THE UNIVERSITY OF OKLAHOMA

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THE CRYSTAL AND MOLECULAR STRUCTURES OF SOME PHOSPHOROUS HETEROCYCLES, A COBALT(III) BAEN COMPLEX WITH GLYCINE AND $\Delta^{1,1'}$-DICYCLOHEXENYL KETONE

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THE CRYSTAL AND MOLECULAR STRUCTURES OF

SOME PHOSPHOROUS HETEROCYCLES,

A COBALT(III) BAEN COMPLEX WITH GLYCINE AND

$\Delta^{1,1'}$-DICYCLOHEXENYL KETONE

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To My Parents

ACKNOWLEDGEMENTS

The career of a graduate student, which culminates in a work such as presented here, is not just a period of acquisition of knowledge, but more importantly of personal growth and development in the arts of thinking and self-control. The primary responsibility of a research director to the graduate student is to help him develop his potential as a creative scientist by giving him paths of self-discovery. It is in these qualities that Dr. Dick van der Helm excells, not only in imparting his knowledge and experience in the field, but in creating the atmosphere in which a student can learn responsibility, self-instruction, and determination to complete a task once started. It is for this that I extend my deepest appreciation to him.

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Many other people and groups are acknowledged at the end of each chapter and in the titles of the chapters. Thanks should be given again here to Dr. Roland Lehr, Michael Wilson, Dr. E. Darrell Berlin, Dr. Mitchell Poling, and the personnel of the O.U. Computing Center.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TABLES

(Continued)

LIST OF FIGURES

LIST OF FIGURES

(Continued)

THE CRYSTAL AND MOLECULAR STRUCTURE OF $\Delta^{1,1'}$-DICYCLOHEXENYL KETONE

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Abstract

The crystals of $\Delta^{1,1'}$-dicyclohexenyl ketone, $C_{13}H_{18}O$, are triclinic, space group $P\bar{1}$. The 2152 data were taken at -110°C with cell dimensions a=9.388(3), b=8.693(5), c=9.385(3) Å, α=104.85(3), β=113.77(3), γ=117.16(2)°. The structure was determined by direct methods and has refined to an R value of 5.1%. The structure is partially disordered at room temperature.

The crystals are colorless, but show a reversible photochromic change when subjected to near ultraviolet radiation. Although the crystals undergo the same color change at low temperature, the reaction is not reversible and the crystals remain colored indefinitely at -110°C. Therefore, in addition to the data collected on the crystal in its clear-form, a data set was collected on the compound in its pink-form at low temperature in an attempt to see a change in conformation or structure.

INTRODUCTION

Crystals of $\Delta^{1,1'}$-dicyclohexenyl ketone (DCK) undergo a reversible photochromic change when subjected to near ultraviolet radiation. The crystals visually change from clear to pink to a deep red depending on the length and intensity of irradiation. The process is readily reversible at room temperature, the crystals losing their color in a matter of minutes when removed from the exciting light. The formation of colored product with irradiation proceeds readily at low temperature, indicating a photochemical reaction, however the loss of color is apparently a thermal process, since the crystals when maintained at a low temperature (less than 0°C) after being irradiated, were seen to remain in the colored form indefinitely.

Several studies of photochromic reactions have been reported in the literature. Photochromism through partial torsion about an essential double bond in bianthrones was studied by Korenstein, Muskzat and Sharafy-Ozeri (1973). An irreversible photochromic reaction of p-nitrophenol was studied by X-ray crystallography by Coppens (1960). An intermolecular reaction was determined to be the basis of the photochromic change in this case. The crystal structures of 2-(2',4'-dinitrobenzyl)pyridine and 4-(2',4'-dinitrobenzyl)pyridine have been determined (Seff and Trueblood, 1968), (Otterson and Seff, 1974) to elucidate the reversible photochromic change observed in the former. An intramolecular tautomeric reaction in which a methylene hydrogen is transferred to the oxygen of the ortho-nitro group and then to the pyridine nitrogen is postulated on the basis of these structural

determinations.

Lehr (1968) studied cyclization reactions of $\Delta^{1,1'}$-dicyclohexenyl ketone, a cross conjugated dienone, in order to resolve the question of conrotatory versus disrotatory ring closure across C(2)-C(2'). Conrotatory closure was observed for the acid catalyzed reaction, whereas disrotatory closure was observed for the photochemical reaction in solution. The reaction products for the photolysis in benzene indicated that hydrogen abstraction at C(6), (C(6')), by the carbonyl O(8) may be involved in the cyclization reaction.

We have determined the structure of the clear-form of $\Delta^{1,1'}$-dicyclohexenyl ketone at room temperature and at -110 degrees C and in the pink-form at -110 degrees C to see if a difference could be observed in the structures. If no difference could be observed it was hoped that an accurate determination of the crystal structure would indicate whether the photochromic change is caused by an inter- or intramolecular reaction and perhaps infer a mechanism.

EXPERIMENTAL

Crystals of $\Delta^{1,1'}$-dicyclohexenyl ketone were grown originally by dissolving a sample of DCK in methanol, adding water until the solution became cloudy and allowing it to stand. Crystals grown in this manner visually appeared excellent, but a high percentage were found to be twinned. A crystal was selected which was not twinned and the space group determined to be $P\bar{1}$ on a G.E. XRD-5 diffractometer. It was necessary to put the crystal in a capillary in order to take

data as the crystals gradually sublimed at room temperature, losing all diffracted intensities in 1-2 days. Data were collected and the structure solved at room temperature in this manner, but as discussed in the next section refinement was not satisfactory due to disorder. It was suspected that this was a type of disorder associated with high thermal motion and therefore we decided to recollect the data at low temperature (-110°C). Since the basic manner of data collection and processing was the same at both room and low temperature a full description is given only for the low temperature data.

Large crystals of DCK had been grown by sublimation. In an attempt to overcome the problem of twinning, crystals of sublimed DCK were cut to appropriate dimensions and mounted on a glass fiber. Since at low temperature loss of intensity due to sublimation was not a problem no capillary was used. No twinning was seen in these crystals. Data was then recollected on a Nonius CAD-4 automatic diffractometer equipped with a low temperature unit. The least squares cell dimensions were determined from averages of the +2θ and -2θ values of 40 reflections, distributed throughout reciprocal space, measured at -110°C. The crystallographic data are shown in Table 1. The 2152 data, including all unique reflections with θ less than 75°, were taken with Ni-filtered CuK_α radiation (λ=1.54178 Å). The data were collected with θ-2θ scans in which the θ scan width was between 1.00 and 1.38 degrees. The 011 and $1\bar{2}0$ reflections were excluded from the data, due to the large intensities and high extinction effects. The maximum scan time was 90 seconds with 2/3 of the time spent while scanning the peak and 1/6 on each the left and right background. There were 19 reflections

Table 1. Crystallographic Data

Formula - $C_{13}H_{18}O$

F.W. - 190.28

F(000) - 208

Space Group - $P\bar{1}$

Z - 2

D_{exp} - 1.120 (room temperature)

D_{calc} - 1.138 (room temperature) H_2O and NaCl solution flotation

$a_{low\ temperature}$ = 9.388(3) Å	$a_{room\ temperature}$ = 9.4909(6) Å
b_{lt} = 8.693(4)	b_{rt} = 8.8044(4)
c_{lt} = 9.385(3)	c_{rt} = 9.4801(4)
α_{lt} = 104.85(3)°	α_{rt} = 103.502(4)°
β_{lt} = 113.77(3)	β_{rt} = 113.103(4)
γ_{lt} = 117.16(2)	γ_{rt} = 117.658(4)
V_{lt} = 524.62 $Å^3$	V_{rt} = 555.08 $Å^3$

which had intensities we considered indistinguishable from the background on the basis that the net count was less than 1.4 $T^{1/2}$ (T=total count). These reflections were assigned intensities equal to 0.7 $T^{1/2}$ for purposes of least squares refinement. Lorentz and polarization corrections were applied to the data. No absorption corrections were made. Each amplitude was assigned a weight given by $w_f=1/sigma_F^2$, where the standard deviation $sigma_F$ (σ_F) of the amplitude was calcualted by

$$\sigma_F = \frac{1}{2}\left[\frac{(\sigma)^2 + ((0.02)P)^2}{(Lp)P}\right]^{1/2}$$

in which

$\sigma = T^{1/2} V$

V = Scan speed

P = [PK-2(R+L)]V

PK = peak count

R = Right background count

L = Left background count

Lp = Lorentz-Polarization factor

Secondary extinction corrections were made on the observed intensities according to the equation $I_{corrected}=I_o \exp(-c_{ext}*P)$. The constant c_{ext} was determined to be 0.000005 from the slope of a plot of log F_c/F_o versus P (net count) for 38 reflections having a F_o greater than 10.

Next an attempt to collect a data set on a crystal in its colored (red) form was made. A mounted crystal was exposed to bright sunlight on a cool day for a period of about 15 minutes, at which

time the crystal appeared to be a deep red color. The crystal was quickly placed in the cold stream of the diffractometer system where it retained its color. Another data set was collected in this manner, however, several crystals were used since the irradiation apparently weakened the structure causing the crystals to fracture and break apart under the force of the cold stream, an effect not observed with crystals in the clear form. Data was collected and reduced in the same manner described for the clear-form data. Least squares cell dimensions were not significantly different from those of the clear-form. A total of 79 reflections were not distinguishable from the background and were treated as described earlier. The weighting scheme was identical to that used previously. Extinction was not apparent and these corrections were therefore not made for this data set.

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by the symbolic addition procedure (Karle and Karle, 1966) using the normalized structure factors derived from the amplitudes of the data set collected at room temperature. The distribution and statistics of the $|E|$'s agree with the theoretical values for the centrosymmetric case. The 164 highest $|E|$'s (greater than 1.65) were used to generate triplets satisfying the Σ_2 relation. The origin was defined by assigning a positive sign to the $52\bar{6}$ and $\bar{2}41$ reflections and a negative sign to the $1\bar{5}7$ reflection. The symbol A was assigned to $\bar{6}06$ reflection, B to the $7\bar{3}1$ and C to the $61\bar{5}$ reflection. The sign of B and C were determined to be negative, the

sign of A was undetermined. Two Fourier synthesis maps based on the signed E's, one assuming a plus sign for A, and the other a minus sign for A were calculated. The map calculated from signs generated by the symbol A having a minus sign yielded a reasonable structure. The carbon and oxygen atom positions from the E-map were used with isotropic thermal parameters in a structure factor calculation and refined by block diagonal least-squares minimization of $\Sigma w_f(|F_o|-|F_c|)^2$. The hydrogen atoms were located from geometrical considerations with the aid of a difference Fourier synthesis map. The hydrogen atoms were included in the structure factor least-squares refinement with isotropic temperature factors. The temperature factors for the non-hydrogen atoms were made anisotropic. The refinement appeared to converge at an $R=(\Sigma||F_o|-|F_c||/\Sigma|F_o|)$ of 0.14. At this point the calculated bond distances between C(4') and C(5') and between C(4) and C(5) were 1.446 Å and 1.499 Å respectively. The major axes of the thermal ellipsoids had values as high as 16.8 $Å^2$ and 13.0 $Å^2$ for atoms C(5') and C(4') and of 9.3 $Å^2$ and 10.2 $Å^2$ for C(4) and C(5). These observations indicated that disorder or a high thermal vibration existed at C(4') and C(5') and to a lesser extent at C(4) and C(5). It was not apparent from a difference map whether the atoms were truly disordered or had a large thermal vibration. Attempts to resolve this problem by refinement of disordered half-atoms was unsatisfactory. Since it was clear that these positions in the cyclohexenyl rings were relatively free to vibrate thermally or exist in two stable half-chair conformations (one conformation having C(4') up and C(5') down relative to the plane of the ring, the other conformation being the opposite) we

decided to retake the data at low temperature in order to possibly isolate one favored conformation. The refined parameters from the room temperature data were used in the refinement of the low temperature data. As mentioned previously data was also collected at low temperature on a crystal in the colored form. This data set was also refined independently using the same starting parameters. Refinement continued on both low temperature data sets until shifts in the parameters were less than 1/3 of their standard deviation. No disorder was seen in the cyclohexene rings at low temperature. The final R values were 0.051 for the low-temperature clear-form data and 0.058 for the red-form low-temperature data. The final difference Fouriers showed no significant residual peaks (greater than 0.3 e/A^3). The average $w_f\Delta F^2$ were independent of F_o and sin θ/λ validating the weighting scheme used in the refinement.

The atomic scattering factors for carbon and oxygen are from the INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY (1962). The scattering factors for the hydrogen atoms were from Stewart, Davidson and Simpson (1965). The final atomic parameters are in Tables 2 and 3.*

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*The final F_o and F_c tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 00000 (18 p.p., 1 microfiche). Copies may be obtained through the Executive Secretary IUC, 13, White Friars, Chester CH 1NZ, England.

Table 2. Atomic Fractional Coordinates and Thermal Parameters (all x 10^4)

The temperature factor is expressed in the form $\exp\{-(h^2b_{11}+k^2b_{22}+\ell^2b_{33}+hkb_{12}+h\ell b_{13}+k\ell b_{23})\}$.

Standard deviations of the last digit are in parenthesis. There are two entries for each atom; the first of these are the parameters derived from data taken on a crystal in the clear form at -110°C, while the second entry is from data taken on a crystal in the pink form.

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{23}	b_{13}	b_{12}
C(1)	-1064(2)	-3086(2)	3080(2)	71(2)	62(2)	44(2)	55(3)	63(3)	75(4)
	-1067(3)	-3087(3)	3077(3)	88(4)	99(4)	68(3)	99(6)	108(6)	115(7)
C(2)	-1788(2)	-2127(2)	2651(2)	73(2)	67(2)	58(2)	74(4)	77(4)	82(4)
	-1788(3)	-2125(3)	2651(3)	83(4)	105(4)	76(3)	110(7)	106(6)	112(7)
C(3)	-3398(2)	-2303(2)	2772(2)	82(2)	93(2)	69(2)	91(4)	90(4)	120(4)
	-3399(3)	-2302(3)	2773(3)	88(4)	132(5)	86(4)	115(7)	112(6)	142(7)
C(4)	-3735(2)	-3232(2)	3895(2)	81(2)	109(3)	72(2)	99(4)	104(4)	109(4)
	-3732(3)	-3233(4)	3898(3)	90(4)	147(5)	93(4)	135(7)	132(7)	147(8)
C(5)	-3788(2)	-5083(2)	3349(2)	100(3)	89(3)	87(2)	116(4)	128(4)	96(4)
	-3786(3)	-5077(4)	3354(3)	103(4)	130(5)	107(4)	156(8)	150(7)	125(8)
C(6)	-1791(2)	-4446(2)	3765(2)	110(3)	93(3)	79(2)	124(4)	128(4)	137(4)
	-1786(3)	-4443(3)	3770(3)	112(4)	136(5)	98(4)	165(7)	151(7)	166(8)
C(1')	989(2)	-2223(2)	1788(2)	75(2)	63(2)	60(2)	70(4)	86(4)	93(4)
	985(3)	-2227(3)	1786(3)	79(3)	95(4)	72(3)	98(6)	101(6)	112(7)
C(2')	-556(2)	-2936(2)	117(2)	75(2)	73(2)	61(2)	74(4)	84(4)	95(4)
	-553(3)	-2939(3)	119(3)	88(4)	104(4)	76(3)	106(7)	110(6)	117(7)
C(3')	-351(2)	-2584(2)	-1298(2)	90(2)	95(3)	59(2)	90(4)	88(4)	124(4)
	-347(3)	-2581(3)	-1298(3)	99(4)	131(5)	77(3)	123(7)	114(6)	145(8)
C(4')	1833(2)	-962(2)	-491(2)	104(3)	93(3)	80(2)	121(4)	125(4)	129(5)
	1837(3)	-966(3)	-491(3)	101(4)	126(5)	87(4)	135(7)	126(7)	135(8)
C(5')	3180(2)	-1286(2)	748(2)	89(2)	125(3)	85(2)	137(4)	127(4)	145(5)
	3172(3)	-1288(4)	737(3)	103(4)	161(5)	114(4)	188(8)	169(7)	182(8)
C(6')	3108(2)	-1079(2)	2377(2)	71(2)	105(3)	66(2)	94(4)	80(4)	106(4)
	3107(3)	-1076(3)	2376(3)	86(4)	145(5)	89(4)	141(7)	119(7)	143(8)
C(7)	675(2)	-2689(2)	3108(2)	76(2)	56(2)	52(2)	54(4)	67(4)	84(4)
	676(3)	-2685(3)	3109(3)	84(4)	88(4)	63(3)	81(6)	87(6)	105(7)
O(8)	1865(1)	-2743(1)	4254(1)	101(2)	122(2)	76(2)	137(3)	105(3)	165(4)
	1866(2)	-2742(3)	4254(2)	103(3)	161(4)	92(3)	167(6)	122(5)	182(6)

Table 3. Hydrogen Atom Parameters (coordinates x 10^3) Standard deviations of last digit in parenthesis.

	x	y	z	B_{iso}
H(C2)1	-121(2)	-119(2)	227(2)	1.7(3) $Å^2$
	-125(4)	-122(4)	226(4)	1.6(5)
H(C3)1	-463(2)	-314(2)	155(2)	2.2(3)
	-462(4)	-315(5)	152(4)	2.2(5)
H(C3)2	-305(2)	-93(2)	330(2)	2.1(3)
	-310(5)	-90(5)	326(4)	2.8(6)
H(C4)1	-499(3)	-362(3)	375(3)	3.1(4)
	-494(4)	-357(4)	379(4)	2.3(6)
H(C4)2	-259(2)	-216(2)	519(2)	1.8(3)
	-259(4)	-211(4)	525(4)	1.7(5)
H(C5)1	-485(2)	-611(2)	202(2)	2.5(3)
	-488(5)	-609(5)	199(4)	2.5(6)
H(C5)2	-410(3)	-577(3)	399(2)	2.8(4)
	-409(5)	-573(5)	399(4)	2.5(6)
H(C6)1	-192(2)	-565(2)	317(2)	2.0(3)
	-189(5)	-572(5)	321(5)	3.4(7)
H(C6)2	-78(2)	-370(2)	510(2)	1.8(3)
	-75(4)	-366(4)	515(4)	2.1(5)
H(C2')1	-191(2)	-381(2)	-24(2)	2.0(3)
	-193(4)	-382(4)	-25(4)	1.7(5)
H(C3')1	-117(2)	-224(2)	-187(2)	2.1(3)
	-123(5)	-221(5)	-190(5)	3.5(7)
H(C3')2	-94(3)	-392(2)	-236(2)	2.1(3)
	-101(5)	-397(5)	-238(4)	2.3(6)
H(C4')1	193(2)	-102(2)	-153(2)	2.1(3)
	193(5)	-101(5)	-156(5)	3.2(7)
H(C4')2	226(3)	44(3)	28(2)	2.4(3)
	229(5)	46(5)	28(5)	3.1(7)
H(C5')1	268(3)	-272(3)	1(3)	2.4(3)
	267(5)	-277(5)	-2(4)	2.6(6)
H(C5')2	459(3)	-23(3)	126(3)	2.4(3)
	461(5)	-27(5)	125(5)	3.0(6)
H(C6')1	367(3)	-163(2)	298(2)	2.4(3)
	367(5)	-161(5)	298(4)	2.6(6)
H(C6')2	392(2)	35(2)	330(2)	2.1(3)
	393(5)	40(5)	333(5)	2.8(6)

RESULTS

A stereoview of the molecule is given in Figure 1. The bond distances and angles obtained from refinement of the data collected at low temperature on a crystal in the clear-form are shown in Figures 2 and 3. A half-normal probability plot (Abrahams and Keve, 1971) was constructed from the positional parameters, to compare the results obtained from refinement of the data set collected on the clear-form and the red-form of DCK at low temperatures. This plot which includes only the non-hydrogen positional parameters is shown in Figure 4. The parameter having the largest observed difference in the two forms and also showing the largest deviation from the expected straight line of Figure 4 is the z coordinate of C(5') which lies about 5 standard deviations from the best straight line through all points. This is an atom which is disordered at room temperature. The remainder of the positional parameters appear to have a linear relation in the half-normal probability plot, giving a slope of 1.01 (standard deviation of 0.04) validating the weighting scheme employed, and an intercept of -.005. The anisotropic temperature factor parameters appear to be increased by an average of about 20% for all carbons and oxygen atoms. In general the same results are seen for the hydrogen atom parameters. Since it is doubtful if a significant difference is observed between the clear and colored forms, all calculated results (distances and angles) shown are from the refined coordinates of the clear-form data. No data is included here for the room temperature data set.

The bond lengths and angles are in good agreement with

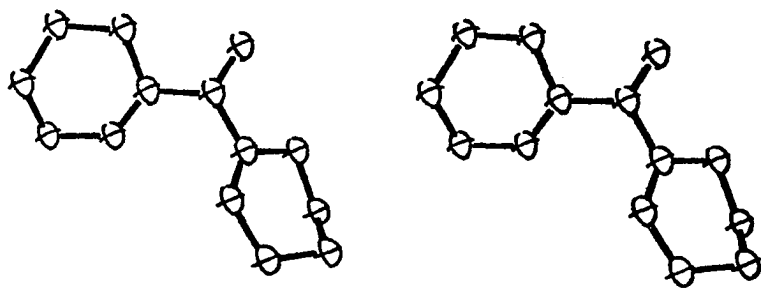

Figure 1 - Stereoview of the DCK molecule using the ORTEP program (Johnson, 1965).

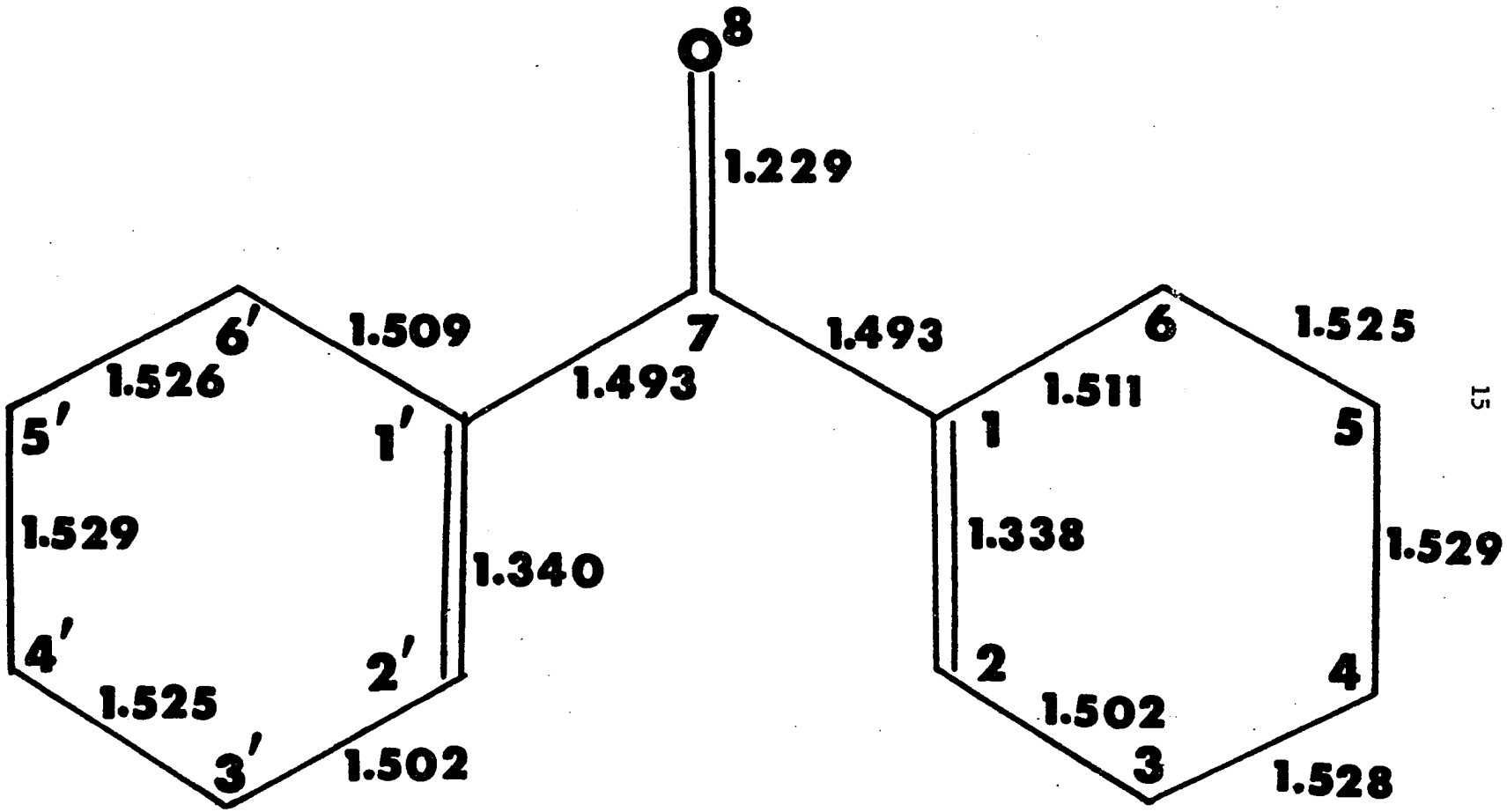

Figure 2 - Numbering scheme and bond distances in Angstroms. Standard deviation for all distances is 0.002 Å.

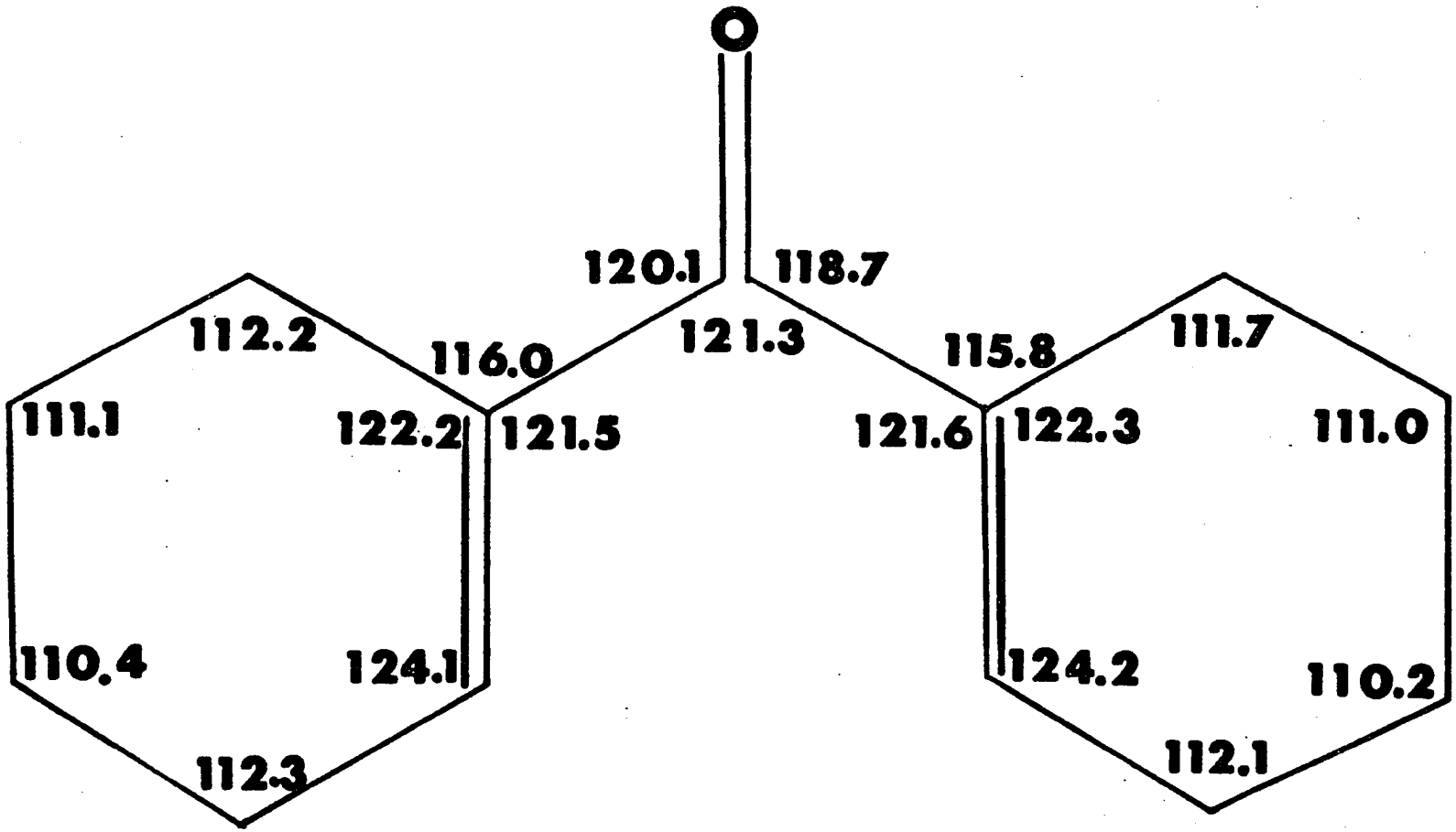

Figure 3 - Bond angles in degrees. Standard deviations of angles are 0.1°.

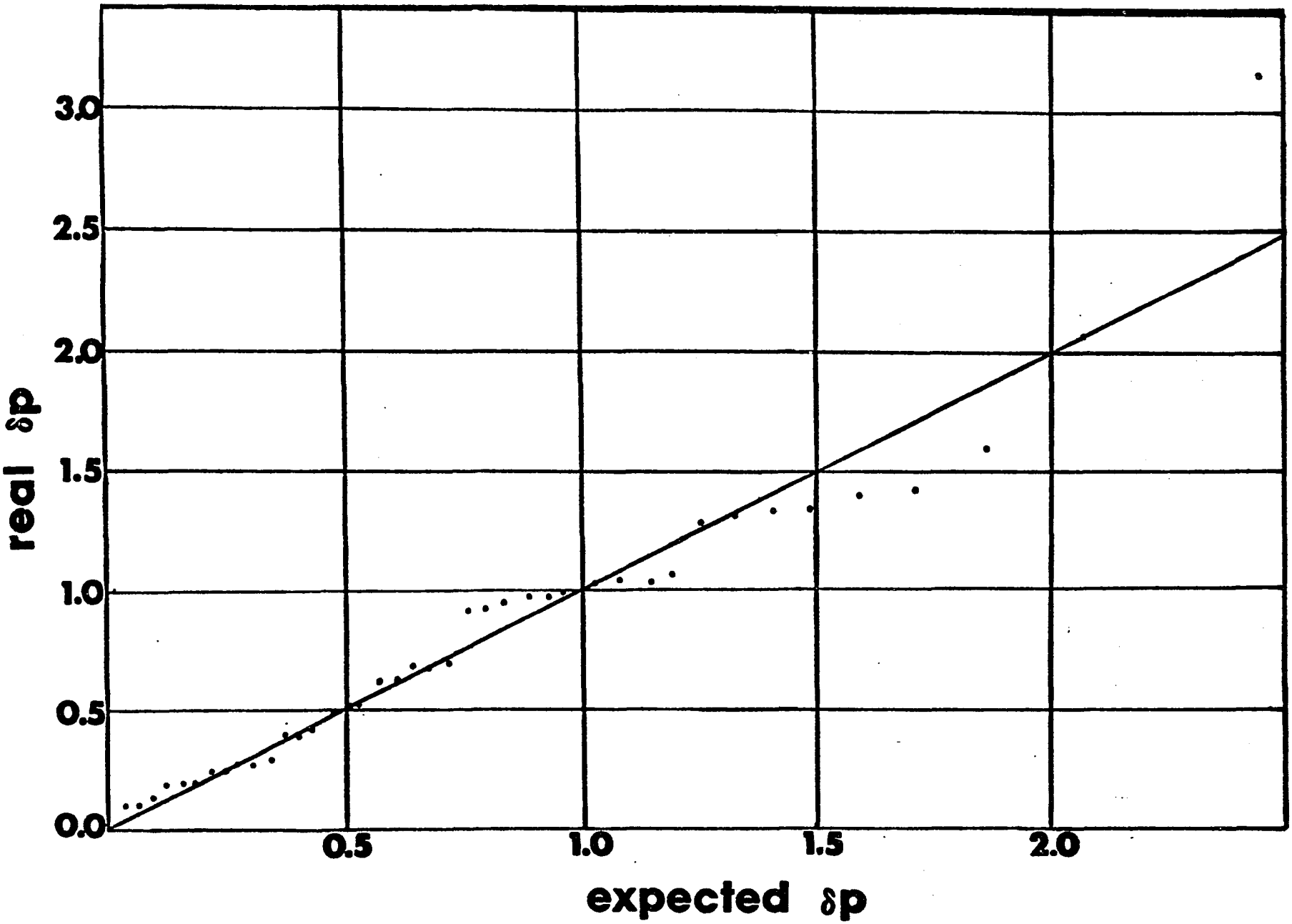

Figure 4 - Half-normal probability plot (Abrahams and Keve, 1971), comparing the final positional parameters of the non-hydrogen atoms as obtained from refinement of the clear and red crystal forms.

accepted values. The distances and angles in the cyclohexene rings compare well with values found in 4-diethylcarbamoyl-1-cyclohexene-5-carboxylic acid (Pedone, Benedetti, Immirizi, and Allegra, 1969). The distances and angles in cyclohexene ring C(1)-C(6) are consistent with the values found in ring C(1')-C(6'). The carbon-hydrogen bond distances vary between 0.96 and 1.01 Å.

Perhaps the most interesting results are seen in the conformational angles (Figure 5). Rotations around the C(1)-C(7) and C(1')-C(7) bonds of 34 and 28 degrees respectively cause the cyclohexene rings to be tilted with respect to the plane of the carbonyl group (C(1)-C(7)-O(8)-C(1')) in opposite directions as can be seen by a view down the C(7)-O(8) bond (Figure 6). This non-planarity results from steric hinderance between H(C2) and H(C2'). The analogous effects have been observed for benzophenone and its derivatives (Rekker and Nauta, 1954). Pattabhi and Venkatesan (1972) determined the rotation for each of the benzene rings away from planarity to be 28 degrees in 3,3'-dibromobenzophenone. In addition to the experimental values reported in this article, Pattabhi and Venkatesan have calculated theoretical values for these twists by semi-empirical energy minimization methods to be 42-45 degrees for the isolated benzophenone molecules and 30 degrees for the molecule 3,3'-dibromobenzophenone in the crystal form. The contact between H(C2) and H(C2') is shown in Figure 7 to be 2.41 Å, which is near the sum of the van der Waals radii of two hydrogen atoms of 2.4 Å (Pauling, 1960). The crowding between H(C2) and H(C2') causes the cyclohexene rings to be tilted in such a manner that disrotatory closure across C(2)-C(2') would be difficult without the system first

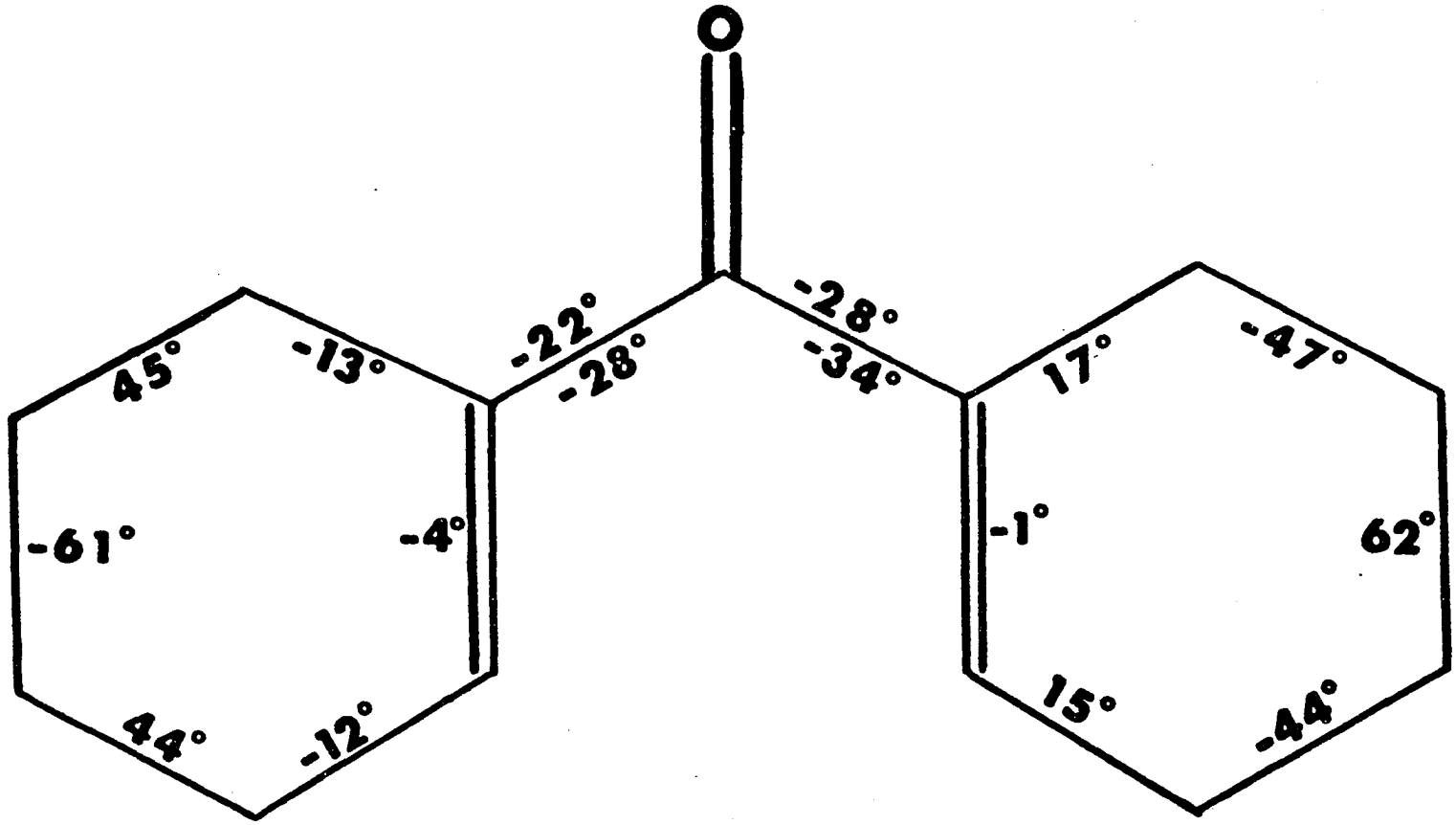

Figure 5 - Conformational angles in DCK. Cis conformation is taken as 0°. Rotation in the right handed sense is given in degrees.

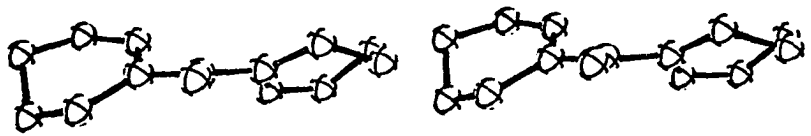

Figure 6 - Stereoview of DCK as viewed down O(8)-C(7) bond, showing twist of rings.

becoming more planar. The rings are in a favorable relation, however, for conrotatory closure.

Bucourt (1964) has calculated the internal dihedral angles for cyclohexene by energy minimization techniques. These theoretical values and the experimental values of Pedone, Benedetti, Imirizi and Allegra (1969) are virtually identical to the torsion angles found in the cyclohexene rings of DCK and illustrated in Figure 5. The tilting of ring C(1)-C(6) from the plane of the carbonyl group is approximately related to the tilt of ring C(1')-C(6') by a 2 fold axis through C(7)-O(8). This can be seen in the identical signs of the torsion angles around C(7)-C(1) and C(7)-C(1'). The potential two-fold symmetry of the DCK molecule is destroyed, however, by the internal conformation of the cyclohexene rings, as shown by the opposite signs of the angles in each ring which indicates that the internal conformations of the rings are related by a mirror plane through C(7)-O(8) perpendicular to the rings.

The result of this difference in conformation of the cyclohexene rings relative to the oxygen is that the torsion around the bond C(1')-C(6') causes H(C6')1 to be moved closer to O(8) and H(C6')2 farther away. If the internal conformation of the cyclohexene rings had been related by a two-fold axis the hydrogens on C(6') would have been equidistant from O(8) as are H(C6)1 and H(C6)2. At room temperature the ring C(1')-C(6') (and to a lesser extent ring C(1)-C(6)) is disordered at C(4) and C(5), indicating that both mirror related conformations are present. As is shown in Figure 7, at low temperature H(C6')1 has a contact of 2.44 Å with O(8) and makes a C-H-O bond angle of 103

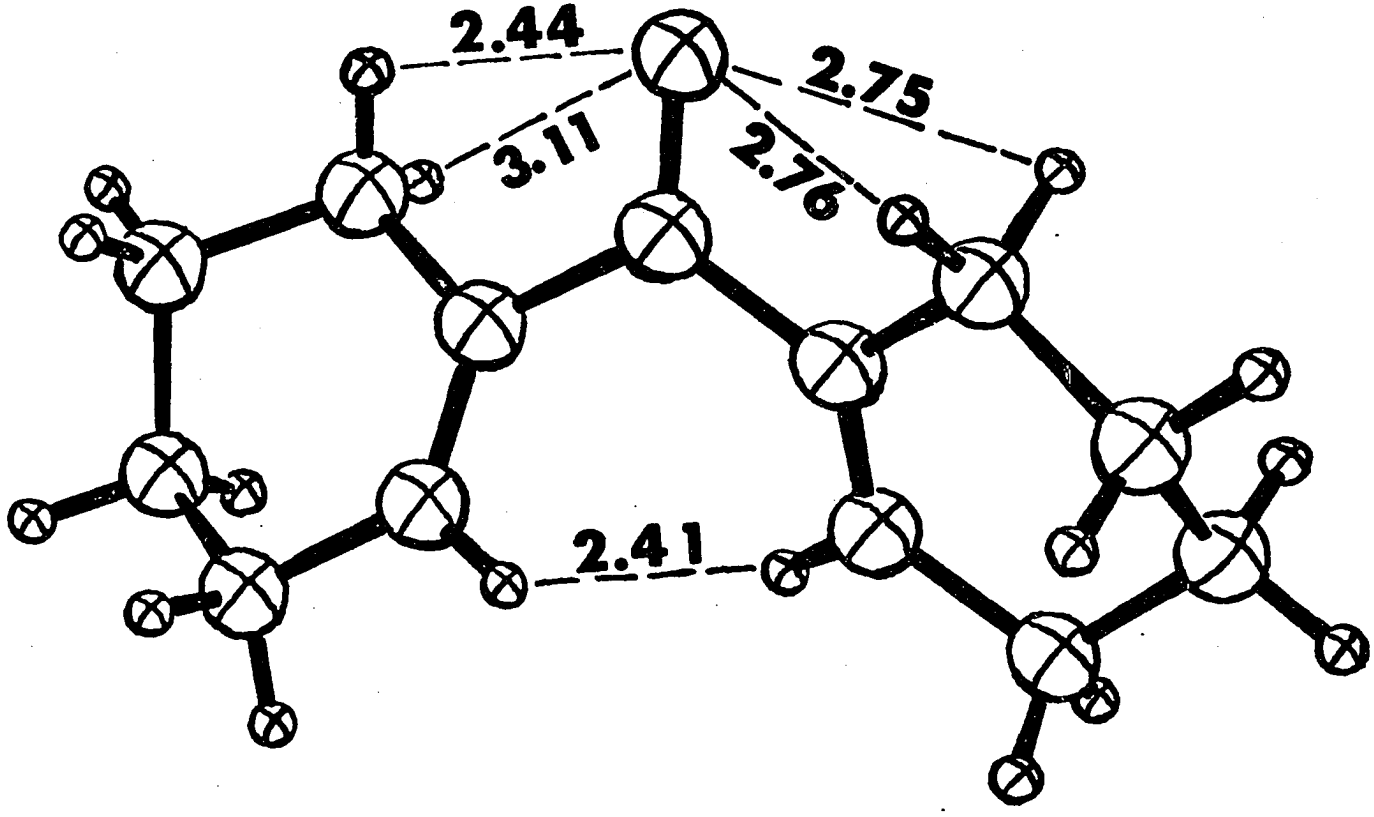

Figure 7 - Drawing of the molecule including the hydrogen atoms. Atoms having a close intramolecular contact are connected by a dotted line. Distance in Angstroms is given.

degrees. Therefore, H(C6')1 is in an excellent position for hydrogen abstraction by O(8) and being in an allylic position is acidic in character. The transfer of H(C6')1 to O(8) would result in a delocalized zwitterion or diradical which would cyclize in solution, as previously stated, but could not in the crystal lattice due to crystal forces.

Another interesting contact, in this case intermolecular, exists between C(3') and H(C3')2 with O(8) of a molecule translated + 1 unit in the b-direction and inverted by a center of symmetry. The hydrogen-oxygen distance is 2.48 Å and the C-H-O bond angle is virtually linear. The H(C3')2 is also allylic and therefore acidic in character and it is therefore just as well possible that an intermolecular transfer of hydrogen occurs yielding a different diradical. There is however no indication from the present results that the C=O distance is increased in the pink-form (clear-form: 1.229(2) Å, pink-form: 1.231(3) Å). This is in agreement with the lack of difference observed in the half-normal probability plot. We therefore have to conclude that the color change is partial and probably only occurring at the surface and that the increase in thermal motion is due to the shock of heating the crystal during irradiation and returning it to the cold stream.

Acknowledgement

The authors extend their gratitude to Dr. Roland E. Lehr and J. Michael Wilson for supplying us with crystals of $\Delta^{1,1'}$-dicyclohexenyl ketone and for their advice and suggestions concerning our experiments. We also wish to express our appreciation to the Computing Center of the University of Oklahoma for putting computer time at our disposal.

References

Abrahams, S. C. and Keve, E. T. (1971). Acta Cryst. A27, 157-165.

Bucourt, R. (1964). Bull. Soc. Chim. Fr., 2080-2088.

Coppens, P. (1960). Thesis, University of Amsterdam, Netherlands.

International Tables for X-ray Crystallography (1962). Vol. III, Birmingham: Kynoch Press, p. 202.

Johnson, C. K. (1965). ORTEP. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Karle, J. and Karle, I. L. (1966). Acta Cryst. 21, 849-859.

Korenstein, R., Muszkat, K. A. and Sharafy-Ozeri, S. (1973). J. Amer. Chem. Soc. 95, 6177-6181.

Lehr, R. (1968). Thesis, Harvard University, Cambridge, Massachusetts.

Ottersen, T. and Seff, K. (1974). Acta Cryst. B30, 955-959.

Pattabhi, V. and Venkatesan, K. (1973). J. Cryst. Mol. Struct. 3, 25-35.

Pauling, L. (1960). The Nature of the Chemical Bond, 3rd ed., Ithaca, N. Y., Cornell University Press, p. 260.

Pedone, C., Benedetti, E., Immirizi, A. and Allegra, G. (1970). J. Amer. Chem. Soc. 92, 3549-3552.

Rekker, R. F. and Nauta, W. Th. (1954). Rec. Trav. Chim. 73, 969-979.

Seff, K. and Trueblood, K. N. (1968). Acta Cryst. B24, 1406-1415.

Stewart, R. F., Davidson, E. R. and Simpson, W. T. (1965). J. Chem. Phys. 42, 3175-3187.

THE CRYSTAL STRUCTURE OF 3-BENZYL-7-CHLORO-2,4-DIOXA-3-PHOSPHABICYCLO[3.3.1]-NONANE, 3-OXIDE, THE REACTION PRODUCT FROM THE MICHAELIS-ARBUZOV REACTION OF 1-PHOSPHA-2,8,9-TRIOXAADAMANTANE WITH BENZYL CHLORIDE.

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ABSTRACT

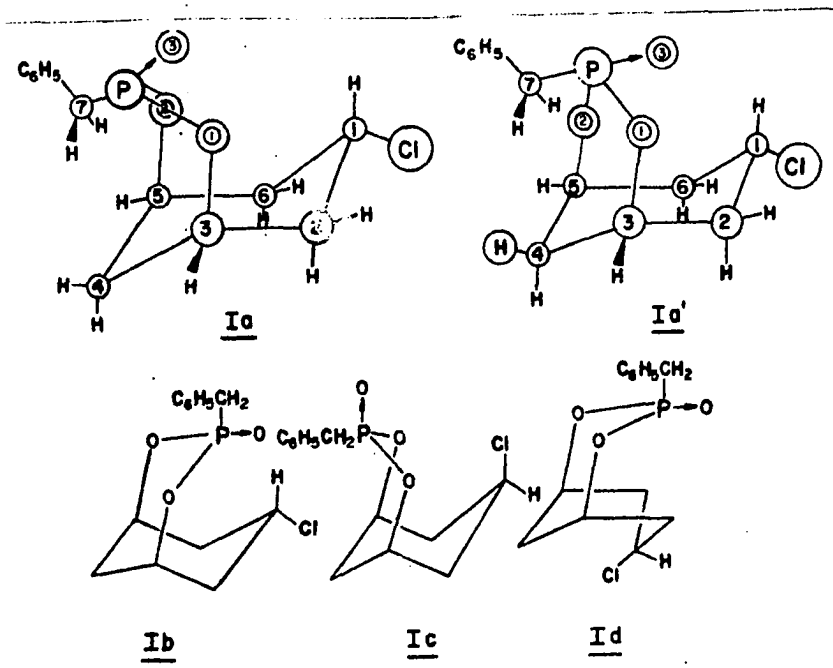
The structure determination is reported for 3-benzyl-7-chloro-2,4-dioxa-3-phosphabicyclo[3.3.1]nonane, 3-oxide via X-ray diffraction analysis. Conformational properties predicted previously for the molecule on the basis of IR, PMR, and dipole moment data are substantiated for the crystal structure with but minor exceptions. Interpretation of the mechanism of formation of the oxide is given. $C_{13}H_{16}ClO_3P$ crystals are monoclinic, space group $P2_1$, $Z = 2$, with $a = 11.672$, $b = 9.777$, $c = 5.833$ Å, and $\beta = 98.30^{\circ}$. Diffractometer intensity data were collected for all unique refractions with $\sin\theta/\lambda$ less than 0.66 $Å^{-1}$, using Zr-filtered molybdenum radiation. The final R value is 7.9% for all 1681 data.

INTRODUCTION

Published single crystal analysis via X-ray diffraction of organophosphorus compounds is relatively scarce in the literature in spite of the well recognized importance of cyclic phosphorus esters, especially in biological systems. We

now wish to report the 3-dimensional crystal analysis of 3-benzyl-7-chloro-2,4-dioxa-3-phosphabicyclo(3.3.1)nonane, 3-oxide, a bicyclic phosphonate.

Carbon-phosphorous bond formation can often be accomplished readily by way of the Michaelis-Arbuzov reaction.[1] It was previously shown that 1-phospha-2,8,9-trioxaadamantane undergoes ring opening when treated with benzyl chloride at 110°C for 24 hr.[2] Infrared, NMR, and dipole moment data[3] favored the conformation Ia rather than Ib, Ic, or Id. It was recognized that single crystal



X-ray analysis would be required before the absolute configuration of solid compound could be established in view of the complexity of PMR data and deviation of calculated dipole moments from the measured values for several conformers.

RESULTS AND DISCUSSION

The results indicate that a modified structure Ia′ is required. The bond lengths of Ia′ are shown in Fig. 1. These distances compare favorably with those reported in other structures containing a 1,3,2-dioxaphosphorinane ring system. A convenient summary of bond distances is found in the crystal and molecular structure of 5,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphorinane.[4] Some reported data and the bond lengths found for the ring system of Ia′ are (in Å):

	Average reported	Ranges reported	Ia′
P=O	1.46	1.393 - 1.48	1.460
P-O	1.55	1.510 - 1.582	1.573, 1.575
C-O	1.47	1.43 - 1.523	1.473, 1.492
C-C	1.53	1.49 - 1.588	1.505, 1.507

These averages are obtained from the X-ray structure determination of 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane[5], 2-bromo-5-bromoethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane[6], 5,5-dimethyl-2-oxo-2 hydroxy-1,3,2-dioxaphosphorinane[7], propane-1,3-diol cyclic phosphate[8], 5-t-butyl-2-methyl-2-oxo-1,3,2-dioxaphosphorinane[8], 5,5-dimethyl-2-oxo-2-phenyl-1,3,2-dioxaphosphorinane[9], and 5,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphorinane[4].

The P-O distances for Ia′ are significantly shorter than those reported for the anion of cyclic uridine-3′5′-phosphate[10] (1.61 Å average). The P-C(7) bond length is comparable to that reported in the structure of 2-oxo-2-phenyl-4,4-dimethyl-1,3,2-dioxaphosphorinane (1.82 Å).[9] The Cl is attached to the

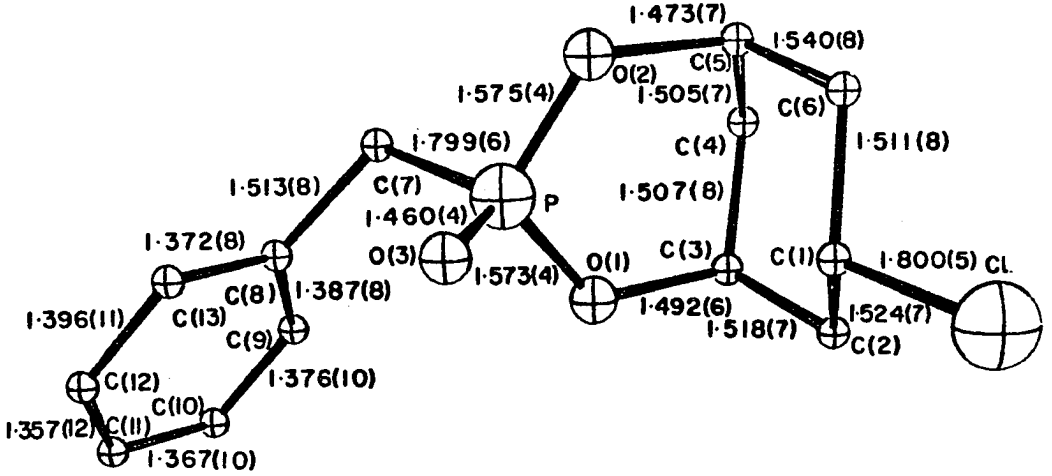


Figure 1. Bond distances in Ia′.

cyclohexyl ring in the equatorial position. Its bond distance (1.800 Å) seems somewhat greater than the generally accepted value of near 1.76 Å.[11]

Bond angles are given in Table I. A tetrahedral arrangement around the phosphorous atom is indicated with the exception of the O(1)-P-O(2) angle which is 107.0° ± 0.2°. This O-P-O angle in the 1,3,2-dioxaphosphorinane ring is in agreement with the value of 106.6 reported by Geise[5] and of 107.5° reported by Verkade[12] in separate systems. The P-O-C angles of 125.5° and 124.4° are quite large, but reasonable in light of the P-O-C angles of 122.6°-125.3° in triphenyl phosphate.[13] The average bond distance in the phenyl ring of Ia′ is 1.376 Å with an average angle between sp^2 bonds of 120.0°.

The cyclohexyl ring is in the chair conformation, while the 1,3,2-dioxaphosphorinane ring forms neither a perfect chair nor a perfect boat, but is intermediate between the two conformations a feature also observed in the structure of cis-4,6-dimethyl-2-oxo-2-triphenylmethyl-1,3,2-dioxaphosphorinane.[14] The calculated O(3)...H(1) distance [H(1) is bonded to C(1)] in the perfect boat-chair is 4.04 Å, and, in the perfect chair-chair, this distance is 0.90 Å.[3] In Ia′ the O(3)...H(1) distance is 2.86 Å, however. Dihedral angles for both rings and around other bonds of interest are listed in Table II. It can be seen in Figure 2, which shows a 3-D view of the molecule, that the atoms C(3), O(1), P, O(2) and C(5) are nearly planar (Table III). Other intramolecular distances of interest are P-C(1): 3.336 Å; P-C(4): 2.976 Å; P-C(3): 2.726 Å; and P-C(5): 2.696 Å.

The tricyclic system conceptually has a mirror plane of symmetry and such is, at least approximately, the observation. The least-squares plane through Cl, C(1), C(4), O(3), P and C(7) is given in Table III. The benzyl group destroys the mirror symmetry of the molecule. The C(7)-C(8) bond is almost trans to the P-O(2) bond rather than trans to the O(3)-P bond (Table II). The phenyl ring shows a small twist around the C(7)-C(8) bond from the preferred conforma-

TABLE I

Bond angles. Standard deviations for the last digit are given in parentheses

C(2)C(1)C(6)	113.1(4)	O(1)PO(3)	113.2(2)
C(2)C(1)Cl	109.6(4)	O(2)PO(3)	112.7(2)
C(6)C(1)Cl	108.9(4)	O(1)PC(7)	105.6(2)
C(1)C(2)C(3)	109.3(4)	O(2)PC(7)	104.4(2)
C(1)C(6)C(5)	112.3(4)	O(3)PC(7)	113.3(3)
C(2)C(3)C(4)	112.7(4)	PC(7)C(8)	112.5(4)
C(6)C(5)C(4)	112.0(5)	C(7)C(8)C(9)	120.9(5)
C(2)C(3)O(1)	108.4(4)	C(7(C(8)C(13)	121.2(5)
C(6)C(5)O(2)	110.0(4)	C(8)C(9)C(10)	121.0(6)
C(4)C(3)O(1)	109.5(4)	C(9)C(10)C(11)	120.4(7)
C(4)C(5)O(2)	108.7(4)	C(10)C(11)C(12)	119.5(7)
C(3)O(1)P	125.5(4)	C(11)C(12)C(13)	120.5(6)
C(5)O(2)P	124.4(3)	C(12)C(13)C(8)	120.6(6)
C(3)C(4)C(5)	109.3(4)	C(13)C(8)C(9)	118.0(6)
O(1)PO(2)	107.0(2)		

TABLE II

Conformational angles in ring systems. The cis conformation Ia′ is taken as 0°. The numbers in the table indicate the righthanded rotation, in degrees, needed to obtain the conformations observed in the structure.

1,3,2-Dioxaphosphorinane Ring

PO(2)-C(5)C(4)	+36.9°
PO(1)-C(3)C(4)	-26.2°
O(2)C(5)-C(4)C(3)	-66.3°
O(1)C(3)-C(4)C(5)	+60.8°
C(3)O(1)-PO(2)	- 2.3°
O(1)P-O(2)C(5)	- 3.5°

Cyclohexyl Ring

C(1)C(2)-C(3)C(4)	+57.8°
C(2)C(3)-C(4)C(5)	-59.9°
C(3)C(4)-C(5)C(6)	+55.5°
C(4)C(5)-C(6)C(1)	-51.8°
C(5)C(6)-C(1)C(2)	+50.3°
C(6)C(1)-C(2)C(3)	-52.4°

Conformational angles around the benzyl group

C(8)C(7)-PO(1)	+75.2°
C(8)C(7)-PO(2)	+187.8°
C(13)C(8)-C(7)P	+77.4°

TABLE III

Least-squares planes. The expression for the planes is Ax + By + Cz = D, where x, y and z are fractional coordinates and D is in Å.

	A	B	C	D
Plane 1	0.470	-9.248	1.824	4.309
Plane 2	4.196	2.868	4.810	2.630

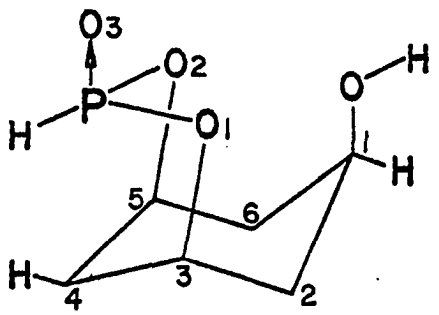
	Δ(1)		Δ(1)		Δ(2)
C(1)	0.030 Å	C(2)	1.265 Å	C(3)	0.030 Å
C(4)	-0.042	C(6)	-1.264	O(1)	-0.028
C(7)	0.056	C(3)	1.200	P	-0.003
O(3)	-0.051	C(5)	-1.256	O(2)	0.033
P	-0.006	O(1)	1.244	C(5)	-0.032
Cl	0.013	O(2)	-1.284	C(4)	0.734
		C(8)	1.118		

Atom positions included in plane (1): C(1), C(4), C(7), O(3), P and Cl.

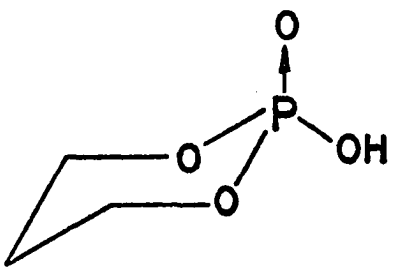
Positions included in plane (2): C(3), O(1), P, O(2) and C(5).

tion of a presumed 90° for the P-C(7)-C(8)-C(13) angle. There is not generally large anisotropic thermal motion in the molecule, although a greater anisotropy is seen in the phenyl ring than elsewhere in the system.

The most interesting comparison for the tricyclic system of the present structure can be made with 3-α-oxo-3-β-hydrio-7-β-hydroxy-2,4-dioxa-3-phosphabicyclo-[3.3.1]nonane (II)[12]. Both in II where the 1,3,2-dioxaphosphorinane system is in the boat conformation and in the cyclic



II



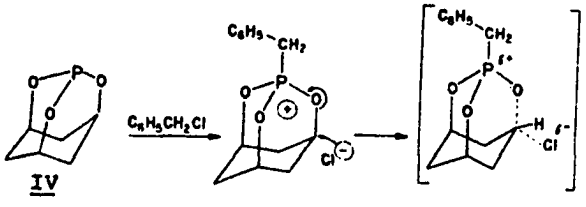
III

phosphate of propane-1,3-diol (III),[15] the chair conformer, the POC angles are considerably smaller than those in the present structure: 121.8° and 121.6° (II), and 120.8° and 116.9° (III) respectively. The 6-membered phosphonate ring system in Ia′ and II has a small but definite conformational freedom, as can be seen from the fact that in Ia′ the smallest intramolecular distance is between H(1)[C1] and P: 2.86 Å. This value is to be compared with a van der Waals contact distance of 3.1 Å, while equatorial H(2)[C(4)] and P are at a distance of 3.05 Å. In II the smallest intramolecular distance is, instead, between H[C(4)] and P: 2.75 Å, while P to hydroxyl oxygen is 3.38 Å, slightly larger than a van der Waals contact. These numbers indicate, for that matter, that the van der Waals radius for phosphorous is smaller, in these structures, than 1.9 Å, which is the generally accepted value. Thus, we conclude that there is neither contact interaction between H(2)[C(4)] and P nor between H(2)[C(4)] and H on P in II. The differences

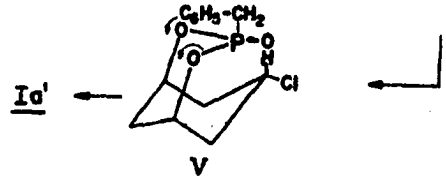
correspond with the fact that the cyclic phosphate ring in II is in the boat conformation. In contrast, in Ia' this ring is in a half chair conformation with atoms C(3), O(1), P, O(2) and C(5) nearly coplanar, and with the differences observed for the POC angles in the two structures. Consequently, the half chair conformation of the 1,3,2-dioxphosphorinane ring system does not result from steric effects imposed by H(2)[C(4)] and H[at C(7)] interactions. The reason for the intuitively less likely conformation in Ia' might well be that it results in a nearly perfect alignment in our molecule of the dipoles formed by the CPO_3 atoms and the C-Cl bond. The angle between the C(7)-P and C(1)-Cl bonds is only 2.3° (Figure 2). In the crystal packing, which can be seen in Figure 3, the bond moments of the column of molecules related by the 2-fold screw axis, which is parallel to the b-cell edge, are situated on top of one another. This gives maximum of interaction which also explains the high melting point (199 - 200.5°C) of the compound.

No intermolecular interactions are noted from the distances between neighboring molecules. The smallest intermolecular distance of 3.29 Å is between C(5) and O(3) of a molecule related by the two-fold screw axis. All other such distances are larger than 3.5 Å.

The conclusion possible now is that in the 1-phospha-2,8,9-trioxaadamantane (IV)-benzyl chloride reaction a nucleophilic displacement occurs by Cl^- on carbon. The resulting heterocyclic ring in the bicyclic system V must undergo a slight inversion around oxygen to yield Ia'.



IV



V

EXPERIMENTAL

The crystals were clear plates with the plate face being the (100) plane. The space group was determined on a G.E. XRD-5 diffraction unit. The least-squares cell dimensions were obtained from the averages of the +2θ- and -2θ-values of 25 pairs of reflections, measured at 25°C, using CuKα radiation (λ = 1.5418 Å). The calculated standard deviations for the cell dimensions were multiplied by a factor 2.5 to account for possible variations in the room temperature during the measurements. The 1681 intensity data, comprising all unique reflections with 2θ less than 56°, were taken with Zr-filtered MoKα radiation (λ = 0.71069 Å) on a Nonius CAD-4 automatic diffractometer. These data were collected with θ - 2θ scans in which the θ scan width was between 0.70° and 0.75° [scan width = (0.7) + (0.1) (tan θ)]. The maximum scan time was 150 sec with 2/3 of the time spent while scanning the peak and 1/6 on each the left and the right background. A total of 344 reflections were assigned as unobserved based on the fact that the net count was less than (1.4) $\sqrt{T}$ (T = total count). The unobserved data were given intensities equal to $\sqrt{T}$. Lorentz, polarization and absorption corrections (μ = 4.097 cm^{-1}) were applied to the data. The program of Coppens, Leiserowitz and Rabinovich[16] was used for the absorption correction, using 216 sampling points. The program utilizes the Gaussian method of numerical integration. The weight assigned to each structure amplitude (W_F) is given by $W_F = 1/(\sigma_F)^2$, where σ_F is the standard deviation of F, and σ_F is calculated as

$$\sigma_F = 1/2\sqrt{\frac{(\sigma)^2 + ((0.05)P)^2}{(Lp)P}}$$

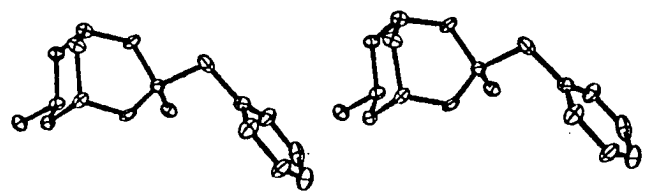


Figure 2. A stereoview[19] of the molecule Ia'.

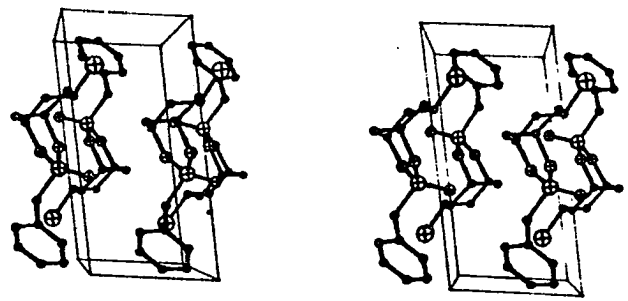


Figure 3. A stereoview[19] of the crystal packing looking down the b-axis onto the a-c plane.

in which $\sigma = (\sqrt{T})v$

v = scan speed

$P = [T - 2(R + L)]v$

T = total count

R = right background count

L = left background count

Lp = Lorentz-polarization factor.

Additional crystal data is given in Table IV.

Structure Solution and Refinement

The chlorine-chlorine and phosphorous-phosphorous vectors were apparent in the Harker section of the Patterson synthesis, although it was not possible to distinguish between the two. Therefore, the highest peak was assigned an arbitrary y-coordinate of 0.5 (fractional coordinates) which served to fix the position of the origin. The position of the other atom was determined from phosphorous-chlorine vectors which agreed with the information of the Harker section. These two atomic positions were used in a structure factor calculation for the purpose of initial phasing (both were inserted as phosphorous, the ambiguity to be solved at a later stage). A difference Fourier was calculated based on these initial phases. This showed the location of the three oxygen atoms, pieces of the two rings and differentiated between the chlorine and phosphorous atoms. Inserting the located atoms in another structure factor calculation and recycling through the structure factor-difference Fourier process twice more led to a complete trial structure. The temperature parameters of the phosphorous and chlorine atoms were made anisotropic and the R index $\left[= \Sigma||kF_o| - |F_c||/\Sigma|kF_o|\right]$ after one cycle dropped to 0.18. All atoms were made anisotropic and refinement continued by block-diagonal least-squares until the parameters were seen to converge. At this point the hydrogen atom positions

TABLE IV

Crystallographic Data:

Formula: $C_{13}H_{16}O_3PCl$

F.W. 286.70

Systematic Absences

0k0; k = 2n + 1

Space group: $P2_1$

11.672 ± 0.001 Å

9.777 ± 0.001 Å

5.833 ± 0.001 Å

$\beta = 98.30^{\circ} \pm 0.01^{\circ}$

Z = 2

$\rho_c = 1.445\ g/cm^3$

F(000) = 300

Volume of data crystal: $2.04 \times 10^{-3}\ mm^3$

were determined from comparison of the difference Fourier with the coordinates calculated by geometrical considerations. The hydrogens were given isotropic thermal parameters, which were 0.5 $Å^2$ larger than those of the atoms to which they are attached.

The refinement was continued until the shifts were less than 1/3 of the calculated standard deviations. The final R index based on the final parameters is 0.079 for all data and 0.061 for the 1337 data which were tagged as observed. The calculated standard deviations are based on all the data. The quantity minimized in the least-squares refinement was $\Sigma W_F(|kF_o| - |F_c|)^2$. The average values of $W_F\Delta F^2$ were independent of $|F_o|$ or sin θ/λ, validating the weighting scheme used in the refinement. Only one of the 344 reflections, which were tagged as unobserved, has a calculated F_c larger than 2 k F_o. A final difference Fourier showed no peaks greater than 0.25 e $\cdot$ $Å^{-3}$ The atomic scattering factors for Cl, P, C and O were taken from the International Tables for X-ray Crystallography (1962),[17] while those for H were those of Stewart, Davidson and Simpson.[18] The final parameters are given in Tables V and VI. A list of the observed and calculated structure factors is available from the authors.

ACKNOWLEDGMENT

The authors extend their gratitude to Dr. F. R. Ahmed who supplied us with copies of his IBM 360 programs and to the Computing Center of the University of Oklahoma for putting computer time at their disposal. Grateful thanks is expressed by one of us (KDB) for a grant from the United States Public Health Service, GM 10367-06; which provided partial support for the early stages of this work. One of us (DvH) gratefully acknowledges partial support via an NIH Career Development Award (K4-GM-42,572).

TABLE V

Parameters of all non hydrogen atoms. The x, y and z are expressed in fractions of the cell edges a, b and c. Anisotropic thermal parameters are in the form: $\exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{23}kl + b_{13}hl + b_{12}hk)]$. Standard deviations for the last digit are given in parentheses.

	$x \times 10^4$	$y \times 10^4$	$z \times 10^4$	$b_{11} \times 10^4$	$b_{22} \times 10^4$	$b_{33} \times 10^3$	$b_{23} \times 10^3$	$b_{13} \times 10^3$	$b_{12} \times 10^3$
C1	-1807(4)	4501(6)	- 175(8)	59(4)	104(6)	23(2)	-2(2)	2(1)	-1(1)
C2	-1739(5)	3590(6)	1962(9)	81(5)	82(6)	29(2)	1(2)	9(2)	0(1)
C3	- 747(4)	4065(6)	3758(8)	76(4)	89(6)	24(2)	8(2)	5(1)	2(1)
C4	- 866(5)	5538(6)	4446(8)	86(5)	106(7)	20(2)	-4(2)	0(1)	0(1)
C5	- 892(5)	6434(6)	2342(8)	90(5)	81(6)	24(2)	-2(2)	2(2)	1(1)
C6	-1854(5)	6007(6)	383(9)	88(5)	78(6)	27(2)	-1(2)	3(2)	1(1)
C7	2282(5)	5424(6)	3596(10)	84(5)	104(8)	34(2)	-6(2)	-4(2)	-1(1)
C8	3204(4)	4333(6)	3649(9)	65(4)	112(7)	29(2)	-2(2)	0(1)	-5(1)
C9	3357(5)	3363(7)	5401(10)	89(6)	139(9)	33(2)	6(2)	2(2)	0(1)
C10	4174(6)	2347(8)	5420(12)	105(7)	128(9)	52(3)	7(3)	-2(2)	1(1)
C11	4841(6)	2261(10)	3681(12)	73(6)	215(13)	60(3)	-2(3)	-14(2)	5(1)
C12	4700(5)	3194(10)	1942(11)	69(5)	276(14)	40(2)	-5(3)	9(2)	2(2)
C13	3889(5)	4245(8)	1931(10)	84(5)	161(10)	37(2)	8(3)	4(2)	-5(1)

TABLE V

(continued)

	$x \times 10^4$	$y \times 10^4$	$z \times 10^4$	$b_{11} \times 10^4$	$b_{22} \times 10^4$	$b_{33} \times 10^3$	$b_{23} \times 10^3$	$b_{13} \times 10^3$	$b_{12} \times 10^3$
O1	357(3)	3882(4)	2784(6)	81(3)	70(4)	35(1)	6(1)	5(1)	3(1)
O2	244(3)	6362(4)	1530(6)	82(4)	83(4)	36(1)	7(1)	5(1)	0(1)
O3	1259(3)	4639(4)	- 705(6)	83(3)	116(5)	31(1)	-2(1)	3(1)	1(1)
C1	-3068(1)	4057(2)	-2192(2)	81(1)	134(2)	29(1)	-4(1)	-2(1)	-2(1)
P	1006(1)	5030(2)	1585(2)	67(1)	73(1)	26(1)	0(1)	2(1)	0(1)

TABLE VI

Hydrogen atom parameters

	$x \times 10^3$	$y \times 10^3$	$z \times 10^3$	B
H(C1)1	-118	423	-90	3.9 [2]
H(C2)1	-243	370	259	4.2
H(C2)2	-153	250	155	4.2
H(C3)1	- 85	345	510	4.1
H(C4)1	-158	568	515	4.4
H(C4)2	- 25	588	560	4.4
H(C5)1	- 95	740	260	4.3
H(C6)1	-255	608	115	4.3
H(C6)2	-170	655	-95	4.3
H(C7)1	278	628	295	5.3
H(C7)2	210	548	526	5.3
H(C9)1	308	328	695	5.5
H(C10)1	423	150	655	6.3
H(C11)1	540	168	385	7.3
H(C12)1	515	325	75	6.8
H(C13)1	393	488	85	5.7

REFERENCES AND NOTES

1. The subject has been reviewed; see R. G. Harvey and E. R. DeSombre, in Topics in Phosphorus Chemistry, M. Grayson and E. J. Griffith, eds. (Interscience Publ. Co., N. Y., 1964), Vol. 1, p. 57. H. G. Henning and G. Hilgetag, Zeit. fur Chemie, 5, 169 (1967); and K. D. Berlin and P. E. Clark, Phosphorus, In Press (1973).
2. K. D. Berlin, C. Hildebrand, J. G. Verkade, and O. C. Dermer, Chem. Ind. (London), 291 (1963).
3. K. D. Berlin, C. Hildebrand, A. South, D. M. Hellwege, M. Peterson, E. A. Pier, and J. G. Verkade, Tetrahedron, 20, 323 (1964) and C. Hildebrand, M.S. Thesis, Oklahoma State University, 1963.
4. L. Silver and R. Rudman, Acta Cryst., B28, 574 (1972).
5. H. J. Geise, Rec. Trav. Chim. Pays-Bas, 86, 362 (1967).
6. T. A. Beinke, Acta Cryst., B25, 413 (1969).
7. W. Murayama and M. Kainosho, Bull. Chem. Soc. Japan, 42, 1819 (1969).
8. M. Haque, C. N. Caughlan, J. H. Hargis, and W. G. Bentrude, J. Chem. Soc. (A), 1786 (1970).
9. R.C.G. Killean, J. L. Lawrence, and I. M. Magennis, Acta Cryst., B27, 189 (1971).
10. C. L. Coulter, Acta Cryst., B25, 2055 (1969).
11. S. Furberg, Acta Chem. Scand., 9, 1557 (1955).
12. D. M. Nimrod, D. R. Fitzwater, and J. G. Verkade, Inorg. Chim. Acta, 2, 149 (1968).
13. G. W. Svetich and C. N. Caughlan, Acta Cryst., 19, 645 (1965).
14. G. B. Drew, J. Rodgers, D. W. White and J. G. Verkade, Chem. Comm., 227 (1971).

15. M. Haque. C. N. Caughlan, and W. L. Moats, J. Org. Chem., 35, 1446 (1970).

16. P. Coppens, L. Leiserowitz, and D. Rabinovich, Acta Cryst., 18, 1035 (1965).

17. International Tables for X-ray Crystallography (Kynoch Press, Birmingham, 1962) Vol. III., p. 202.

18. R. F. Stewart, E. R. Davidson, and W. T. Simpson, J. Chem. Phys., 42, 3175 (1965).

19. C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Single Crystal Analysis of (-)-(S)-6-Benzyl-5,6,7,8-tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidinium Bromide

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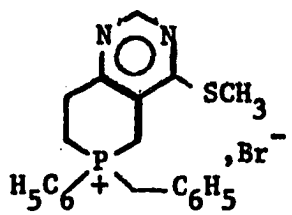
Single crystal X-ray analysis was obtained on the title compound which belonged to the space group $P2_1$. The phosphorinane ring in the molecule is a distorted half chair with phosphorus 0.6 Å out of the plane. The (-)-enantiomer exhibits respiration related cytotoxicity in B. subtilis but not in P. fluorescens and sarcoma 180. However, the (-)-isomer did not inhibit growth in either organism.

Biological activity of organophosphorus compounds is primarily associated with phosphates and phosphonates.[2] Very little biological data has been recorded on any carbon-phosphorus (C-P) heterocycle (only C and P in the ring).[3] We recently developed a general synthesis of phosphorino[4,3-d]pyrimidines,[4] and we report herein an X-ray analysis of one member of the family, i.e. 1, m.p. 250-251°, $[\alpha]_D^{25}$ -77° (c .0120, CH_3OH). There is some structural relationship to 2[5] whose X-ray analysis and biological utility will be reported shortly.



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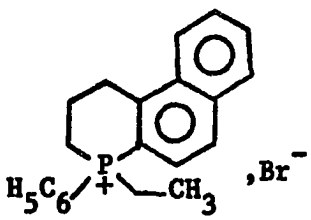


2

The activity of the general family of 5,6,7,8,-tetrahydroquinazolines, of which 1 could be classified as a member (P has been substituted for carbon), is well known in medicinal chemistry.[6,7]

Experimental Section

X-Ray Analysis. A pure sample of the resolved enantiomer 1 ($[\alpha]_D^{25}$ = -77° m.p. 250-1°) was prepared as previously reported.[4] A suitable crystal for X-ray analysis was obtained by slow evaporation of an ethanol-hexane solution. The crystal was then cut to the appropriate size with a razor blade. The space group was determined on a G.E. XRD-5 diffractometer. Weissenberg photographs showed the crystal to be usable for an accurate structure determination. The least squares cell dimensions were obtained from the averages of the +2θ and -2θ values of 40 reflections measured at 25°C. The crystallographic data are shown in Table I. The 2323 data, comprising all unique reflections with 2θ less than 75° were taken with Ni-filtered CuKα radiation (λ = 1.54178 Å) on a Nonius CAD-4

Table I. Crystallographic Data

FORMULA- $C_{21}H_{22}N_2SP^+Br^-$

F.W.- 445.41

F(000)- 456

SPACE GROUP- $P2_1$

Z=2

SYSTEMATIC ABSENCES oko k = 2n + 1

D_{exp} = 1.4074 (Flotation at 30 degrees C in bromobutane/CCl_4)

D_c = 1.395

μ = 45.38 cm^{-1}

a = 11.087(6)

b = 8.7629(9)

c = 12.181(5)

β = 116.38(3)

VOLUME OF CRYSTAL = 2.11 x 10^{-2} mm^3

automatic diffractometer. These data were collected with θ-2θ scans in which the θ scan width was between 0.80 and 1.10 degrees. The maximum scan time was 180 seconds with 2/3 of the time spent while scanning the peak and 1/6 on each the left and right background. There were 22 reflections assigned as unobserved based on the fact that the net count was less than (1.4) $T^{1/2}$ (T = Total count). The unobserved data were given intensities equal to 0.7 $T^{1/2}$. Lorentz, polarization and absorption corrections were applied to the data. The absorption coefficients varied between 0.310 and 0.516 as calculated by the Gaussian method of numerical integration. Each structure amplitude is assigned a weight given by $w_F = 1/\text{sigma}_F^2$, where the standard deviation sigma_F (σ_F), of the amplitude is given by

$$\sigma_F = 1/2 \left[\frac{(\sigma)^2+((0.05)P)^2}{(L_p)P}\right]^{1/2}$$

in which $\sigma = T^{1/2}V$

V = scan speed

P = [PK-2(R+L)]V

PK = Peak count

R = Right background count

L = Left background count

L_p = Lorentz-Polarization factor

Biological Analysis (Methods and Materials). Bacillus subtilis W23 (prototrophic strain) and Pseudomonas fluorescens NND were maintained on 0.5% glucose salts minimal medium.[8] Mouse sarcoma 180 ascites tumor was maintained by intraperitoneal transplantation of 1 x 10^6 cells each week in female CD1 mice (Charles Rivers Laboratories, North Wilmington, Mass.).

B. subtilis and P. fluorescens which had been incubated in glucose minimal medium for 12-14 hrs at 37°C were harvested and suspended in phosphate buffer (0.1 M; pH 7.0) containing 0.5% w/v glucose. The absorbance (540nm) of the suspension was adjusted to 0.50 using a Coleman Junior II Spectrophotometer

(18 mm light path) and 0.5 ml of this suspension used as an inoculum in the respiration test. The sarcoma 180 cells were removed from the peritoneal cavity of mice after 7 days incubation and suspended in phosphate buffered glucose to a cell density of 5×10^5 cells/ml. From this suspension 0.5 ml was used as an inoculum in the respiration test.

The respiration test was conducted using the procedure of Buskirk and co-workers.[9] The end point in the test was determined using a series of control tubes containing serial dilutions of the respective test organism. The results, as indicated by the decolorization of methylene blue, and shown in Table II, were scored as follows: (-), clear; (+1), near clear; (+2), near blue; and (+3), blue.

Structure Solution and Refinement. The bromine-bromine vector was easily distinguishable in the Harker section of the Patterson synthesis. An arbitrary y-coordinate of 0.25 was assigned to this vector peak thereby fixing the position of the origin. Bromine-sulfur and bromine-phosphorous vectors were then located and used to determine the positions of the sulfur and phosphorus. At this point it was impossible to distinguish between sulfur and phosphorous, therefore both positions were put into a structure factor calculation as sulfur along with the bromine ion position. Phases of the structure factors calculated from these heavy atom positions were used to generate a difference Fourier synthesis. Eight additional atoms were located from this map and it was possible to distinguish between the sulfur and phosphorous atoms. The positions were included in another structure factor calculation and a subsequent difference Fourier showed the location of the remainder of the non-hydrogen atoms. Refinement continued by block diagonal least squares using anisotropic thermal parameters until convergence at an $R = (\Sigma||F_o|-|F_c||/\Sigma|F_o|)$ of 0.047. The quantity minimized was $\Sigma w_F(|F_o|-|F_c|)^2$. Anomalous dispersion corrections were made for

Table II. Respiration Studies with 1.

Compound	Test Conc.[α]	Test Organism		
		B. subtilis	P. fluorescens	SA-180
1(+)	275 µg/ml	+2	-	-
1(-)	275 µg/ml	+3	-	-

[α]Concentration is expressed as µg/ml of compound in suspension.

bromine, sulfur, and phosphorus with the anomalous scattering factor curve for sulfur also being used for phosphorous due to computational limitations. The absolute configuration was determined by comparing observed values of I_{hkl} and $I_{\bar{h}\bar{k}\bar{l}}$ with calculated values of F^2_{hkl} and $F^2_{\bar{h}\bar{k}\bar{l}}$. A total of twenty five pairs of reflections were used and all were in agreement with the opposite absolute configuration. The configuration of the molecule was therefore changed by changing the sign of all y coordinates. After three more cycles of least squares refinement a difference Fourier was calculated for the purpose of locating the hydrogen atoms. The positions of 19 hydrogen atoms were located from geometrical considerations and verified with the difference Fourier. The methyl hydrogens were not located. These 19 hydrogens were included in the structure factor calculations but their positions were not refined. Three strong reflections were seen to be affected by secondary extinction and were therefore excluded from the refinement. Refinement was continued until the shifts in the parameters were less than 1/3 of their standard deviation. The final R value for all 2323 data was 0.038. A final difference Fourier showed peaks between 0.85 e./$\mathring{A}^3$ and -0.71 e/$\mathring{A}^3$ around the bromine ion, but no other peaks greater than 0.36 e./$\mathring{A}^3$. Only a disperse positive region was seen in the area where the methyl hydrogens would be expected. The average $w_f\Delta F^2$ were independent of F_o and sin θ/λ, validating the weighting scheme used in the refinement. The final parameters are given in Tables III and IV (structure factor table appears in the microfilm edition of this journal).

The atomic scattering factors for Br^-, S, P, C, N and the anomalous scattering factors for Br^-, and S were taken from the INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY (1962).[10] The scattering factors for the hydrogen atoms were from Stewart, Davidson, and Simpson (1965).[11]

Table III. Atomic fractional coordinates and thermal parameters (all x 10^4).

The temperature factor is expressed in the form $\exp\{-(h^2b_{11}+k^2b_{22}+l^2b_{33}+hkb_{12}+hlb_{13}+klb_{23})\}$. Standard deviations for the last digit are in parentheses.

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{23}	b_{13}	b_{12}
Br(1)	1547.6(4)	-2539.9(8)	1921.7(4)	161.2(5)	93.5(4)	96.2(3)	2.7(7)	51.2(6)	4.3(9)
S(1)	-2746(1)	1673(1)	991(1)	128(1)	102(1)	125(1)	-35(2)	156(2)	-22(2)
N(1)	-3731(4)	-3309(6)	1196(4)	173(5)	149(6)	145(5)	20(10)	155(8)	-33(10)
C(2)	-4099(5)	-2119(7)	1701(5)	166(6)	163(8)	128(5)	22(9)	170(9)	-46(11)
N(3)	-3834(4)	-609(5)	1683(4)	144(4)	140(6)	118(4)	3(8)	159(7)	-14(8)
C(4)	-3147(3)	-251(5)	1071(3)	91(3)	104(5)	84(3)	11(6)	64(5)	4(7)
C(5)	-1910(4)	-822(4)	-200(3)	110(4)	81(4)	75(3)	-5(6)	69(5)	-9(6)
P(6)	-2019.7(8)	-2123(1)	-1353.2(8)	81.1(7)	87(1)	73.4(6)	-19(1)	55(1)	9(1)
C(7)	-1727(4)	-3919(5)	-582(4)	122(4)	98(5)	107(4)	-10(7)	83(7)	30(7)
C(8)	-2741(5)	-4178(5)	-61(5)	175(6)	95(5)	137(5)	7(8)	154(9)	-17(9)
C(9)	-3046(4)	-2843(5)	561(3)	112(4)	119(6)	88(3)	26(7)	66(5)	-15(7)
C(10)	-2722(3)	-1334(4)	458(3)	85(3)	109(5)	69(3)	1(6)	45(5)	1(6)
C(11)	-3222(8)	2561(10)	2076(7)	341(12)	149(8)	262(9)	-117(16)	492(19)	-76(18)
C(12)	-709(3)	-1674(5)	-1804(3)	88(3)	119(5)	87(3)	-37(7)	70(5)	-7(6)
C(13)	-927(3)	-2249(5)	-3031(3)	80(3)	138(7)	89(3)	-34(7)	71(5)	-12(7)
C(14)	-756(5)	-3765(6)	-3207(4)	128(4)	151(7)	115(4)	-86(9)	110(7)	-25(9)
C(15)	-956(6)	-4272(9)	-4377(6)	161(6)	274(13)	154(6)	-234(16)	148(10)	-92(15)
C(16)	-1305(6)	-3194(12)	-5331(5)	183(7)	458(24)	120(5)	-162(19)	150(11)	-144(23)
C(17)	-1499(8)	-1685(12)	-5143(5)	253(10)	358(19)	108(5)	26(16)	150(12)	-80(24)
C(18)	-1288(5)	-1221(7)	-3970(5)	152(5)	195(9)	117(4)	34(11)	128(8)	-29(12)
C(19)	-3643(3)	-2088(5)	-2627(3)	84(3)	161(6)	76(3)	-12(7)	71(5)	1(7)
C(20)	-4194(4)	-3436(8)	-3255(5)	108(4)	260(11)	132(5)	-197(13)	89(7)	-32(12)
C(21)	-5460(5)	-3351(11)	-4302(5)	109(4)	450(20)	120(5)	-254(18)	67(8)	-81(16)
C(22)	-6123(4)	-1972(11)	-4652(4)	88(4)	503(22)	76(3)	-5(14)	43(5)	-22(15)
C(23)	-5587(4)	-686(10)	-4001(5)	99(4)	348(15)	124(5)	173(16)	44(8)	27(14)
C(24)	-4329(4)	-701(7)	-2992(5)	104(4)	184(8)	120(4)	95(10)	66(7)	9(9)

Table IV. Hydrogen atom parameters (coordinates x 10^3)

	x	y	z	Biso.
H(C2)	-464	-237	213	6.19 A^{o2}
H(C5)1	-97	-72	46	4.09
H(C5)2	-227	20	-54	4.09
H(C7)1	-185	-480	-114	5.04
H(C7)2	-82	-398	13	5.04
H(C8)1	-360	-452	-73	5.84
H(C8)2	-236	-501	58	5.84
H(C12)1	-60	-55	-187	4.37
H(C12)2	18	-213	-124	4.37
H(C14)	-51	-451	-252	5.47
H(C15)	-83	-534	-455	8.13
H(C16)	-143	-352	-616	9.22
H(C17)	-175	-93	-583	9.17
H(C18)	-144	-13	-383	6.37
H(C20)	-371	-442	-300	6.85
H(C21)	-588	-427	-480	8.64
H(C22)	-701	-191	-539	8.31
H(C23)	-612	27	-429	7.74
H(C24)	-392	26	-253	5.88

Structural Results. The absolute configuration around the assymetric phosphorous in (-)-(S)-6-benzyl-5,6,7,8-tetrahydro-4-(methylthio)-6-phenyl-phosphorinio(4,3-d)-pyrimidinium bromide (1) as determined by the anomalous scattering technique is shown in Figure 1. The name assigned to 1 is that provided by Chemical Abstracts, Nomenclature Division.

The bond lengths and angles are shown in Figures 2 and 3. The methylthio group attached to the pyrimidine ring shows a short sulfur-carbon distance of 1.757 Å between the sulfur and C(4). A $C(sp^2)$-S single bond distance is known to be 1.79 Å. In several thiopurine and thiopyrimidine structures sulfur has been observed in the thion rather than the mercapto form, having an average bond length of 1.673 Å.[12] Although in a methylthio derivative complete double bond formation of the sulfur to the pyrimidine ring is not possible, some additional overlap is indicated by the shortening of the C(4)-S bond. An almost identical distance has been observed in a methylthio derivative of adenine.[13] No corresponding lengthening of the sulfur-methyl bond is seen, its length of 1.804 Å being in agreement with the accepted $C(sp^3)$-S value of 1.812. The length of this bond is somewhat uncertain however due to high thermal motion of the methyl carbon. The methylthio group lies approximately in the plane of the pyrimidine ring. The torsion angle around the C(4)-S bond is 9 degrees. The sulfur lies 0.028 Å and the methyl carbon 0.32 Å out of the least squares plane through the pyrimidine ring. A very similar situation is seen in the methylthio adenine derivative in which the methylthio group is even more (although not completely) coplanar with the pyrimidine ring system. The C(4)-S-C(11) angle of 102.1 degrees is identical with that found previously. The distances and angles in the pyrimidine ring are not significantly different from those found in pyrimidine itself.[14] Although within 3 standard deviations of the

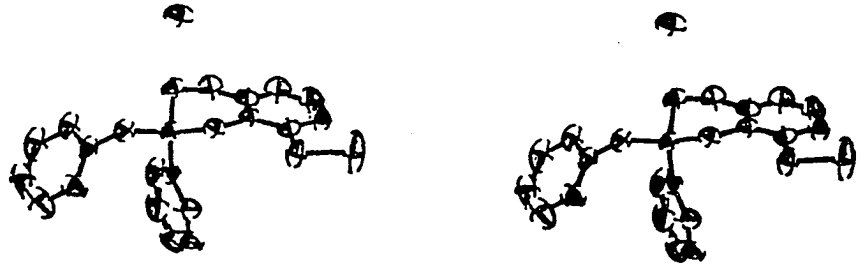


Figure 1 - Stereoview of molecule showing 50% probability thermal ellipsoids and correct absolute configuration using the ORTEP program.[25]

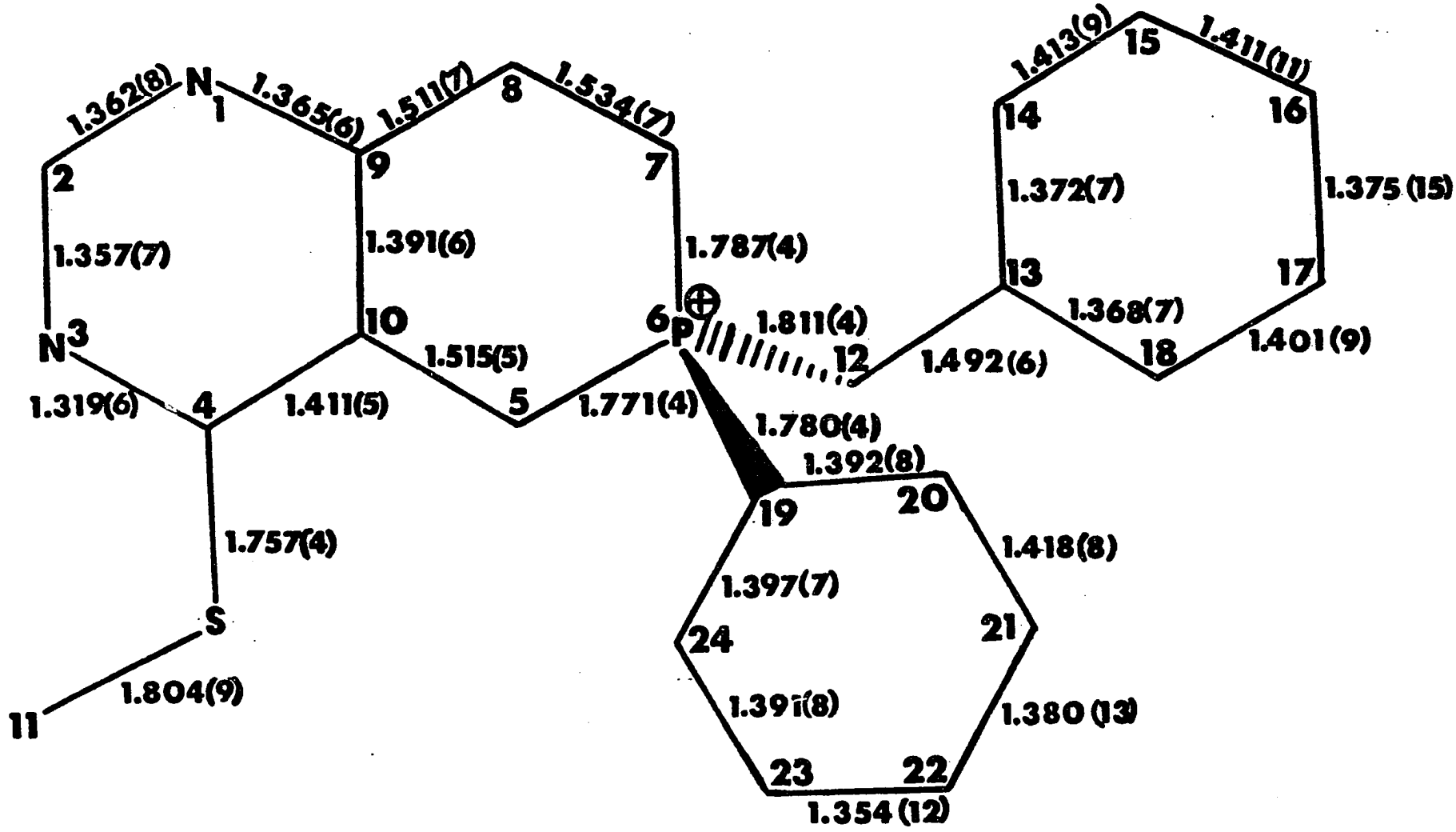


Figure 2 - Bond distances in Angstroms. Standard deviations are in parentheses.

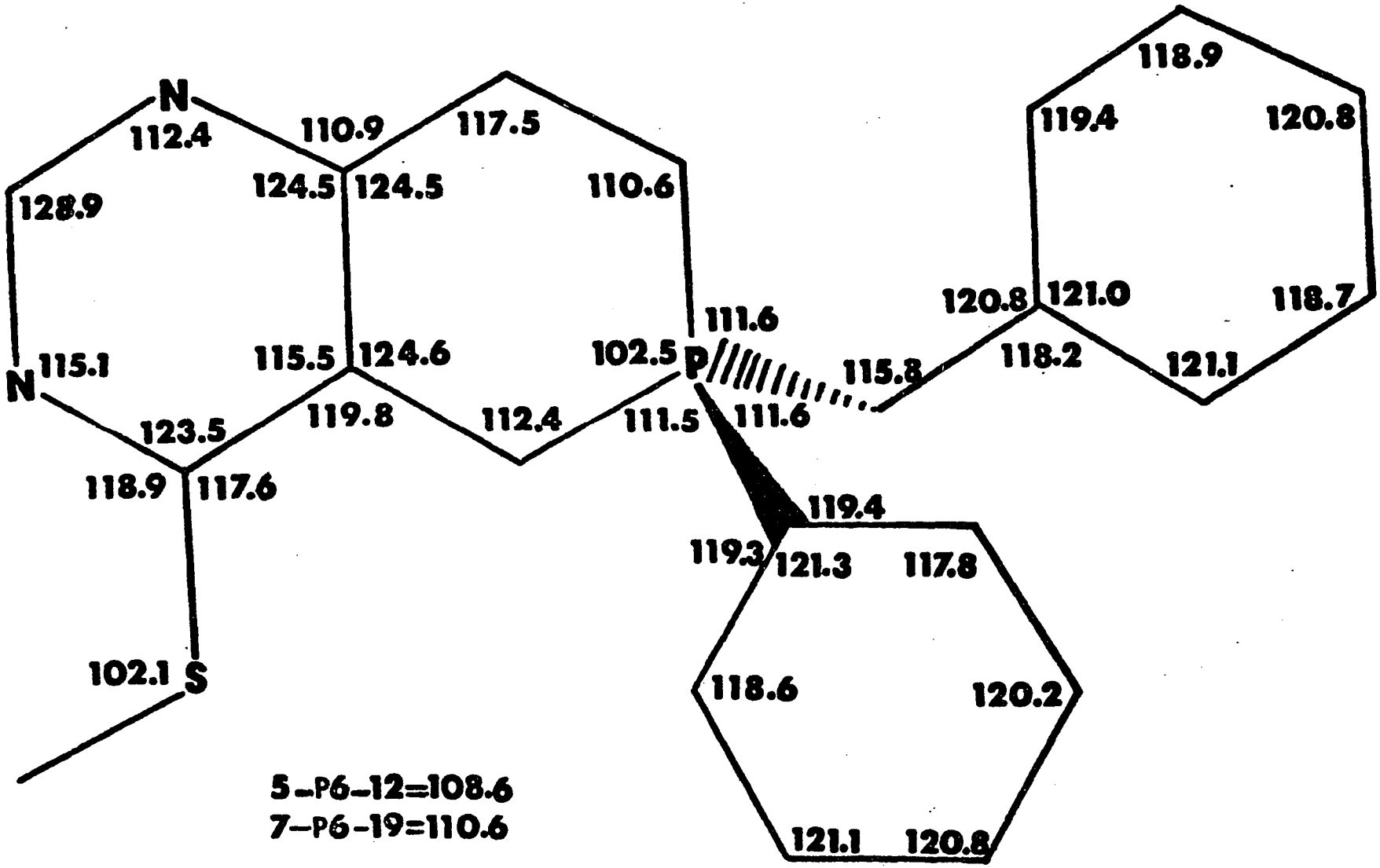


Figure 3 - Bond angles in degrees. Standard deviations are 0.2 degrees around the phosphorous and range from 0.3-0.7 in the remainder of the molecule.

values found in pyrimidine, the N(3)-C(4) distance appears short by 0.03 Å and the N(1)-C(2) distance long, by 0.03 Å, but no correction has been made for thermal motion which may be significant. The thermal ellipsoids of these atoms appear reasonable, however. Singh's rule[15] is seen to be obeyed in that the internal bond angle at a nitrogen in the pyrimidine ring is significantly less than 120 degrees when no third attachment is present and greater than 120 degrees when an extra-annular hydrogen is attached. A least squares plane calculated through the pyrimidine ring shows the ring is planar to within 0.012 Å. Distances from this plane are shown in Table V.

Phosphorous-carbon distances have been found to vary greatly depending on the valency, ionization, and hybridization.[16] For example, the covalent bonds around a phosphonium ion should be more polar in character due to increased difference in electronegativity between carbon and phosphorous and therefore shorter than a phosphorous-carbon bond in a non-ionic system. The most appropriate comparison is therefore with another tetravalent phosphonium ion. A recently determined and accurate structure of benzyl triphenylphosphonium ion[17] shows an average phosphorous-phenyl distance of 1.790 Å and a P-C (benzyl) distance of 1.811 Å. These are in good agreement with the values of 1.780 and 1.811 found in this structure. An average P^+-C (phenyl) distance of 1.785 Å was found in 2,4,4'6-tetraphenyl-4-phosphonia-pyran perchlorate[18] and 1.796 Å in a tetraphenylphosphonium ion.[19] The value of 1.818 Å for a P-C (benzyl) distance in benzylmethylphenylpropylphosphonium bromide[20] is also in agreement with our result. Since a $P(sp^3)$-$C(sp^2)$ distance can be expected to be shorter than a $P(sp^3)$-$C(sp^3)$ distance, it is not surprising to find a longer distance to the benzyl than phenyl carbon. Covalent radii of $C(sp^3)$ hybrids are known to be 0.03-0.04 Å greater than the covalent radii of $C(sp^3)$ hybrids. The P(6)-C(5) and P(6)-C(7) bonds in the phosphorinane ring are shorter than would be expected

Table 5. Least-square planes

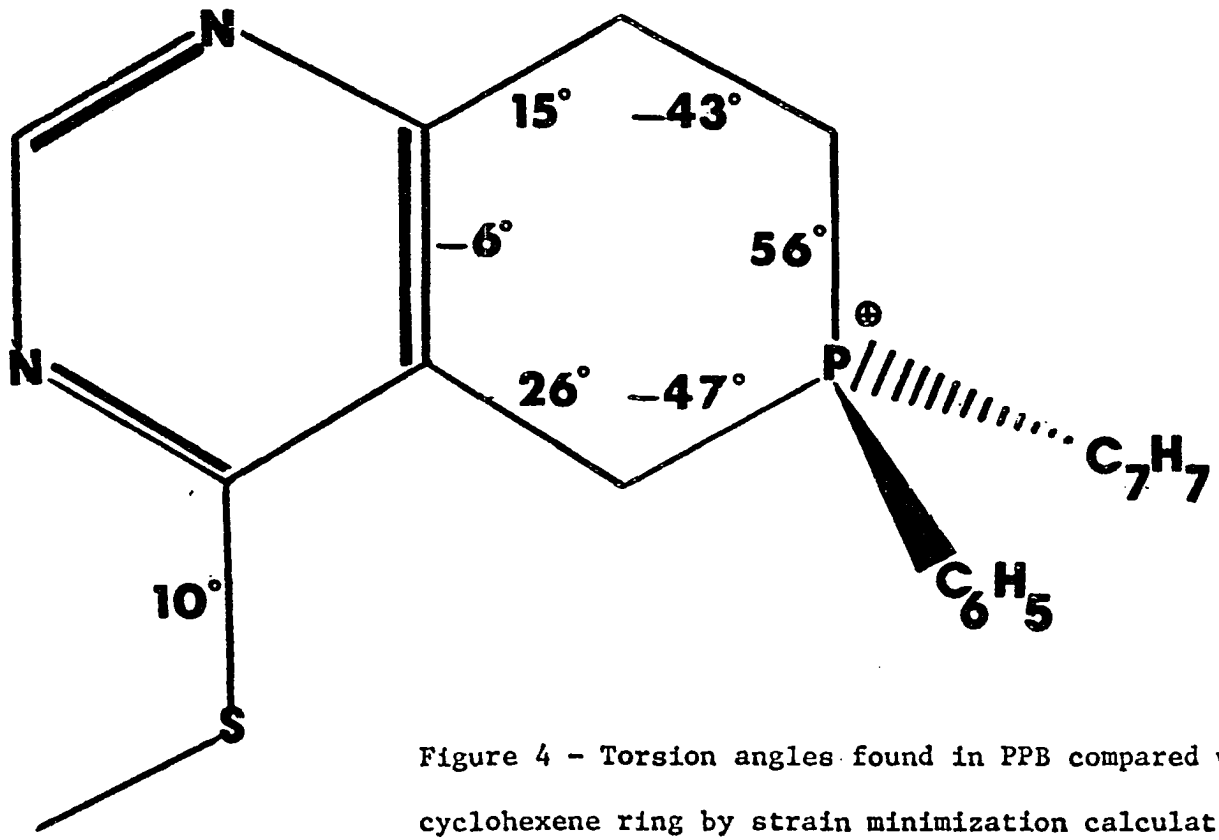
Plane[a]	Atoms	A	B	C	D
1	N(1),C(2),N(3) C(4),C(9),C(10)	6.062	-0.917	6.106	-1.241
2	C(13),C(14),C(15) C(16),C(17),C(18)	10.557	1.499	-2.392	-0.595
3	C(19),C(20),C(21) C(22),C(23),C(24)	8.775	1.538	-10.672	-0.721

	Δ(1)		Δ(2)		Δ(3)
N(1)	0.012 A°	C(13)	0.004 A°	C(19)	0.007 A°
C(2)	-0.012	C(14)	0	C(20)	-0.014
N(3)	0	C(15)	-0.008	C(21)	0.006
C(4)	0.010	C(16)	0.014	C(22)	0.010
C(9)	-0.003	C(17)	-0.010	C(23)	-0.017
C(10)	-0.007	C(18)	0.002	C(24)	0.008
S(1)	0.028			P(6)	0.067
C(11)	0.320				
C(5)	0.036				
P(6)	-0.615				
C(7)	0.198				
C(8)	-0.075				
Br	3.580				

[a] The equations of the planes are expressed in the form Ax + By + Cz = D, where x, y and z are fractional coordinates and D is the distance from the origin in A°.

and in fact closer to P-C(sp^2) than P-C(sp^3) lengths. Although difficult to explain, this shortening may be due to hybridization of the phosphorous orbitals to fit into the ring system or simply from the geometrical strain of the ring trying to accommodate these long bonds. Primarily, however, the geometrical strain on the 6-membered phosphorous containing ring system is relieved in the conformational angles and bond angles. Conjugation in the ring can limit relief of strain by twist around bonds. In this case strain is relieved by expansion of the endocyclic angle at C(8) and contraction of the C(5)-P(6)-C(7) bond angle. The angle at C(8) is expanded to 117.5 degrees from the expected tetrahedral value and from that of 111.6 degrees found in a cyclohexene ring.[21] The bond angle C(5)-P(6)-C(7) is seen to be contracted to 102 degrees from its expected tetrahedral value. The other method of strain relief is in the conformation of the ring or twist around the bonds. A comparison of the conformational angles found in an analogous cyclohexene ring (which are predicted by strain minimization calculations)[22] with those found in PPB is shown in Figure 4. It is seen that the greater twist angle around C(4)-C(5) takes P(6) farther out of the plane of the ring system than C(7). This can also be seen in the deviation of these atoms from the plane through the pyrimidine ring. The phosphorinane ring exists in a distorted half chair conformation with the phosphorous 0.6 Å out of the plane through the fused rings and C(7) out of the plane in the opposite direction by 0.2 Å as is shown in Table V.

The average bond distance in the phenyl ring is 1.389 Å with an average bond angle of 120 degrees. In the benzyl ring the average values are 1.390 Å and 120 degrees. The accepted length of a carbon-carbon aromatic bond is 1.394 Å. The rings are essentially planar as is shown in Table V. The phosphorus lies out of the plane of the phenyl ring by 0.07 Å. The positions of the hydrogens were not refined and therefore the carbon-hydrogen distances vary only



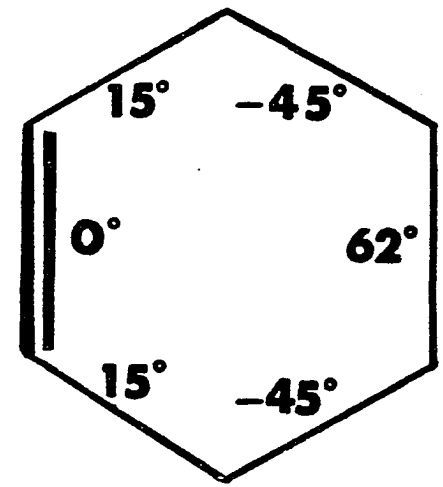


Figure 4 - Torsion angles found in PPB compared with those predicted for cyclohexene ring by strain minimization calculations.[22]

from 0.98-1.01 Å. Thermal ellipsoids show large in plane rocking vibrations in the benzyl and phenyl rings as can be seen in Figure 1. The methylthio methyl is seen to have a large vibration perpendicular to the pyrimidine ring. This high thermal motion is to be associated with large standard deviations at these positions.

The Br^- lies 4.20 Å from the phosphorous ion and 4.15 Å from the phosphorus ion related by a two fold screw operation and a translation of -1 in y. The Br^- has a 3.75 Å contact with C(7) and a 3.61 Å contact with a screw related C(7). Atoms C(5) and C(12) are 3.69 and 3.73 Å respectively from the bromine generated by a screw operation. There are no other bromine-carbon contacts less than 3.8 Å. Closest contacts and ionic bonds are shown in the packing drawing of Figure 5. No intermolecular contacts of less than 3.45 Å are observed between non-hydrogen atoms.

Biological Results. The results of the respiration test (Table II) indicate that both optical isomers of compound 1 exhibit respiration related cytotoxicity in B. subtilis but not in P. fluorescens or sarcoma 180. The "negative" isomer appears to be the more active as indicated by its blue (+3) end-point as compared to the near blue (+2) end-point of the "plus" isomer. Thus, the compound inhibits oxidative respiration in B. subtilis when methylene blue is readily available as an electron acceptor.

Bacterial growth studies were carried out as described earlier.[23] The experiments involved the growth of Bacillus subtilis W23 and Pseudomonas fluorescens NND in liquid culture on glucose minimal medium. The first compound was prepared in aqueous solution and added to the growth medium just prior to cell inoculation. Growth was measured by the change in absorbance at 540 nm.

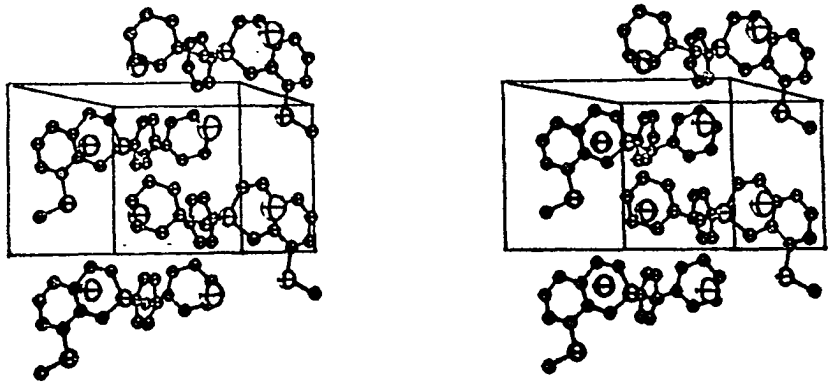


Figure 5 - Stereodiagram of the crystal packing viewed down the a* axis (perpendicular to the bc plane) using the ORTEP program.[25]

The compounds influence on mammalian cell growth was evaluated using the human tumor cell line, KB. The method[24] involves a determination of the relative plating efficiency of control KB cells compared to cultures supplemented with up to 250 μg/ml of the test compound.

Discussion. The ability of 1 to inhibit respiration of B. subtilis is the first example we could find recorded for a C-P heterocycle phosphonium salt with bacterial systems. The respiration test[9] was negative for P. fluorescens and sarcoma 180. Unfortunately, 1 at concentrations as high as 91 μg/ml did not inhibit growth of B. subtilis or P. fluorescens. At concentrations up to 250 μg/ml no inhibition of growth of KB cells was observed. Consequently, the respiration test using methylene blue as an artificial electron acceptor may serve as a diagnostic probe of very selective biological activity.

The X-ray data is the first we could find recorded on a fused bicyclic C-P heterocycle with nitrogen in the ring which does not contain phosphorous. It is apparent the structural differences between 1 and 2 result in a dramatic effect on the biological activity of 1 in the systems tested. In both systems, the phosphorous-containing ring exists in a half-chair conformation. Obviously, the structure-activity relationship in C-P heterocycles is just as subtle as in other families of heterocycles and must await wide range screening before definitive predictions are feasible.

Acknowledgments. One of us (KDB) gratefully acknowledges partially support of this work by the U.S.P.H.S., National Cancer Institute, grant CA 11967. We also express our gratitude to Dr. Kurt Leoning, Director of Nomenclature, Chemical Abstracts, for discussions on the naming of the title compound. One of us (DvdH) gratefully acknowledges support by an N.I.H. Development Award, K4-GM-42,572.

Supplementary Material Available

A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 x 148 mm, 24 x reduction,negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number 00000.

References

1. Research Associate, 1973, present address Department of Chemistry, Cameron State College, Lawton, Oklahoma.

2. For summaries of studies in the areas, see: a. C. Fest and K. J. Schmidt, "The Chemistry of Organophosphorus Pesticides, Reactivity, Synthesis, Mode of Action, Toxicology," Springer-Verlog, New York, N.Y., 1973; b. "Organic Phosphorus Compounds," Vols. 1-7, G. M. Kossalopoff and L. Maier, eds., Wiley-Interscience, 1972, New York, N.Y. (A series devoted to many aspects of organophosphorus chemistry); c. "Organophosphorus Chemistry," S. Trippett, Senior Reporter, The Chemical Society, Vols. 1-5, London, 1970; and d. D. F. Heath , "Organophosphorus Poisons, Anticholinesterase and Related Compounds," Pergamon Press, New York, N.Y., 1961.

3. For summaries, see T. E. Snider, Ph.D., Dissertation, Oklahoma State University, 1972, and W. R. Purdum and K. D. Berlin, J. Org. Chem., 39, In Press, 1974.

4. T. E. Snider and K. D. Berlin, J. Org. Chem., 38, 1657 (1973).

5. C. H. Chen and K. D. Berlin, J. Org. Chem., 36, 2791 (1971).

6. W. L. F. Armarego, Fused Pyrimidines, Part I Quinazolines, D. J. Brown, ed., "The Chemistry of Heterocyclic Compounds," A. Weissberger, ed., Interscience, New York, N.Y., 1967.

7. G. P. Ellis, The Literature of Medicinal Chemistry, in "Progress in Medicinal Chemistry," Vol. 6, G. P. Ellis and G. B. West, ed., Plenum Press, New York, N.Y., 1969, p. 266.

8. G. K. Best and N. N. Durham, Arch. Biochem. Biophys. 105, 120 (1964).

9. H. H. Buskirk, J. A. Crim, G. J. Van Giessen and H. G. Petering, J. Natl. Cancer Inst. 51, 135 (1973).

10. INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY, Vol. III (Kynoch Press, Birmingham, p. 202).

11. R. F. Steward, E. R. Davidson, and W. T. Simpson, J. Chem. Phys. 42, 3175 (1965).

12. G. H.-Y Lin, M. Sundarlingam, and S. K. Arora, J. Amer. Chem. Soc. 93, 1235 (1971).

13. R. K. McMullan, M. Sundarlingam, J. Amer. Chem. Soc. 93, 7050 (1971).

14. P. J. Wheatly, Acta. Cryst. 13, 80 (1960).

15. C. Singh, Acta. Cryst. 19, 861 (1965).

16. J. J. Daly, PERSPECTIVES IN STRUCTURAL CHEMISTRY, Vol. 3 (Wiley, New York, p. 165 and references therein). (1969).

17. A. C. Skapski and F. A. Stephens, J. Cryst. Mol. Struct. 4, 77 (1974).

18. J. Guilheim, Cryst. Struct. Comm. 3, 227 (1974).

19. P. Goldstein, K. Seff, and K. N. Trueblood, Acta. Cryst. B24, 778 (1968).

20. A. F. Peerdeman, J. C. P. Holst, L. Horner, and H. Winkler, Tetrahedron Letters, 811 (1965).

21. C. Pedone, E. Benedetti, A. Immirizi, and G. Allegra, J. Amer. Chem. Soc. 92, 3549 (1970).

22. R. Bucort, Bull. Soc. Chim. Fr., 2080 (1964).

23. R. W. Chestnut, D. F. Haslam, or N. N. Durham, and K. D. Berlin, Can. J. Biochim. 50, 516 (1972).

24. M. L. Higgins, R. W. Chestnut, F. R. Leach, J. G. Morgan, K. D. Berlin and N. N. Durham, Steroids, 19, 301 (1972).

25. C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, (1965).

Single Crystal Analysis of 1-Ethyl-1,2,3,4-tetrahydro-1-phenylbenzo[h]-phosphinolinium Bromide-Evidence for Antimicrobial Activity by the salt.

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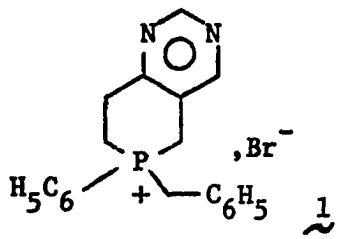
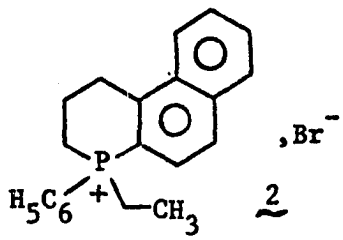
Analysis via X-ray diffraction of a single crystal of the title compound has revealed the space group as $P2_1/c$. The ring containing phosphorus is a near perfect half-chair conformation. Marked growth inhibition of Bacillus subtilis and KB cells by the phosphonium salt was observed, the data on the KB cells being the first recorded for tissue culture cells with a bicyclic carbon-phosphorus heterocycle.

Carbon-phosphorus (C-P), bicyclic heterocycles containing only carbon and phosphorus in the heterocyclic ring have not been investigated very extensively for biological activity since synthetic methods for these compounds are facile only for small, single-ring systems.[2] Although the phosphorino[4,3-d] pyrimidine 1 in the previous work[3] displayed little activity



1



2

in bacteria or KB cell lines, 1-ethyl-1,2,3,4-tetrahydro-1-phenylbenzo[h]-phosphinolinium bromide(2) (NSC 145185) has confirmed activity against P-388 lymphocytic leukemia as discovered in the testing program of the National Cancer Institute. We now wish to report the X-ray analysis of this salt and additional screening data in microbial systems and with the KB cell line.

Experimental Section

X-Ray Analysis. A crystal suitable for X-ray analysis was obtained by an equilibrium diffusion of water into a dimethylsulfoxide solution. The crystal was seen to by monoclinic and of good quality from oscillation and Weissenberg photographs. The space group was determined to be $P2_1/c$ on a G.E. XRD-5 diffractometer. Data were originally collected with MoKα radiation to minimize absorption effects. The structure was solved using this data, but refinement was unsatisfactory due to the large number of weak and unobserved reflections. To increase the number of observed intensities a second data set was collected with Cu radiation. A total of 3873 data were collected on

a Nonius CAD-4 automatic diffractometer using Ni-filtered CuKα radiation (λ = 1.5418 Å). These were all unique reflections with 2θ less than 75°. These data were collected with θ-2θ scans in which the θ scan was between 0.80 and 1.10 degrees. The maximum scan time was 120 seconds with 2/3 of the time spent while scanning the peak and 1/6 on the left and right background. The least squares cell dimensions were determined from averages of the +2θ and -2θ values of 40 reflections measured at 25°C. The crystallographic data are shown in Table I. There were 361 reflections assigned as unobserved based on the fact that the net count was less than $(2.0)T^{1/2}$ (T = total count). The unobserved data were given intensities equal to $1.55\ T^{1/2}$. Lorentz, polarization and absorption corrections were applied to the data. The absorption coefficients varied between 0.308 and 0.600 as calculated by the Gaussian method of numerical integration. Each structure amplitude was assigned a weight given by $w_f = 1/\sigma_F^2$, where the standard deviation σ_F of the amplitude is given by

$$\sigma_F = 1/2\left[\frac{(\sigma)^2 + ((0.05)P)^2}{(L_p)P}\right]^{1/2}$$

in which

$\sigma = T^{1/2}V$

V = scan speed

P = (PK-2(R+L))V

PK = peak count

R = right background count

L = left background count

L_p = Lorentz-Polarization factor

Biological Analysis (Methods and Materials). Bacterial growth studies were carried out as described earlier[3,4] in which Bacillus subtilis W23 and Pseudomonas fluorescens NND were grown in liquid culture on glucose minimal

Table I. Crystallographic Data

FORMULA - $C_{21}H_{22}P^{+}Br^{-}$

F.W. - 385.30

F(000) - 792

SPACE GROUP - $P2_1/c$

Z = 4

SYSTEMATIC ABSENCES h01: 1 = 2n

0k0: k = 2n

D_{exp} = 1.3544 g/cm^3 (Flotation at 20 degrees C in hexane/CCl_4)

D_c = 1.357 g/cm^3

μ = 40.38 cm^{-1} (CuKα radiation)

a = 8.2623(2) A°

b = 16.5378(8) A°

c = 15.1167(9) A°

β = 114.116°(3)

VOLUME OF CELL = 1885.3 A°^{3}

medium. An aqueous solution of the test compound containing 0.9% dimethyl sulfoxide (final concentration) was prepared and added to the growth medium just prior to cell inoculation. Growth was measured by the change in absorbance at 540 nm.

Cell culture studies were carried out as described previously[5] and involved a determination of the relative plating efficiency of the human tumor cell line, KB, growing in medium containing the test compound. The cells were cultured for 10 days in 60 x 15 mm plastic tissue culture dishes containing 5 ml of medium plus the designated test compound. The cells were then stained and growth was determined by microscopic colony counts.

Structure Solution and Refinement. As mentioned previously the structure of 1-ethyl-1,2,3,4-tetrahydro-1-phenylbenzo(h)phosphinolinium bromide (2) was solved using data collected with MoKα radiation. The position of the bromine ion was determined from the bromine-bromine vector peak in the Harker section and Harker line of the Patterson synthesis. Phases of the structure factors calculated from the bromine position were used to generate a difference Fourier which showed the location of the phosphorus ion. Phases calculated from these positions were refined by one cycle of block diagonal least squares minimization of $\Sigma w_f(|F_o|-|F_c|)^2$ and then used to calculate another difference Fourier map which showed all but three carbons. These were included in a similar procedure and the remaining non-hydrogen atom positions were determined. The atom positions were refined by least-squares until the calculated shifts in the positions converged. The non-methyl hydrogen atom positions were located from geometrical considerations and the aid of a difference Fourier. At this point it was decided to retake the data with CuKα radiation to increase the number of observed intensities. The final parameters from refinement of the Mo data were used as

starting parameters for refinement of the data collected with Cu radiation. All non-hydrogen atoms were refined with anisotropic thermal parameters and all hydrogens with isotropic temperature factors. At this point the anomalous contributions of Br and P were included in the calculations. Refinement converged at an $R = (\Sigma||F_o|-|F_c||/\Sigma|F_o|)$ of 3.9%. A difference Fourier was calculated which showed the location of the 3 methyl hydrogens. Their positions were included in subsequent least-squares refinement and they were given isotropic temperature factors. The refinement converged at a final R of 0.0364 for all data at which point the shifts were less than standard deviations and the $\Sigma w_f(|F_o|-|F_c|)^2$ showed negligible change. A final difference Fourier showed peaks between -0.64 and +0.55 $e/\mathring{A}^3$ around the bromine ion. The next largest peak is -0.28 $e/\mathring{A}^3$ near the phosphorus ion position.

The average $w_f\Delta F^2$ were independent of F_o and sin θ/λ, validating the weighting scheme used in the refinement. The final parameters are given in Tables II and III (structure factor tables appear in the microfilm edition of this journal).

The atomic scattering factors for Br, P and C and the anomalous scattering factors for Br and P were taken from the International Tables For X-Ray Crystallography.[6] The scattering factors for the hydrogen atoms were from the literature also.[7]

Results and Discussion. A stereoview of the molecule showing the thermal ellipsoids is illustrated in Figure 1. The bond lengths and angles are shown in Figures 2 and 3. The parameters shown are those obtained from refinement of the data collected with Cu radiation. These distances and angles, however, were not significantly different from those obtained in refinement of the data gathered with Mo radiation when compared with the standard deviations of the

Table II. Atomic fractional coordinates and thermal parameters (all $\times 10^4$). The temperature factor is expressed in the form $\exp\{-(h^2b_{11}+k^2b_{22}+\ell^2b_{33}+hkb_{12}+h\ell b_{13}+k\ell b_{23})\}$. Standard deviations for last digit are in parenthesis.

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{23}	b_{13}	b_{12}
Br(1)	8414.3(3)	6088.2(2)	6043.4(2)	171.4(4)	49.9(1)	60.0(1)	11.0(2)	80.7(4)	-1.6(3)
P(1)	6063.3(7)	5109.2(3)	3091.1(4)	135.8(8)	34.2(2)	44.2(2)	1.8(3)	64.8(7)	-3.1(6)
C(2)	8166(3)	5604(2)	3494(2)	155(4)	47(1)	63(1)	-2(2)	80(4)	-22(3)
C(3)	8396(4)	5976(2)	2633(2)	214(5)	56(1)	83(2)	13(2)	135(5)	-51(4)
C(4)	8503(3)	5320(2)	1958(2)	203(5)	72(1)	68(2)	29(2)	142(5)	4(4)
C(5)	6781(4)	4289(2)	743(2)	306(7)	60(1)	60(1)	19(2)	158(5)	68(5)
C(6)	5463(5)	3749(2)	332(2)	382(8)	54(1)	52(1)	3(2)	134(6)	75(5)
C(7)	2843(5)	3017(2)	309(2)	367(8)	43(1)	57(1)	-13(2)	16(5)	25(5)
C(8)	1680(4)	2861(2)	707(2)	302(7)	41(1)	72(2)	-6(2)	-32(5)	-34(4)
C(9)	1762(4)	3298(2)	1534(2)	241(6)	52(1)	76(2)	-1(2)	40(5)	-62(4)
C(10)	3078(4)	3862(2)	1949(2)	201(5)	48(1)	61(1)	-11(2)	61(4)	-35(3)
C(11)	4351(3)	4013(1)	1574(2)	207(5)	37(1)	46(1)	2(1)	54(4)	20(3)
C(12)	4214(4)	3590(2)	727(2)	293(6)	40(1)	48(1)	-2(2)	51(4)	44(4)
C(13)	5793(3)	4576(1)	2002(1)	184(4)	39(1)	44(1)	5(1)	76(3)	15(3)
C(14)	6994(3)	4723(2)	1591(2)	214(5)	50(1)	50(1)	25(2)	105(4)	54(3)
C(15)	6073(3)	4493(1)	4077(2)	165(4)	42(1)	48(1)	6(2)	82(3)	-2(3)
C(16)	7018(4)	3681(2)	4171(2)	275(6)	49(1)	86(2)	45(2)	157(6)	57(4)
C(17)	4370(3)	5868(1)	2790(2)	147(3)	35(1)	53(1)	7(1)	69(3)	-5(3)
C(18)	4240(3)	6343(2)	3516(2)	182(4)	44(1)	71(2)	-15(2)	73(4)	12(3)
C(19)	2999(4)	6961(2)	3267(3)	220(5)	42(1)	108(2)	-15(2)	148(6)	8(4)
C(20)	1903(4)	7109(2)	2305(2)	210(5)	42(1)	120(2)	47(3)	162(6)	37(4)
C(21)	2020(4)	6630(2)	1599(2)	243(6)	68(2)	85(2)	63(3)	107(5)	87(5)
C(22)	3240(4)	6011(2)	1830(2)	234(6)	57(1)	58(1)	32(2)	88(5)	48(4)

Table III. Hydrogen Atom Parameters (Coordinates x 10^3)

Atom	x	y	z	B($A^{\circ 2}$)
H(C2)1	829(4)	602(2)	401(2)	6.2(7)
H(C2)2	901(4)	523(2)	377(2)	5.9(6)
H(C3)1	730(4)	639(2)	227(3)	8.2(9)
H(C3)2	947(4)	625(2)	284(2)	6.6(7)
H(C4)1	856(4)	560(2)	135(2)	6.6(7)
H(C4)2	962(4)	500(2)	229(2)	6.9(7)
H(C5)	750(4)	443(2)	40(3)	8.3(9)
H(C6)	523(5)	344(2)	-29(3)	9.5(10)
H(C7)	271(4)	272(2)	-29(2)	7.2(8)
H(C8)	75(5)	248(2)	44(3)	8.9(9)
H(C9)	89(4)	321(2)	182(2)	6.8(7)
H(C10)	314(4)	413(2)	252(2)	5.7(6)
H(C15)1	664(3)	485(2)	468(2)	5.1(6)
H(C15)2	476(3)	440(2)	398(2)	6.0(6)
H(C16)1	624(5)	339(2)	358(3)	9.0(9)
H(C16)2	700(5)	340(2)	475(3)	9.9(10)
H(C16)3	814(5)	379(2)	422(3)	9.7(11)
H(C18)	495(4)	624(2)	416(2)	5.5(6)
H(C19)	276(4)	721(2)	366(2)	7.2(8)
H(C20)	105(4)	755(2)	210(2)	6.5(7)
H(C21)	132(4)	673(2)	95(2)	6.8(7)
H(C22)	318(4)	564(2)	130(2)	6.2(7)

Standard deviation of the last digit is in parentheses.

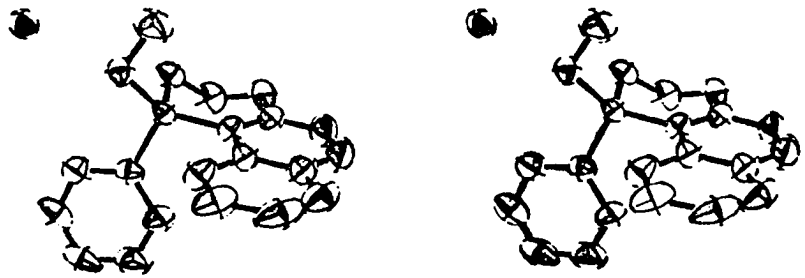


Figure 1 - Stereoview of molecule showing 50% probability thermal ellipsoids using the ORTEP program.[22]

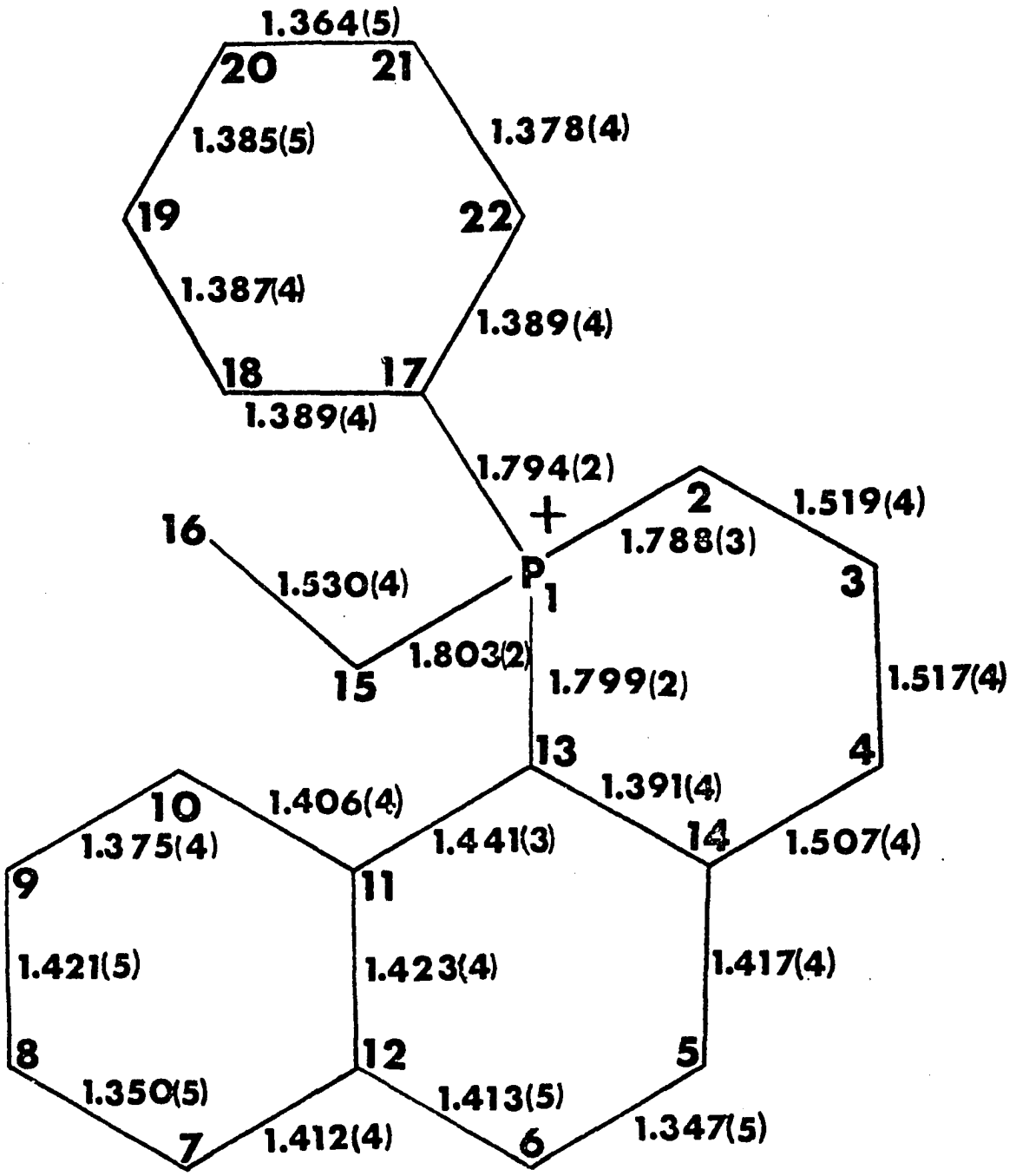


Figure 2 - Bond distances in Angstroms. Standard deviations are in parentheses. Numbering scheme is shown.

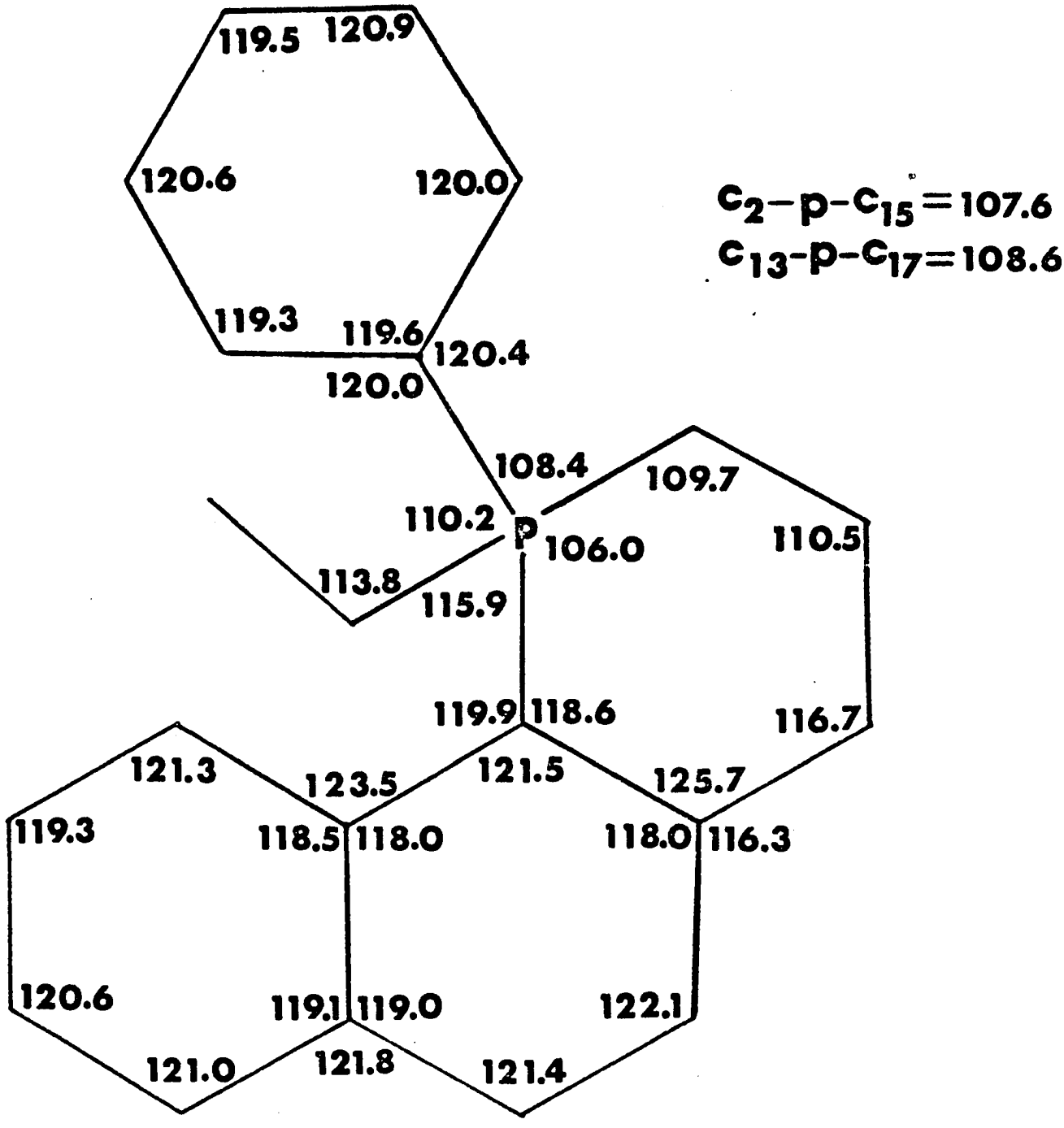


Figure 3 - Bond angles in degrees. Standard deviations are 0.1^{o} around the phosphorous ion and range from $0.2-0.3^{o}$ in the rest of the molecule.

distances and angles obtained in that refinement. The fused ring system of this structure may be considered a relative of the naphthalene and phenanthrene systems.

The bond lengths in the aromatic nucleus C(5) up to C(14) are in agreement with those found in naphthalene,[8] with the exception of C(11)-C(13) and C(13)-C(14). These distances are more than three standard deviations longer than the values of 1.425 Å and 1.361 Å in naphthalene. These bond lengths are intermediate between the naphthalene values and those of 1.464 Å and 1.416 Å in phenanthrene.[9] The lengthening of these bonds when compared to naphthalene may be explained as due to the withdrawl of electrons from the aromatic bonds by the positively charged phosphorus. No significant shortening is seen in the C(4)-C(14) distance when compared to a normal $C(sp^2)$-$C(sp^3)$ distance.

This is the second structure of a phosphonium ion contained in a fused carbon ring system and a comparison may therefore be made with (-)-(S)-6-benzyl-5,6,7,8-tetrahydro-4-(methylthio)-phenylphosphorino[4,3-d]pyrimidinium bromide (1) formerly determined.[3] The major difference in the environment of the phosphorus ion in the two structures is that in 1 the phosphorus is one carbon removed in its ring position from the sp^2 hybridized carbons of the aromatic nucleus, whereas in the present structure 2 the phosphonium ion is directly attached to the aromatic ring. In the discussion of the structure of 1 it was noted that a P^+-$C(sp^2)$ distance to a phenyl ring was 1.780 Å which was consistent with previous structures[10-12] and shorter than a P^+-$C(sp^3)$ distance of 1.818 Å by about 0.03 Å, again consistent with other data[13] and the known difference in radii between sp^2 and sp^3 carbons. It was also seen in 1 that the P^+-$C(sp^3)$ endocyclic bonds were shortened to 1.771 Å and 1.787 Å, values approaching P^+-$C(sp^2)$ distances. In 2 a somewhat different situation is seen in that the four P^+-

carbon bonds show less variation in their lengths. Again the exocyclic P^+-C(15)(sp^3) bond length is greater than the P^+-C(17)(sp^2) length, although the difference is only 0.009 Å in this case. The P^+-C(2) distance agrees with short endocyclic bonds found in 1, but P^+-C(13) is significantly longer than P^+-C(sp^3) endocyclic bonds found previously when it would be expected to be shorter on the basis that it is a P^+-C(sp^2) bond. Clearly, more data from different structures is necessary before a generalization about phosphonium ion-carbon bond lengths is justified.

The C(2)-P^+-C(13) endocyclic bond angle is observed to be 106°; a fairly large increase over the value of 102.5° found in 1. This approach toward a tetrahedral condition may reflect a less strained phosphorinane ring conformation in 2. The angle C(13)-P^+-C(15) is expanded to 115.9° presumably due to the crowding between H(C10) and H(C15). These two hydrogens have a separation of only 2.10 Å compared to a value of 2.4 Å for the sum of their van der Waals radii.[14] The P^+-C(13)-C(14) angle is similar than that found in 1 and observed in a cyclohexene ring,[15] and this may also be an effect of the crowding between C(10) and C(15). A significant expansion is seen in the bond angles C(3)-C(4)-C(14) and C(4)-C(14)-C(13) to accommodate the long phosphorus-carbon bonds into the 6-membered ring.

The conformation of the phosphorinane ring can be seen in deviations of the atoms of the ring from the best plane through the "naphthalene-like" rings of C(5) up to C(14). The equation of this plane and deviations are shown in Table IV. Figure 4 shows the conformations of 1 and 2 reviewed down the least squares plane. It can be seen that 2 is in a much more perfect half-chair conformation, while 1 is significantly more twisted. The conformation of the phosphorinane ring can also be seen in Figure 5. A comparison of the dihedral

Table IV. Least-Squares Planes

Plane		A	B	C	D
1	C(5), C(6), C(7), C(8), C(9), C(10), C(11), C(12), C(13), C(14)	3.222	-11.918	5.499	-2.512
2	C(17), C(18), C(19), C(20), C(21), C(22)	6.385	10.419	-5.828	7.270

	Δ(1)		Δ(2)
C(5)	-0.007 Å	C(17)	0.008 Å
C(6)	-0.014	C(18)	-0.003
C(7)	0.002	C(19)	-0.005
C(8)	0.032	C(20)	0.009
C(9)	-0.007	C(21)	-0.004
C(10)	-0.028	C(22)	-0.004
C(11)	-0.004		
C(12)	-0.009	^{1}Br	0.924
C(13)	0.025		
C(14)	0.011	P(1)	0.124
P(1)	0.076		
C(2)	0.385		
C(3)	-0.457		
C(4)	-0.012		
$^{1}Br^{-}$	1.291		
$^{2}Br^{-}$	0.537		
$^{3}Br^{-}$	1.152		
$^{4}Br^{-}$	-8.046		
C(15)	1.356		
C(16)	2.680		
H(C15)1	1.445		
H(C15)2	0.990		
H(C16)1	2.451		
H(C16)2	3.327		
H(C16)3	2.938		

The equations of the planes are expressed in the form Ax + By + Cz = D, where x, y and z are fractional coordinates and D is the distance from the origin in Å. See Table V for Br^{-} designations.

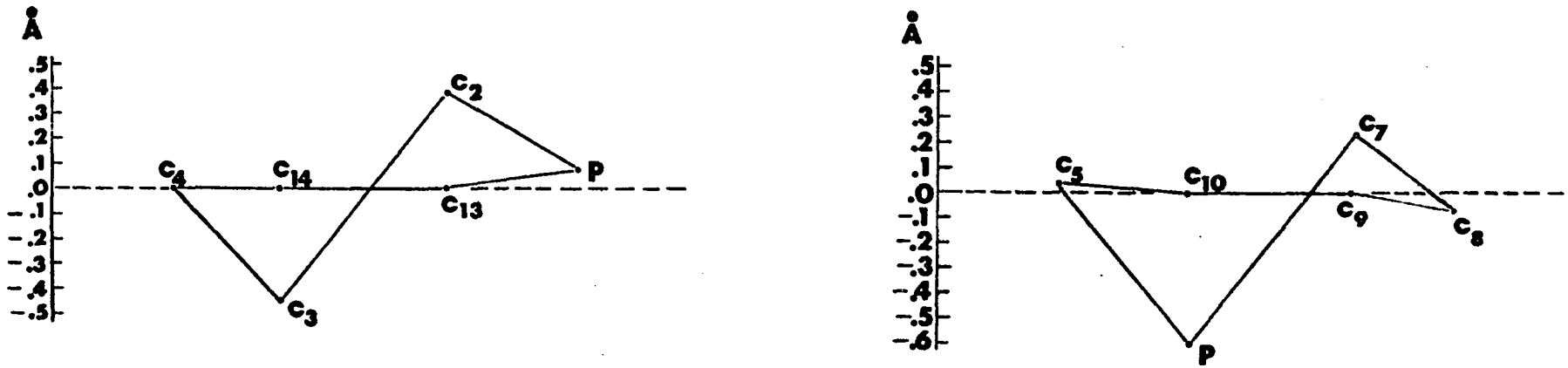


Figure 4 - View of the conformation of the phosphorinane rings of 1 (right) and 2 (left) showing deviations from the least squares plane through the aromatic ring systems.

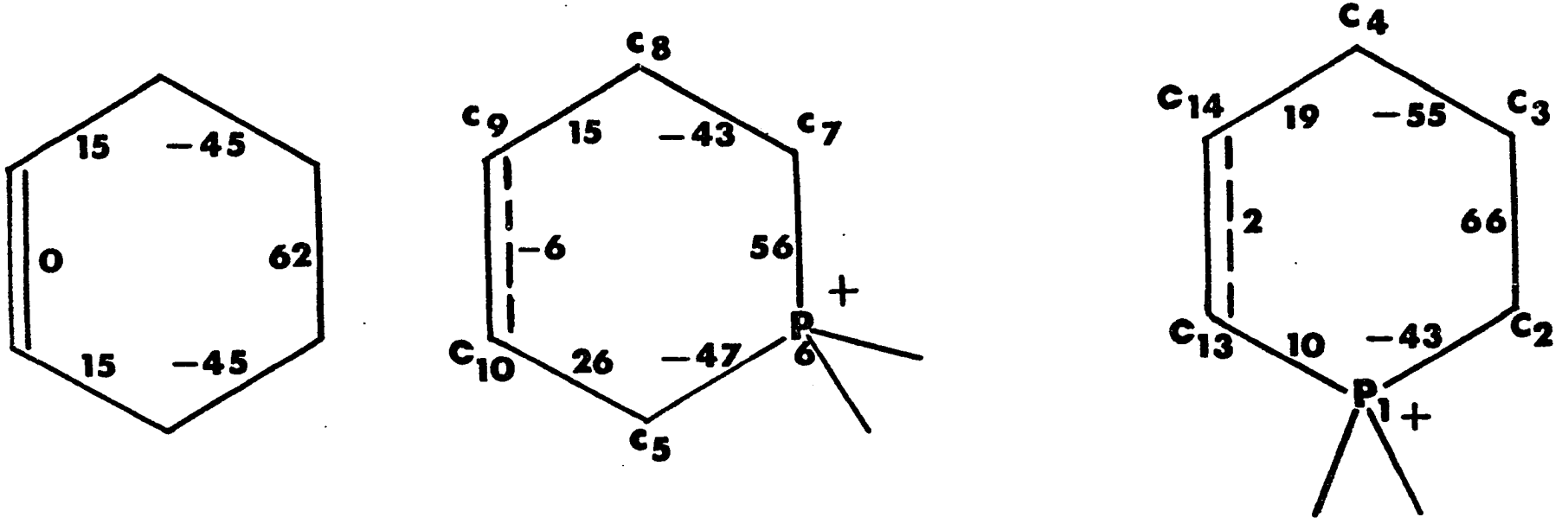


Figure 5 - Torsion angles found by strain minimization calculations for cyclohexene[23] (left), in phosphorinane ring of 1 (center), and in phosphorinane ring of 2 (right).

angles in cyclohexene,[12] 1 and 2 is made. The smaller 10° twist around the P^+-C(13) bond in 2 utilizes the longer phosphorus - carbon bonds which result in an approximately equal removal of C(2) from the plane of the ring as C(3) by the larger 19° twist around the C(14)-C(4) bond.

The ethyl group attached to the phosphonium ion is rotated somewhat over the plane of the partially saturated ring of the fused ring system so that C(16) lies approximately trans to the phenyl ring attached to phosphorus. The conformational angle around C(17)-P-C(15)-C(16) is 161°. The distances of C(15) and C(16), and the hydrogens attached to these carbons from the plane of the fused ring system is given in Table IV.

A least square plane through the phenyl ring (Table IV) shows no significant deviation from planarity. The phosphonium ion, however, lies 0.12 Å out of this plane.

The bromine ion position listed in Table II lies 4.384 Å from the phosphorus ion. A number of close Br-C contacts are observed between various symmetry related bromine ions and the heterocyclic cation which bring the hydrogens on the carbons to a distance from the bromine ions which is less than the sum of the ionic and covalent radii (r_{Br^-}= 1.95 Å, r_H = 1.2 Å) of 3.15 Å. These contacts are shown in Table V. The bromine ions generated by various symmetry operations are denoted with superscripts. $^1Br^-$ lies near C(2), C(15) and C(18), having a contact of 2.85 Å with H(C15)1. $^2Br^-$ approaches C(10), C(9), and C(15) again. This time H(C15)2 is only 2.73 Å from the bromine ion ($^2Br^-$). (The close contact of the hydrogens of C(15) with C(10) and two bromine ions should be noted.) $^3Br^-$ comes nearest C(7) and C(8) and $^4Br^-$ nearest C(20). The positions of these bromine ions relative to the plane through the ring system is shown in Table IV. There are no carbon-carbon intermolecular contacts of less than 3.45 Å.

Table V. Intermolecular Contacts Involving Br^-

Bromine designation	Equivalent Position (generated by symmetry and translation)
$^1Br^-$	x,y,z
$^2Br^-$	1-x, 1-y, 1-z
$^3Br^-$	1-x, -1/2 + y, 1/2 - z
$^4Br^-$	-1 + x, 1 1/2 - y, -1/2 + z

Contact	Distance
P(1)-$^1Br^-$	4.384 Å
C(2)-$^1Br^-$	3.86
C(15)-$^1Br^-$	3.85
C(18)-$^1Br^-$	3.99
H(C15)1-$^1Br^-$	2.85
H(C2)1-$^1Br^-$	3.04
H(C18)-$^1Br^-$	3.11
C(10)-$^2Br^-$	3.71
C(9)-$^2Br^-$	3.86
C(15)-$^2Br^-$	3.76
H(C15)2-$^2Br^-$	2.73
H(C10)-$^2Br^-$	2.96
C(7)-$^3Br^-$	3.70
C(8)-$^3Br^-$	3.93
H(C7)-$^3Br^-$	2.92
C(20)-$^4Br^-$	4.04
H(C20)-$^4Br^-$	3.09

A large librational motion can be seen in the thermal ellipsoids of carbons 5,6,7, and 8 with the maximum magnitude of the major axis ranging up to 11.7 $\mathring{A}^2$. An in-plane rocking motion of the phenyl ring can be seen as can a vibration of the terminal ethyl carbon perpendicular to the P^+-C(15) bond. The final carbon-hydrogen bond distances varied between 0.81 and 1.09 $\mathring{A}$.

It is worthy of note that the pmr spectra at 60 and 100 MHz of 2 (in $DCCl_3$)[16] showed two triplets for the methyl group of the ethyl function attached to phosphorus. Signals at δ 1.00 and 1.32 (relative to TMS) revealed J_{PCCH} = 20.5 Hz and J_{HCCH} = 7.5 Hz while the aromatic protons all occurred as a multiplet at δ 7.35-8.45. Assuming a near anti arrangement of C(17)-P and C(15)-C(16) bonds constitute a heavily preferred conformation in solution (as is true in the crystal-see previous discussion and Figure 1), a reason for the large J_{PCCH} coupling is still not intuitively obvious unless perhaps a Karplus-type description is applicable[17] for the P-C-C-H arrangement in this conformation. Inspection of molecular models implies that a near anti arrangement of C(15)-C(16) and P-C(13) bonds could be tolerable also which would place C(17)-P and C(15)-C(16) bonds in a near syn arrangement. In either of these conformations, unless C-H rotation in the methyl group is heavily restricted, an anti or syn arrangement for P-C-C-H (CH_3) is conceivable and quite possible in solution. The magnitude of this type of coupling has been observed in other phosphonium salts such as $CH_3P^+(t\text{-}C_4H_9)_3$[$J_{PCCH}$ = 15 Hz],[18] $HP^+(C_6H_5)(C_2H_5)_2$[J_{PCCH} = 21.5 Hz],[19] and $HP^+(C_2H_5)(i\text{-}C_3H_7)_2$[$J_{PCCH}$ = 20.6 Hz].[19] In all of these systems, as probably in 2, restricted rotation of C-CH_3 bonds may impose a preferred conformation around the phosphorus atom on the spectrum in solution.

The growth of B. subtilis, a gram-positive organism, was inhibited for approximately 6 hours in the presence of compound 2 (91 μg/ml) while at the same time the control culture (containing only 0.9% DMSO) had reached maximum stationary phase (Figure 6). Growth in the presence of 2 was inititated by 7 hours of incubation and proceeded at approximately the control rate. The action of the compound appears to be bacteriostatic since growth is initiated (during continued incubation). Growth of cells in the presence of compound 2 following 7 hours of incubation may occur as a result of decomposition. Stability tests utilizing compounds with similar structures have shown that under the aerobic bacterial growth conditions used in these studies, a compounds half-life may be as short as 1 hour. The growth of P. fluorescens, a gram-negative organism, was not affected by the presence of the test compound 2.

Table VI shows the effects on KB human tumor cells using compound 2 in which a concentration of 1.5 μg/ml inhibited cell growth by 70% while a concentration as low as 3 μg/ml caused approximately a 90% inhibition of cell growth. These data indicate that the compound is a good inhibitor of B. subtilis growth and an extremely potent inhibitor of KB cell growth. Pharmacological and in vivo tumor studies are under way which will describe the full potential of this active compound.

It is apparent that the marked biological activity of phosphonium salt 2 compared to that of 1 is significant since it is reproducible in several systems. Conceivably, the bonding and steric factors around phosphorus are crucial parameters for activity. In 2, the crowding of the ethyl group causes distortion of the tetrahedral arrangement around phosphorus. Similarly, the C-P bond distances do not follow a pattern similar to that in 1.

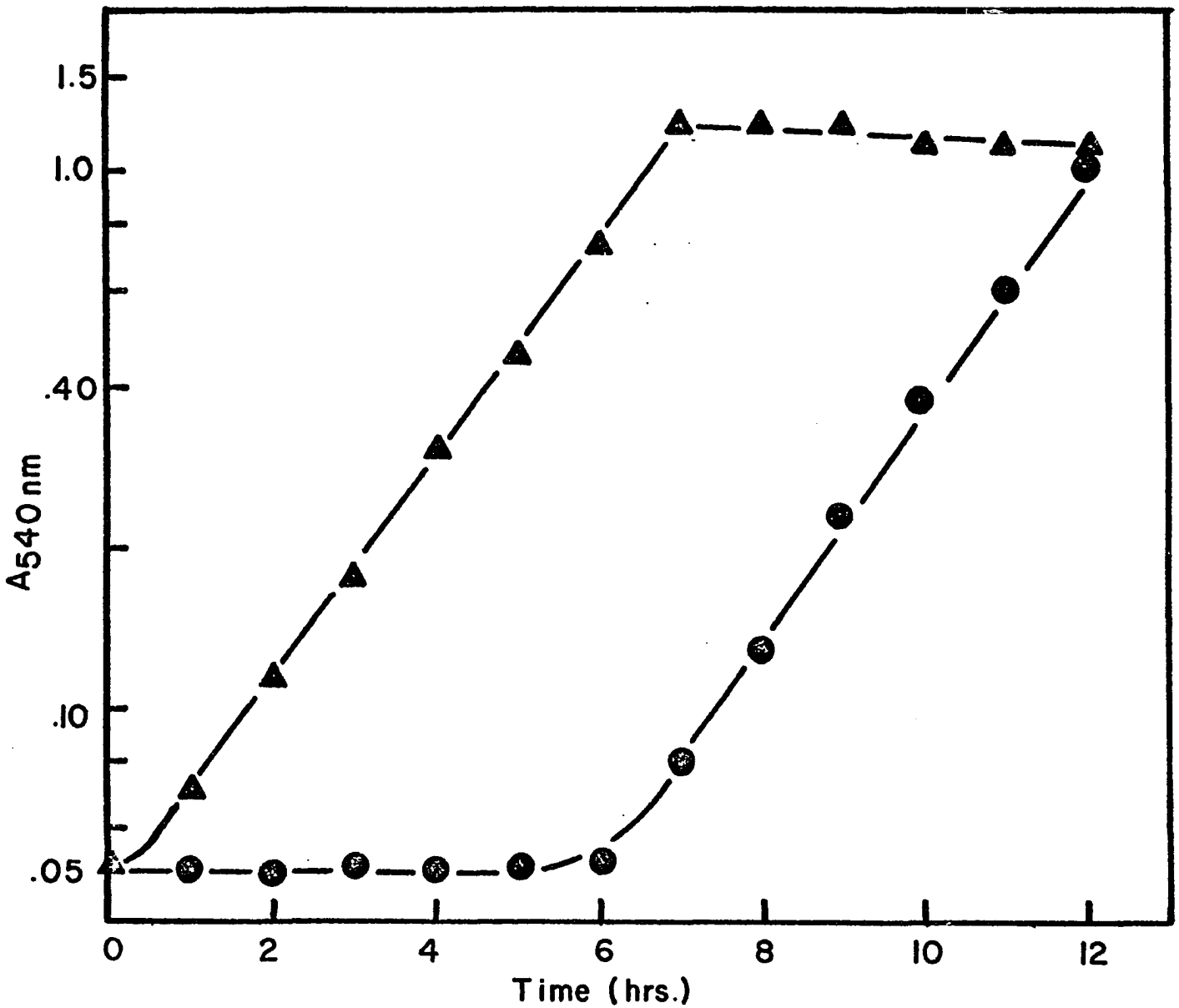
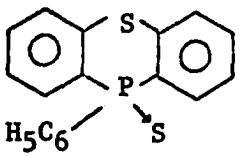


Figure 6 - Effect of growth of compound 2 on B. subtilis, W23; ▲-control, ●-compound 2 at 91 µg/ml.

Table VI. Effect of Compound 2 on KB Cell Growth

	Percent Inhibition concentration µg/ml			
Treatment	0	1.5	3.0	6.0
None	0	-	-	-
Compound 2	-	71	94	100

From a search of the literature, a C-P heterocycle with confirmed biological activity has not been subjected to X-ray analysis. Although not a C-P heterocycle by our definition, the two phosphorus-containing, tricyclic heterocycles 3 and 4 contain sulfur and oxygen, respectively, in the ring system and show biological activity.



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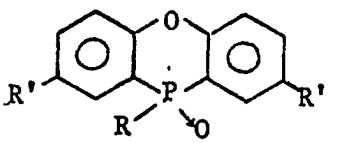

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Fungicidal activity has been recorded for 3[20] and a broad spectrum of action including anti-Parkinson activity, has been noted for 4.[21] No structural analysis was found for either of these compounds.

From a preliminary observation, such factors as C-P bond length, ring size, and angular strain at phosphorus in phosphonium salts may be important for activity. These and other parameters are being investigated.

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Supplementary Material Available. A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 x 148 mm, 24 x reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. Remit check or money order for $3.00 for photocopy or $2.00 for microfilm, referring to code number 00000.

References

1. Research Associate, 1971-1975.
2. a) D. M. Hellwege and K. D. Berlin, "Carbon-Phosphorus Heterocycles," in Topics In Phosphorus Chemistry, Vol. VI., Interscience, 1969, pp. 1-186. b) and T. E. Snider, C. C. Chen, and K. D. Berlin, Phosphorus, 1, 81 (1971).
3. S. R. Holbrook, D. van der Helm, W. Taylor, R. W. Chesnut, N. N. Durham, M. L. Higgins, T. E. Snider, and K. D. Berlin, J. Med. Chem., submitted (1974).
4. R. W. Chesnut, D. F. Haslam, N. N. Durham, and K. D. Berlin, Can. J. Biochem., 50, 516 (1972).
5. M. L. Higgins, R. W. Chesnut, F. R. Leach, J. G. Morgan, K. D. Berlin, and N. N. Durham, Steroids, 19,301 (1972).
6. INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY, Vol. III, Kynoch Press, Birmingham, p. 202, 1962.
7. R. F. Stewart, E. R. Davidson and W. T. Simpson, J. Chem. Phys., 42, 3175 (1975).
8. D. W. J. Cruickshank, Acta. Cryst., 10, 504 (1957).
9. M. I. Kay, Y. Okaya, and D. E. Cox, Acta. Cryst., B27, 26 (1971).
10. A. C. Skapski, and F. A. Stephens, J. Cryst. Mol. Struct., 4, (1974).
11. J. Guilheim, Cryst. Struct. Comm., 3, 227 (1974).
12. P. Goldstein, K. Seff, and K. N. Trueblood, Acta. Cryst., B24, 778 (1968).
13. A. F. Peerdeman, J. C. P. Holst, L. Horner, and H. Winkler, Tetrahedron Letters, 811 (1965).
14. L. Pauling, "The Nature of The Chemical Bond," 3rd ed., Cornell University Press, Ithaca, N.Y., 1960, p. 260.
15. C. Pedone, E. Benedetti, A. Immirizi and G. Allegra, J. Amer. Chem. Soc., 92, 3549 (1970).

16. C. H. Chen and K. D. Berlin, J. Org. Chem., 36, 2791 (1971) and unpublished results.

17. For a summary of the data on this phenomena, see G. Mavel in "Annual Reports on NMR Spectroscopy," Academic Press, New York, 1973, pp. 30-34.

18. S. E. Fishwick and J. A. Flint, Chem. Comm., 182 (1968).

19. S. O. Grim and W. McFarlane, Can. J. Chem., 46 2071 (1968).

20. E. H. Braye, (to Union Carbide Corporation), U. S. Patent 3,449,426 (1969); Chem. Abstr., 71, 91649 (1969).

21. S. J. Strycker (Dow Chemical Company) U. S. Patent 3,576,863 (1971); Chem. Abstr., 75, 2068 (1971).

22. C. K. Johnson, ORTEP. Report ORNL-2794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1965.

23. R. Bucort, Bull. Soc. Chim. Fr., 2080 (1964).

The Crystal and Molecular Structure of trans-potassium N,N'-ethylenebis(acetylacetoniminato)-diglycinatocobaltate (III) hexahydrate

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ABSTRACT

The crystal structure of trans-potassium N,N'-ethylenebis(acetylacetoniminato)-diglycinatocobaltate (III) hexahydrate $K[Co(C_{16}H_{26}O_6N_4)\cdot 6H_2O]$ has been determined by heavy atom methods and refined by three dimensional least squares techniques. The crystals are orthorhombic, space group $P2_12_12_1$, Z=4, with a=14.385(5), b=18.056(8), and c=10.037(6) Å. Intensity data for all unique reflections less than 56 degrees in 2θ were collected on an automatic diffractometer using MoKα radiation. The final R value for all 3525 data was 5.0%. The glycine residues are coordinated to the cobalt as unidentate ligands through the terminal amino groups. The cobalt-N(amino)-C^{α} bond angles are both near 120 degrees. The cobalt lies in the plane of the baen chelate ring. The waters of hydration serve principally to form intermolecular bonds between the carboxyl oxygens.

INTRODUCTION

Metal complexes of tetradentate Schiff bases such as bis (acetylacetoniminato)-ethylenediamine (baen) have been widely studied as model molecules having properties similar to the cobalamines, such as vitamin B_{12}, and cobalt corrinoids in general. A review of the structural determinations of metal complexes with Schiff bases has been published (Calligaris, Nardin, and Randaccio, 1971).

The cobalamines are labile for apical ligand substitution, which may be important in their functions as coenzymes for transmethylation reactions. Also metal complexes with Schiff bases are known to reversibly bind molecular oxygen as an apical ligand. In order to study the lability of the apical ligands of Co(III) - baen complexes Fuji (1972) synthesized a series of complexes of Co(III)-baen with two unidentate amino acids as apical ligands. Intermolecular exchange reactions of the anionic amino acid apical ligands were studied by NMR. Amino acids with unidentate coordination to metal ions are rare in the literature. Although some of these complexes have been reported, (Fujita, Yasui, and Shimura, 1965), (Yasui, Hidaka, and Shimura, 1966), (Alexander, and Busch, 1966) to our knowledge this is the first X-ray structural determination of a complex containing an amino acid as an unidentate ligand. We have therefore determined the structure of $K[Co(baen)gly_2]\cdot 6H_2O$ to expand on the study of the unusual behavior of cobalt chelated with unsaturated cyclic ligands, to investigate the coordination of the labile apical ligands and to see the effect, if any, of unidentate coordination on the simplest amino acid, glycine.

EXPERIMENTAL

Synthesis of $K[Co(baen)gly_2]\cdot 2H_2O$ has been reported by Fuji (1972). Recrystallization was from a water-acetone solution. It was necessary to mount the crystal in a glass capillary to prevent decomposition of the crystals. The decomposition probably reflected a loss or gain of water of hydration. The space group was determined to be $P2_12_12_1$ on a G.E. XRD-5 diffractometer. A total of 3525 data were collected with MoKα radiation (λ = 0.71069 Å) on a Nonius CAD-4 automatic diffractometer. These were all unqiue reflections with 2θ scans less than 56 degrees. These data were collected with θ-2θ scans in which the θ-scan was between 0.80 and 0.92 degrees. The maximum scan time was 180 seconds with 2/3 of the time spent while scanning the peak and 1/6 on each the left and right background. The least squares cell dimensions were determined from averages of +2θ and -2θ values of 40 reflections measured at 25 degrees Centigrade. The crystallographic data are shown in Table 1. There were 306 reflections which could not be distinguished from the background on the basis that the net count was less than $(1.4)T^{1/2}$ (T = total count). These reflections were assigned intensities equal to $(0.7)T^{1/2}$ for the purpose of least-squares refinement. Lorentz, polarization and absorption corrections were applied to the data. The program of Coppens, Leiserowitz and Rabinovich (1965) was used to make the absorption correction, (μ=8.83 cm^{-1}) using 216 sampling points. The absorption coefficients varied between 0.768 and 0.864 as calculated by the Gaussian method of numerical integration. Each structure amplitude was assigned a weight given by $w_F=1/\sigma_F^2$ where the standard deviation σ_F of the amplitude is given by

$$\sigma_F = 1/2\left[\frac{(\sigma)^2+(0.05)P)^2}{(Lp)P}\right]^{1/2}$$

Table 1. CRYSTALLOGRAPHIC DATA

Formula: $K[Co(C_{16}H_{26}O_6N_4]\cdot 6H_2O)$

F.W. 576.54

Systematic Absences: h00, h=2n+1

0k0, k=2n+1

00l, l=2n+1

Space Group: $P2_12_12_1$

a= 14.385(5) Å

b= 18.056(8) Å

c= 10.037(6) Å

V= 2606.97 $Å^3$

Z= 4

D_c= 1.469 g/cm^3

D_o= 1.472 g/cm^3

(measured by flotation in CCl_4/benzene at 23 degrees C)

F(000)= 1216

in which:

$\sigma = T^{1/2} V$

V = scan speed

P = [Pk-2(R+L)]V

Pk = peak count

R = right background count

L = left background count

Lp = Lorentz-Polarization factor

STRUCTURE DETERMINATION AND REFINEMENT

The position of the cobalt ion was located by examination of the three Harker sections of a sharpened Patterson map. A superposition map calculated from an unsharpened Patterson showed the location of the potassium ion. The cobalt and potassium positions were used in a structure factor calculation and refined by block diagonal least-squares with isotropic temperature factors for 5 cycles to an $R=([\Sigma||F_o|-|F_c||/\Sigma|F_o|)$ of 0.36. The quantity minimized by least-squares was $\Sigma w_f(|F_o|-|F_c|)^2$. At this point a difference Fourier synthesis showed all atoms of the chelate ring and the cobalt coordination. These atoms were included in structure factor least-squares calculations which refined to an R of 0.28. Another difference Fourier was calculated which yielded the remainder of the non-hydrogen atom positions including the oxygen atoms of six water molecules. All non-hydrogen atoms were given anisotropic temperature factors and included in several more cycles of least-squares refinement. The non-methyl hydrogens of the cobalt complex were located from geometric considerations and a difference Fourier. Their positions and isotropic temperature factors were included in subsequent refinement. After convergence of the least-

squares at R of 0.062, the methyl hydrogens and the hydrogens of the water molecules were located. Again these hydrogens were given isotropic temperature factors and their parameters included in refinement. The molecule, although containing no assymetric center did appear to have an absolute conformation in the crystal form. In order to determine the absolute conformation, several hundred data were recollected using CuKα radiation to maximize the anomalous dispersion effects. The I(hkl) and I($\bar{h}\bar{k}\bar{l}$) obtained in this manner were compared to corresponding pairs of F_c^2(hkl) and F_c^2($\bar{h}\bar{k}\bar{l}$) calculated by including the anomalous scattering factors of Co and K for CuKα radiation in a structure factor calculation using the refined parameters. It was determined that the structure had been refined in the correct absolute conformation. The anomalous dispersion corrections to the scattering factors of K and Co for MoKα radiation were now included in the structure factor refinement. Refinement continued until the shifts in all non-hydrogen parameters were less than 2/3 σ. The final R value for all 3525 data was 0.050. A final difference Fourier synthesis showed peaks ranging from 0.89 e./Å^3 to -0.66e./Å^3 located near the Co ion position. No other peaks greater than 0.35e./Å^3 occurred in the map. The average values of $w_f\Delta F^2$ were independent of F_o and sinθ/λ validating the weighting scheme employed in the refinement.

The atomic scattering factors for Co^{+3}, K^+, O, C, N and the anomalous scattering factors for Co and K were taken from the INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY (1962). The scattering factors for the hydrogen atoms were from Stewart, Davidson, and Simpson (1965). The final atomic parameters are given in Tables 2 and 3.*

*The final F_oF_c tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 00000 (14 p.p., 1 microfiche). Copies may be obtained through the Executive Secretary IUC, 13 White Frairs, Chester CH 1NZ, England.

Table 2. Atomic fractional coordinates and thermal parameters. (all x 10^4)

The temperature factor is expressed in the form exp $\{-(h^2b_{11}+k^2b_{22}+\ell^2b_{33}+hkb_{12}+h\ell b_{13}+k\ell b_{23})\}$

Standard deviations for the last digit are in parenthesis.

Atom	X	Y	Z	b_{11}	b_{22}	b_{33}	b_{23}	b_{13}	b_{12}
K(1)	-264.4(9)	2585.5(6)	-2211.3(11)	57.7(6)	30.7(3)	97.7(11)	33.5(10)	-36.5(16)	-25.9(9)
Co(1)	270.6(3)	1051.2(2)	383.6(4)	22.4(2)	12.0(1)	42.6(3)	-4.2(4)	2.3(6)	-0.5(3)
O(1)	-783(2)	1530(1)	-390(3)	23(1)	18(1)	64(3)	2(3)	1(3)	2(1)
C(2)	-1641(3)	1401(2)	-61(4)	25(2)	19(1)	83(5)	-25(4)	-4(4)	2(2)
C(3)	-1926(3)	938(2)	949(5)	26(2)	27(1)	102(5)	-9(4)	23(5)	-6(3)
C(4)	-1333(3)	533(2)	1797(4)	44(2)	17(1)	88(5)	-12(4)	40(6)	-17(3)
N(5)	-433(2)	521(2)	1663(3)	39(2)	13(1)	55(3)	-4(3)	15(4)	-2(2)
C(6)	158(4)	144(2)	2644(5)	57(3)	24(1)	80(4)	31(4)	21(6)	3(3)
C(7)	1071(4)	-31(3)	2040(5)	61(3)	28(2)	87(5)	32(5)	1(7)	22(4)
N(8)	1326(2)	557(2)	1087(3)	30(2)	18(1)	65(3)	-11(3)	-21(4)	13(2)
C(9)	2182(3)	622(2)	663(4)	30(2)	22(1)	88(5)	-32(4)	-29(5)	13(2)
C(10)	2428(2)	1128(2)	-366(5)	22(2)	28(1)	111(5)	-20(5)	23(5)	-4(3)
C(11)	1841(3)	1560(2)	-1085(4)	28(2)	18(1)	73(4)	-18(4)	23(5)	-8(2)
O(12)	948(2)	1606(1)	-905(3)	28(1)	20(1)	55(2)	2(2)	9(3)	-3(2)
C(13)	-2342(3)	1821(3)	-884(5)	32(2)	34(2)	112(6)	-2(5)	-30(6)	10(3)
C(14)	-1796(4)	118(4)	2925(7)	71(4)	45(2)	161(8)	66(8)	107(10)	4(5)
C(15)	2944(3)	140(3)	1222(6)	39(2)	37(2)	147(7)	-19(6)	-56(7)	38(4)
C(16)	2192(3)	2041(3)	-2205(5)	42(2)	30(2)	116(6)	4(5)	55(6)	-16(3)
N(17)	460(2)	1894(2)	1614(3)	30(2)	16(1)	58(3)	-12(3)	-3(4)	-2(2)
C(18)	-294(3)	2135(2)	2499(4)	31(2)	22(1)	84(4)	-28(4)	14(6)	-6(3)
C(19)	-112(3)	2875(2)	3210(4)	41(2)	20(1)	62(4)	-11(4)	1(5)	7(3)
O(20)	486(2)	3302(2)	2743(3)	56(2)	19(1)	73(3)	-2(3)	9(4)	-20(2)
O(21)	-583(2)	2986(2)	4226(4)	61(2)	29(1)	116(4)	-55(3)	66(5)	-14(2)
N(22)	171(2)	284(2)	-999(3)	31(2)	16(1)	56(3)	-10(3)	-4(4)	-4(2)
C(23)	-550(3)	-286(2)	-949(5)	40(2)	22(1)	87(5)	-31(4)	11(5)	-12(3)
C(24)	-642(3)	-723(2)	-2242(4)	30(2)	19(1)	78(4)	-14(4)	-9(5)	6(2)
O(25)	-991(2)	-1359(2)	-2136(3)	47(2)	21(1)	96(3)	-27(3)	-2(4)	-12(2)
O(26)	-384(3)	-437(2)	-3312(3)	67(2)	25(1)	76(3)	-18(3)	3(5)	-10(3)
O(27)	-1433(3)	3873(2)	-3912(4)	65(2)	43(1)	169(5)	-94(5)	68(6)	-28(3)
O(28)	1616(2)	1617(2)	4214(3)	55(2)	34(1)	108(4)	-13(4)	-9(5)	4(3)
O(29)	1781(2)	3180(2)	4797(4)	44(2)	41(1)	107(4)	-6(4)	-10(5)	18(2)
O(30)	-1333(2)	1914(2)	-4278(4)	47(2)	42(1)	122(5)	16(4)	2(5)	3(3)
O(31)	-36(3)	3429(2)	38(3)	112(3)	31(1)	87(4)	17(3)	-17(5)	-40(3)
O(32)	168(2)	1000(2)	-4089(4)	60(2)	29(1)	134(4)	23(4)	-9(5)	0(3)

Table 3. Hydrogen Atom Parameters (coordinates x 10^3)

Atom	x	y	z	B(Å)
H(C3)	-262(3)	83(2)	101(4)	4(1)
H(C6)1	16(3)	55(2)	341(5)	5(1)
H(C6)2	-17(3)	-31(3)	299(5)	5(1)
H(C7)1	159(3)	-15(3)	268(5)	5(1)
H(C7)2	99(3)	-54(3)	141(5)	5(1)
H(C10)	308(3)	116(2)	-54(4)	4(1)
H(C13)1	-227(3)	175(2)	-181(4)	3(1)
H(C13)2	-301(4)	169(3)	-52(7)	8(2)
H(C13)3	-220(3)	236(2)	-75(4)	3(1)
H(C14)1	-167(4)	23(4)	385(8)	10(2)
H(C14)2	-247(5)	23(4)	290(7)	9(2)
H(C14)3	-167(4)	-36(4)	283(7)	9(2)
H(C15)1	356(4)	29(3)	79(6)	6(1)
H(C15)2	294(3)	11(3)	228(6)	6(1)
H(C15)3	274(5)	-45(4)	107(8)	10(2)
H(C16)1	185(4)	184(4)	-295(7)	10(2)
H(C16)2	277(4)	190(3)	-244(6)	7(2)
H(C16)3	207(3)	257(3)	-200(5)	4(1)
H(N17)1	95(3)	179(2)	206(4)	3(1)
H(N17)2	60(3)	224(2)	84(5)	4(1)
H(C18)1	-83(3)	218(3)	204(5)	5(1)
H(C18)2	-29(4)	168(3)	328(6)	9(2)
H(N22)1	17(3)	58(2)	-162(4)	3(1)
H(N22)2	83(3)	5(2)	-101(4)	3(1)
H(C23)1	-45(3)	-65(2)	-22(4)	4(1)
H(C23)2	-112(3)	-7(3)	-86(5)	5(1)
H(O27)1	-125(3)	368(3)	-453(5)	5(1)
H(O27)2	-195(4)	367(4)	-393(7)	9(2)
H(O28)1	122(3)	146(3)	465(5)	4(1)
H(O28)2	173(3)	201(2)	448(4)	3(1)
H(O29)1	146(4)	344(3)	414(6)	9(2)
H(O29)2	153(3)	333(3)	560(5)	6(1)
H(O30)1	-129(5)	237(4)	-484(8)	10(2)
H(O30)2	-184(3)	179(3)	-454(6)	5(1)
H(O31)1	16(3)	354(2)	70(5)	4(1)
H(O31)2	14(3)	381(3)	-23(5)	5(1)
H(O32)1	0(3)	59(2)	-392(5)	5(1)
H(O32)2	-28(4)	124(3)	-438(6)	8(2)

RESULTS

A stereoview of the structure of the anion and location of the cation of trans-potassium N,N'-ethylenebis (acetylacetoniminato)diglycinatocobaltate (III) hexahydrate is shown in Figure 1. The six waters of hydration are excluded here for clarity. The bond lengths and numbering scheme are shown in Figure 2.

As expected, the glycines are seen to coordinate to the cobalt ion as unidentate, trans apical ligands. Coordination occurs through the amine nitrogen with the carboxyl group carrying a negative charge. The cobalt ion lies approximately in the plane of its tetradentate (baen) ligand as shown by various least-squares planes calculated through the chelated ring system (Table 4). The C(14) and C(15) methyl groups lie out of the planes through the respective chelate rings while both groups are displaced approximately the same amount out of the planes and in opposite directions. The bond lengths in the (baen) chelate ring are within three standard deviations of the average values reported in the review of Calligaris, Nardin, and Randaccio (1971), with the exception of C(6)-C(7) distance (1.481 Å) which is slightly shorter than the average of 1.503 Å and much shorter than a normal $C(sp^3)$-$C(sp^3)$ distance of 1.54 Å. In the structure of $[CH_2{=}CHCo(baen)H_2O]$ (Bruckner, Calligaris, Nardin and Randaccio, 1968) the cobalt-oxygen distances in the chelate ring are 1.913 Å and 1.930 Å (standard deviation 0.007 Å), and the cobalt-nitrogen distances are 1.888 Å and 1.892 Å (standard deviation 0.008 Å). These values are in good agreement with the cobalt-ligand distances in the baen chelate ring reported here.

The conformation of the baen chelate ring is shown by the conformational angles of Table 5 or the deviations from the least-squares planes shown in Table

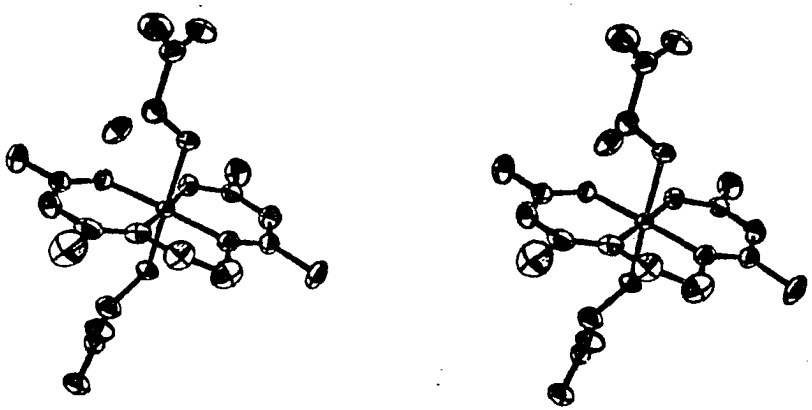

Figure 1 - Stereoview of the cation and anion (waters of hydration not shown) with 50% probability ellipsoids using the Ortep program (Johnson, 1965)

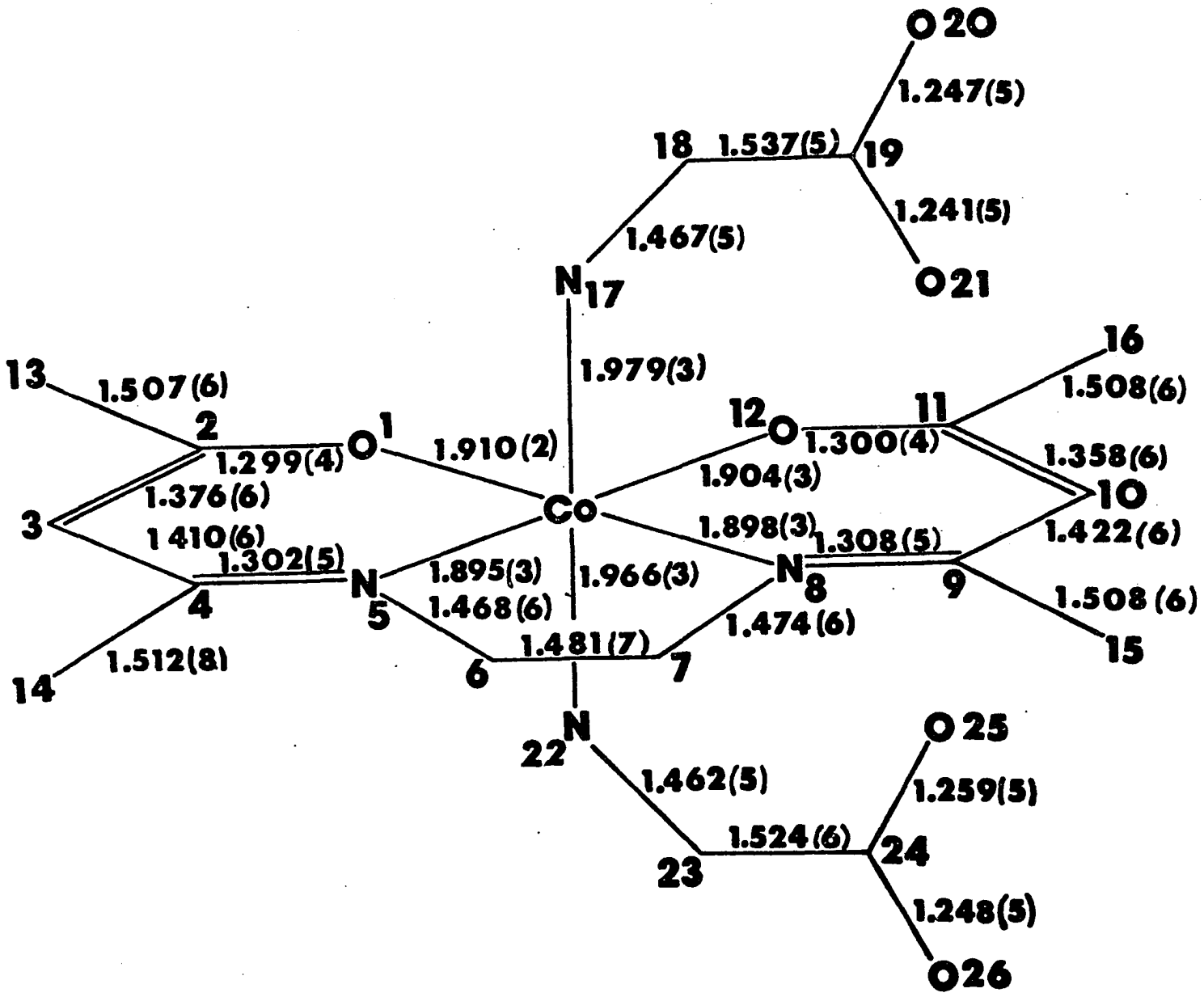

Figure 2 - Numbering scheme and bond distances in Angstroms with the standard deviation of the last digit given in parentheses.

Table 4. Least Squares Planes

The equations of the planes are in the form Ax + By + Cz = D, where x, y, and z are fractional coordinates and D is the distance from the origin in A.

Plane 1 O(1), C(2), C(3), C(4), N(5), C(6), C(7), N(8), C(9), C(10), C(11), O(12), Co(1)

A	B	C	D
1.569	13.606	6.507	1.681

2 Co(1), O(1), C(2), C(3), C(4), N(5)

A	B	C	D
0.947	13.766	6.462	1.746

3 Co(1), N(8), C(9), C(10), C(11), O(12)

A	B	C	D
1.931	13.265	6.675	1.707

4 Co(1), O(1), O(12), N(5), N(8)

A	B	C	D
1.625	13.490	6.575	1.705

Co(1)	0.041 Å	Co(1)	-0.025 Å	Co(1)	-0.004 Å	Co(1)	0.009 Å
O(1)	0.024	O(1)	0.034	N(8)	0.013	O(1)	-0.025
C(2)	-0.071	C(2)	-0.011	C(9)	-0.018	O(12)	0.020
C(3)	-0.090	C(3)	-0.024	C(10)	0.014	N(5)	0.020
C(4)	0.004	C(4)	0.022	C(11)	-0.006	N(8)	-0.024
N(5)	0.042	N(5)	0.004	O(12)	0.002	C(6)	0.253
C(6)	0.260	C(13)	-0.033	C(15)	-0.137	C(7)	-0.232
C(7)	-0.228	C(14)	0.137	C(16)	-0.049		
N(8)	-0.008						
C(9)	-0.061						
C(10)	-0.003						
C(11)	0.025						
O(12)	0.064						
K(1)	0.357						
C(13)	-0.146						
C(14)	0.101						
C(15)	-0.233						
C(16)	0.005						

Table 5. Conformational Angles

Co-O(1)-C(2)-C(3)	4°	Co-N(17)-C(18)-C(19)	190°
O(1)-C(2)-C(3)-C(4)	1	N(17)-C(18)-C(19)-O(20)	20
C(2)-C(3)-C(4)-N(5)	-4	Co-N(22)-C(23)-C(24)	168
C(3)-C(4)-N(5)-Co	2	N(22)-C(23)-C(24)-O(26)	-24
C(4)-N(5)-Co-O(1)	2	C(18)-N(17)-Co-N(5)	-39
N(5)-Co-O(1)-C(2)	-5	C(23)-N(22)-Co-N(5)	19
Co-N(5)-C(6)-C(7)	-28		
N(5)-C(6)-C(7)-N(8)	34		
C(6)-C(7)-N(8)-Co	-26		
C(7)-N(8)-Co-N(5)	9		
N(8)-Co-N(5)-C(6)	11		
Co-N(8)-C(9)-C(10)	4		
N(8)-C(9)-C(10)-C(11)	-4		
C(9)-C(10)-C(11)-O(12)	3		
C(10)-C(11)-O(12)-Co	-2		
C(11)-O(12)-Co-N(8)	1		
O(12)-Co-N(8)-C(9)	-2		

4. The six membered acetylacetoniminato rings are planar while the ethylene carbon atoms C(6) and C(7) are symmetrically displaced above and below the coordination plane in a 'half-chair' conformation of the five membered ring, putting the hydrogens on these carbons in a gauche relationship. The baen ligand can also exist in a planar conformation in which both ethylene carbons lie on the same side and above or below the coordination plane (Calligaris, Nardin, and Randaccio, 1972).

Several factors should be noted with respect to the apical glycine ligands. The cobalt-nitrogen bond lengths, Co-N(17) and Co-N(22) are between values reported for cobalt glycine and glycylglycine metal-amino distances ranging from 1.949 Å to 2.00 Å (Buckingham, Cresswell, Dellaca, Dwyer, Gainsford, Marzilli, Maxwell, Robinson, Sargeson, and Turbull, 1973), (Gillard, McKenzie, Mason and Robertson, 1966), (Hsu, 1971) and compare favorably with the cobalt-axial nitrogen distance in wet cyanocobalamin of 1.97 Å (Brink-Shoemaker, Cruickshank, Hodgkin, Kamper and Pilling, 1964). The $N-C^{\alpha}$ distances of 1.462 Å and 1.467 Å in this structure, however, are over four standard deviations shorter than the average value for amino acids of 1.487 Å as tabulated by Marsh and Donohue (1967) and the same average value is found for coordinated α-amino acids (Freeman, 1967).

Freeman (1973) states that the only geometrical requirement for coordination of amino acids through the terminal amino group is that the metal-N(amino)-C^{α} angle should be near the tetrahedral value of 109.5 degrees (standard deviation 1° for amino acids). Both glycinato groups in this structure show expansion of this bond angle to near 120°. Some close intramolecular contacts between the hydrogens on C(18) and C(23) with the baen chelate ring may necessitate this expansion of bond angles. H(C18)1 is 2.71 Å from O(1) and H(C18)2 is 2.65 Å

from N(5). In a similar manner the distance from H(C23)1 to N(5) is 2.84 Å and H(C23)2 has contacts of 2.88 Å, 2.82 Å and 2.90 Å with C(2), C(3), and C(4) respectively. Clearly a tetrahedral value for the Co-N(amino)-C^{α} bond would cause these atoms to be unacceptably close (shortening these distances by approximately 0.3 Å). A smaller expansion of the bond angles N(17)-C(18)-C(19) and N(22)-C(23)-C(24) from the average value of 110.5° (Freeman, 1967) is also seen. All other parameters of the glycinato ligand are consistent with accepted values. Bond angles are shown in Figure 3. Standard deviations are between 0.1 and 0.4°.

The conformational angles are given in Table 5. The dihedral angles for the C^{α}-C(carboxyl) bonds are 20 and 24 degrees which is in the range of values from 0-27 degrees found for the various glycine modifications and peptides with terminal glycine residues whose structures are known (Marsh and Donohue, 1967).

The cobalt coordination is a distorted octahedron. The smallest angle of 83.8° is observed between O(1) and O(12). The greatest expansion is to 95.2° between N(8) and O(12). The angle between the apical ligands is not linear, but 173°. All the angles are listed in Table 6.

The potassium ion is at a distance of 3.879 Å from the cobalt ion and is surrounded by five oxygen atoms. Two water molecules O(30) and O(31), the negatively charged O(1) and O(12) and the carboxyl oxygen O(25) make up the potassium sphere of closest contact shown in Figure 4.

The six waters of hydration serve the function of forming intermolecular hydrogen bonding networks between the cobalt chelate anions and potassium cations. All hydrogens of the water molecules are involved in hydrogen bonds. The carboxyl oxygens are involved in this network as acceptors of water hydrogens, with O(25) being in close contact with the potassium ion. The carboxyl oxygens

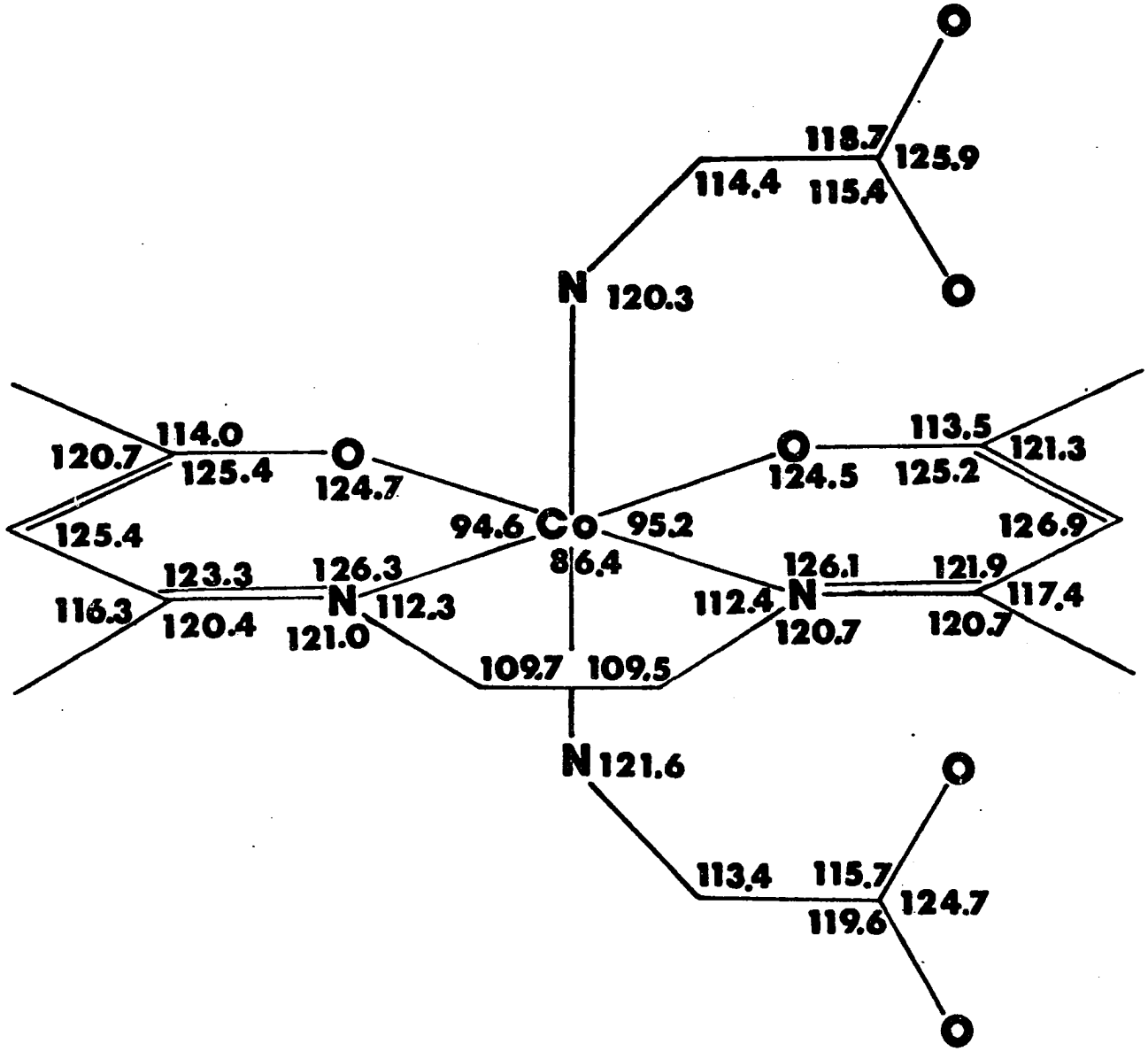

Figure 3 - Bond angles in degrees. Standard deviations between 0.1° and 0.4°.

Table 6. Bond angles in cobalt coordination sphere

Standard deviation for the last digit is given in parentheses.

N(5)-Co-N(8)	86.4(1)	N(8)-Co-O(12)	95.2(1)
N(5)-Co-N(17)	92.3(1)	N(17)-Co-N(22)	173.0(1)
N(5)-Co-N(22)	94.8(1)	N(17)-Co-O(1)	98.8(1)
N(5)-Co-O(1)	94.6(1)	N(17)-Co-O(12)	87.1(1)
N(5)-Co-O(12)	178.3(1)	N(22)-Co-O(1)	88.5(1)
N(8)-Co)N(17)	91.1(1)	N(22)-Co-O(12)	85.9(1)
N(8)-Co-N(22)	89.4(1)	O(1)-Co-O(12)	83.8(1)
N(8)-Co-O(1)	177.8(1)		

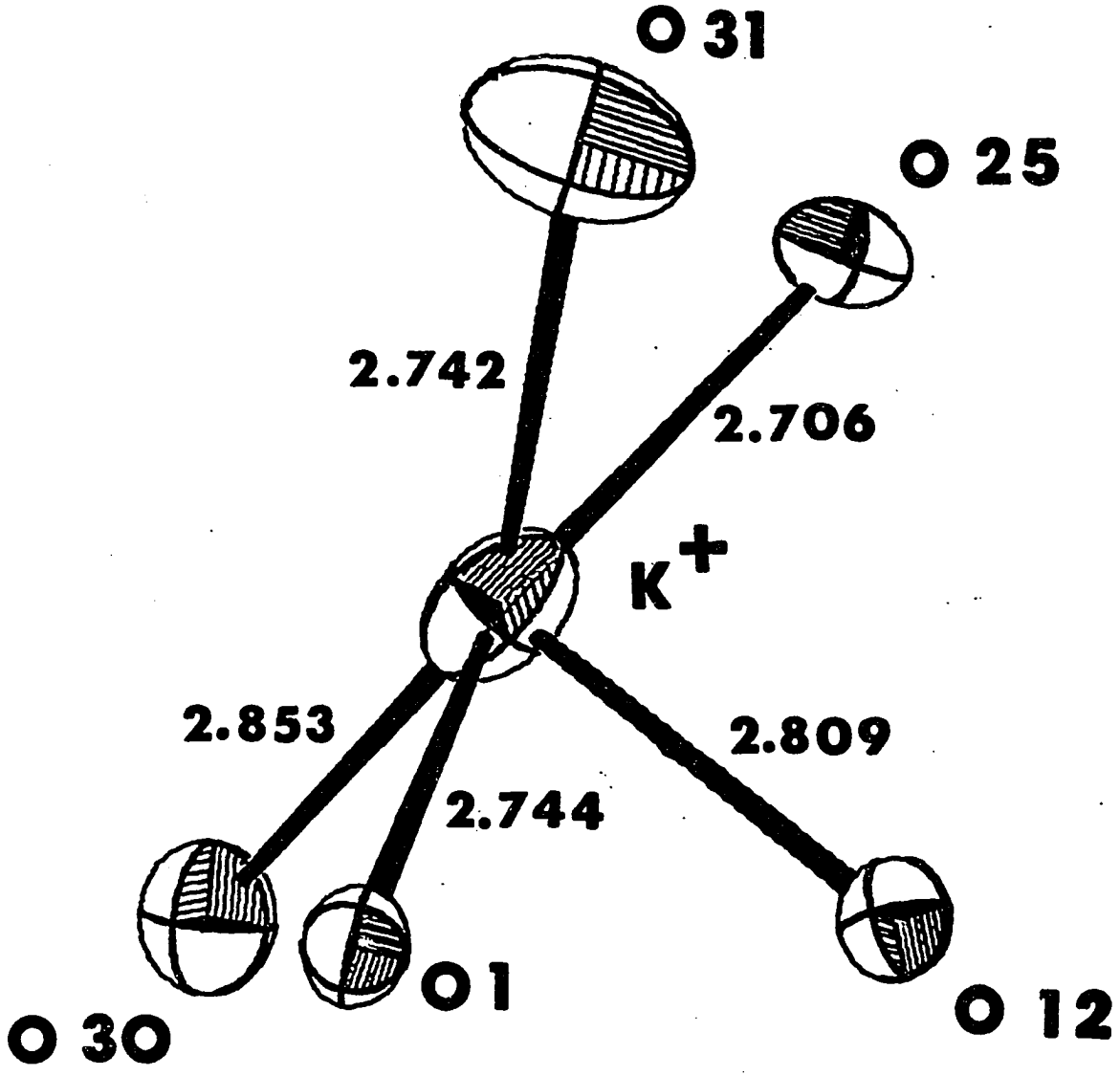

Figure 4 - Sphere of coordination of the potassium cation. Distances are given in Angstroms.

are connected intermolecularly by spirals of hydrogen bonds around screw axes in primarily the x and y directions. The water molecules O(29) and O(31) directly bridge carboxyl oxygens O(20) and O(25) (-x, -1/2+y, 1/2-z) and O(26) (-x, 1/2+y, -1/2-z). The hydrogen bonding and packing viewed down the a-axis is shown in Figure 5. The H-bond distances are shown in Table 7.

The thermal parameters for all non-hydrogen atoms appear reasonable and low enough that little effect should be seen in the bond distances. The hydrogen atom distances vary between 0.75 Å and 1.12 Å.

DISCUSSION

Several interesting factors are observed in relation to the rapid intermolecular exchange of apical amino acid ligands observed in solution by Fuji for this type of molecule. The cobalt-apical nitrogen distances do not show significant lengthening when compared to other structures containing Co-N ligands. A sufficient number of accurate structures of similar compounds does not exist to make any statement concerning small changes in these bond lengths. It appears however, that the weakness of this apical coordination bond, reflected in its lability in solution may be observed in the Co-N(amino)-C^{α} bond angles observed to be near 120 degrees. If normal tetrahedral sp^3 hybridization is assumed (and as previously stated all other metal-terminal amino-C^{α} bond angles have been found to be near 109.5°), the effect would be less efficient overlap of the nitrogen and cobalt orbitals. The reason for this bond angle expansion may be due to either or both; steric crowding of the C^{α} carbons and the trans-effect of the opposite apical nitrogen (Costa and Mestroni, 1968), (Firth, Hill, Pratt, Thorp and Williams, 1969). Five coordinate complexes of baen chelates are easily isolated and have been characterized (Brückner, Calligaris, Nardin and Randaccio, 1968). Therefore due to the low energy of a five coordinate inter-

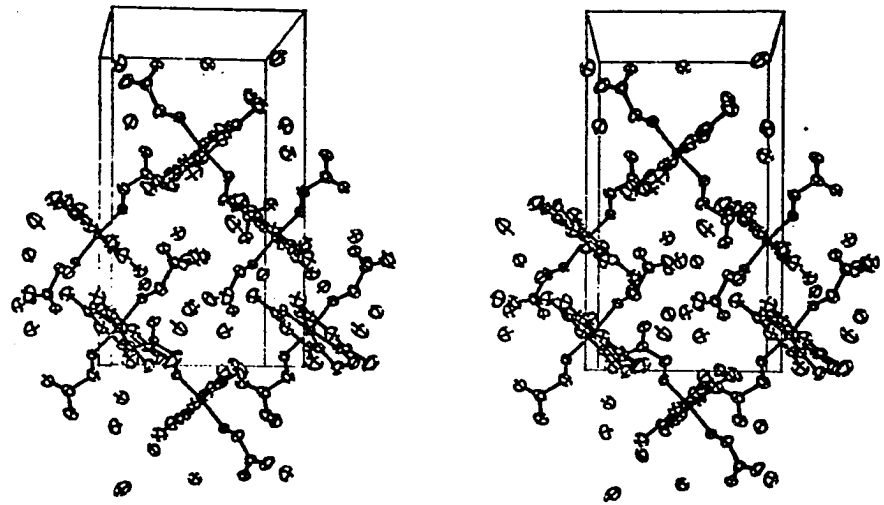

Figure 5 - Packing drawing showing hydrogen bonding scheme. View is down the a-axis.

Table 7. Hydrogen Bonding

Donor (X)	Acceptor (Y)	Hydrogen (H)	X-H----Y	H----Y	X----Y
O(27)	O(21)[a]	H(027)1	163.5°	2.009 Å	2.749 Å
O(27)	O(28)[b]	H(027)2	165.9	2.149	2.959
O(28)	O(32)[c]	H(028)1	180.0	2.142	2.912
O(28)	O(29)	H(028)2	164.5	2.130	2.892
O(29)	O(20)[d]	H(029)1	141.1	1.994	2.787
O(29)	O(25)[a]	H(029)2	180.0	1.810	2.738
O(30)	O(21)[b]	H(030)1	148.3	1.771	2.676
O(30)	O(29)	H(030)2	158.6	1.995	2.767
O(31)	O(20)	H(031)1	151.3	2.145	2.826
O(31)	O(26)[e]	H(031)2	153.1	2.025	2.749
O(32)	O(26)	H(032)1	173.2	2.032	2.822
O(32)	O(30)	H(032)2	156.2	1.947	2.725

a. x, y, z - 1

b. -1/2 + x, 1/2 - y, -z

c. x, y, z + 1

d. -x, 1 1/2 + y, 1/2 - z

e. -x, 1/2 + y, -1/2 - z

mediate, the rate of replacement reactions is fast. Since the trans-effect and probable stability of the five coordinate intermediate is increased by increasing the electron donating ability of the apical ligand one would expect nitrogen to have an even larger effect than the alkyl ligands previously studied (Hill, Morallee and Pellizer, 1969).

The shortening of the N-C^{α} bond when compared to previous structures although small is an unexpected effect of the coordination of the amino acid and may be related to the lability of the apical ligands.

Due to the π-electron delocalization through the tetradentate chelate and the cobalt ion there is a tendency for the chelate to be planar as is observed in tetracoordinate Schiff base complexes. Additions of fifth and sixth coordinate apical ligands result in steric interactions causing deviations from planarity in the chelate system (Calligaris, Nardin, and Randaccio, 1972). Such non-planarity is observed in this structure at C(6) and C(7) leading one to suspect steric crowding may indeed be significant.

The baen-cobalt chelate itself can potentially contain a plane of symmetry. The lack of symmetry in this structure may be attributed to the glycine ligands which must destroy such symmetry for steric reasons.

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References

Alexander, M. D. and Busch, D. H., (1966). Inorg. Chem., 5, 1590-1593.

Brink-Shoemaker, C., Cruickshank, D. W. J., Hodgkin, D. C., Kamper, J. and Pilling, D. (1964). Proc. R. Soc. (A), 278, 1-26.

Brückner, S., Calligaris, M., Nardin, G. and Randaccio, L. (1968). Inorg. Chim. Acta, 2, 416-421.

Buckingham, D. A., Cresswell, P. J., Dellaca, R. J., Dwyer, M., Gainsford, G. J., Marzilli, L. G., Maxwell, I. E., Robinson, W. T., Sargeson, A. M. and Turnbull, K. R. (1973). J. Amer. Chem. Soc., 96, 1713-1725.

Caligaris, M., Nardin, G., and Randaccio, L., (1972). Coord. Chem. Rev., 7, 385-403.

Coppens, P., Leiserowitz, L. and Rabinovich. D. (1965). Acta Cryst., 18, 1035-1038.

Costa, G. and Mestroni, G., (1968). J. Organometal. Chem., 11, 325-332.

Freeman, H. C. (1967). Advanc. Prot. Chem., 22, 257-424.

Freeman, H. C., (1973). Inorganic Biochemistry, Vol. I, p. 124, edited by G. L. Eichhorn. New York: Elsevier.

Fuji, Y., (1972). Bull. Chem. Soc. Japan, 45, 3084-3092.

Fujita, J., Yasui, T., and Shimura, Y., (1965). Bull. Chem. Soc. Japan, 38, 654-660.

Gillard, R. D., McKenzie, E. D., Mason, R., and Robertson, G. B. (1966). Nature, 209, 1347-1348.

Hill, H. A. O., Morallee, K. G., and Pellizer, G. (1969). J. Chem. Soc. (A), 2096-2101.

Hill, H. A. O., Pratt, J. M., Thorp, R. G., Ward, B., and Williams, R. J. P. (1970). Biochem. J., 120, 263-269.

Hsu, I.-N. (1971). Thesis, University of Oklahoma, Norman, Oklahoma.

International Tables for X-ray Crystallography (1962). Vol. III, p. 202, 214 Birmingham: Kynoch Press.

Johnson, C. K. (1965). ORTEP Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Marsh, R. E., and Donohue, J., (1967). Advanc. Prot. Chem. 22, 235-256.

Stewart, R. F., Davidson, E. R. and Simpson, W. T. (1965). J. Chem. Phys. 42, 3175-3187.

Yasui, T., Hidaka, J., and Shimura, Y., (1966). Bull. Chem. Soc. Japan 39, 2417-2424.