in Bis(trichlorosilyl)tetracarbonylruthenium

Sir:

Exchange or displacement reactions of ^{13}CO or $C^{18}O$ with metal carbonyls and their derivatives provide a powerful tool in mechanistic studies, since the site of the labeled ligand in the coordination sphere can be determined by a suitable vibrational analysis. In most reported cases (*e.g.*, $XMn(CO)_5$,[1,2] $I_2Fe(CO)_4$[3]) the labeled carbon monoxide is distributed statistically among the nonequivalent sites of the product molecule.

In order to observe preferential enrichment in specific sites, not only must the introduction at a specific site be kinetically favored, but, as pointed out by Brown,[4] nondissociative exchange between sites must be slow; that is, the molecule in question must be stereochemically rigid under the conditions of the experiment. Two systems have recently been reported which appear to meet these criteria: *o*-phenanthrolinetetracarbonylchromium[5] and piperidinepentacarbonylmolybdenum.[6] In both compounds, carbonyl groups trans to the nitrogen ligands exchanged more slowly by a factor of 3 or 4.

We now report our discovery of the novel properties of *cis*-$Ru(CO)_4(SiCl_3)_2$ (**1**), which exchanges *two* equatorial carbonyl ligands while the axial carbonyls do not exchange at all.[7] We believe that this behavior has important implications for the understanding of the five-coordinate intermediate in dissociative metal carbonyl reactions.

Bis(trichlorosilyl)tetracarbonylruthenium has been prepared[8] as an equilibrium mixture of cis and trans isomers which may be separated by fractional sublimation; the isomers are not interconverted at an observable rate at room temperature in solution or in the solid state.[9] A solution of **1** in *n*-heptane at room temperature was placed under *ca.* 1 atm of ^{13}CO (95.5% enriched) and the ir spectrum was examined at intervals over an 18-hr period. The spectrum of the final enriched product showed no change over an additional 24 hr. The initial and final spectra are shown in Figure 1. By means of the usual energy-factored vibrational analysis, the major bands in the final spectrum were shown to correspond to those calculated for the equatorially disubstituted form of **1**.[10] At intermediate stages of the exchange, bands predicted for equatorially monosubstituted **1** were observed, but these became weak as the exchange neared completion. At no stage were any of the predicted bands uniquely characteristic of mono- or diaxially substituted **1** observed. In fact, even a qualitative consideration of Figure 1 indicates that the exchange is stereospecific. The asymmetric stretching vibration of the axial set of carbonyls[7] (B_1 in all-^{12}CO molecule of C_{2v} symmetry, A'' in the C_s molecule 5, and B_1 in the equatorially di-^{13}CO molecule) cannot couple to other vibrations of the molecule. Hence its position and intensity will remain unchanged if the axial set is not substituted, and this is observed for the 2084-cm^{-1} band.

The rate constant for the exchange of **1** with 95.5% enriched ^{13}CO (26.6°, *n*-heptane, 750 mm) was 1.04×10^{-4} sec^{-1}. The value was unchanged within experimental error when 95.5% ^{13}CO was diluted with nitrogen to ^{13}CO contents of 60, 40, and 20%, thereby establishing that the reaction follows overall first-order kinetics. From runs at 20.2 and 34.8°, we estimate $\Delta H^{\pm} = 26.7 \pm 1.0$ kcal and $\Delta S^{\pm} = 3.0 \pm 3.0$ eu.

Under similar conditions, *trans*-$Ru(CO)_4(SiCl_3)_2$ (**2**) undergoes no exchange with ^{13}CO, but ultraviolet irradiation under ^{13}CO rapidly brings about its conversion to the cis isomer which is stereospecifically enriched exclusively in the equatorial positions.[11]

The foregoing results can be rationalized in terms of a common five-coordinate intermediate having the geometry designated in **3**, with both trichlorosilyl groups in equatorial positions of the trigonal bipyramid, as indicated in Scheme I.

The favored intermediate **3** might appear to be capable of reaction with ^{13}CO to form the enriched

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(4) T. L. Brown, *Inorg. Chem.*, **7**, 2673 (1968).

(5) M. Dokiya, R. D. Johnston, and F. Basolo, *ibid.*, **9**, 996 (1970).

(6) D. J. Darensbourg, M. Y. Darensbourg, and R. J. Dennenberg, *J. Amer. Chem. Soc.*, **93**, 2807 (1971).

(7) In accord with normal practice in these cis octahedral carbonyl systems, we take the trichlorosilyl ligands to lie in the equatorial plane, as the drawings suggest. We take the C_2 axis as *z* and the equatorial plane as the *yz* plane.

(8) Details of the synthesis from $Ru_3(CO)_{12}$ and Cl_3SiH will shortly be submitted for publication.

(9) See, however, R. K. Pomeroy and W. A. G. Graham, *J. Amer. Chem. Soc.*, **94**, 274 (1972).

(10) Force constants used were $k_{ax} = 17.96$, $k_{eq} = 17.91$, $k_{ax,ax} = 0.42$, $k_{eq,eq} = 0.19$, and $k_{ax,eq} = 0.22$ mdyn $Å^{-1}$. Calculated frequencies (cm^{-1}) for various species are as follows: all-^{12}CO, 2149.6, 2102.8, 2084.2, 2093.3; axial mono-^{13}CO, 2139.9, 2099.2, 2050.4, 2093.3; equatorial mono-^{13}CO, 2145.0, 2099.4, 2054.2, 2084.2; equatorial di-^{13}CO, 2140.5, 2064.6, 2084.2, 2046.6. Observed band positions are listed in the caption to Figure 1.

(11) During the isomerization of unenriched **2** under ^{13}CO, the first new bands to appear were those of equatorially monosubstituted **1**. Therefore **2** goes *directly* to enriched **1** and is not converted to unenriched **1** with *subsequent* ^{13}CO exchange.