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The Crystal Structure of *N*, *N'*-Bis-(4-ethoxyphenyl)acetamidinium Bis-*p*-nitrophenylphosphate Monohydrate

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The crystal structure of *N*,*N'*-bis-(4-ethoxyphenyl)acetamidinium bis-*p*-nitrophenylphosphate monohydrate has been determined. It is representative of a class of complexes that form when local anesthetics react with phosphodiesters. Its formula is $[C_2H_5OC_6H_4N(H)\overset{\cdot\cdot\cdot}{-}C(CH_3)\overset{\cdot\cdot\cdot}{-}N(H)C_6H_4OC_2H_5]^+$ $[O_2NC_6H_4OP(O)_2OC_6H_4NO_2]^- \cdot H_2O$. The *N*,*N'*-bis-(4-ethoxyphenyl)acetamidinium cation, which is the protonated form of the local anesthetic phenacaine, contains a delocalized double bond, resonating equally between adjacent C–N bonds as illustrated in the formula. Delocalization of the double bond imparts a formal charge of $+\frac{1}{2}$ to each nitrogen atom and makes the C–N bond orders equal. The lengths found for these bonds are 1·318 and 1·319 Å. The CO–P–OC valency angle in bis-*p*-nitrophenylphosphate is 97·2° which is much smaller than 102·7°, the average of this angle observed in 8 analyses of other phosphate diesters. Unusually large differences occur in the structural details of the bis-*p*-nitrophenylphosphate anion when the local anesthetic in the complex is changed from phenacaine to procaine. In the latter complex, the CO–P–OC angle is 103·3° and the Klyne–Prelog conformations of the torsion angles around the CO–P–OC bonds are *-sc*, *-sc*, whereas in the complex with phenacaine they are *ap*, *sc*. Molecular packing is markedly different in the two crystals. The water molecule in this crystal structure enters into three hydrogen bonds that are in an almost trigonal planar arrangement. Crystals are monoclinic. Space group is $P2_1/c$, $Z=4$. Unit-cell dimensions are $a=10{\cdot}703$ (5), $b=28{\cdot}236$ (6), $c=15{\cdot}901$ (5) Å, $\beta=138{\cdot}67$ (5)°. Intensities were measured on a Picker automated diffractometer with Cu $K\beta$ radiation. The coordinates of 35 atoms were obtained by the direct method and the remainder of the structure was determined from Fourier syntheses. Refinement by least-squares techniques converged to an R index of 0·052 for 4392 observed reflections.

Introduction

Interest in the three-dimensional structures of local anesthetic–phosphodiester complexes has been generated by the suggestion that a complex of this kind is formed when a local anesthetic molecule binds to a phospholipid in neural membrane and that the resultant adduct is instrumental in blocking nerve conduction (Feinstein, 1964; Feinstein & Paimre, 1966; Blaustein & Goldman, 1966; Sax & Pletcher, 1969). To elucidate the intermolecular bonding in these complexes, the crystal structure of *N*,*N'*-bis-(4-ethoxyphenyl)acetamidinium bis-*p*-nitrophenylphosphate monohydrate, commonly designated as phenacaine bis-*p*-nitrophenylphosphate monohydrate, was determined and is reported in this paper, A structure analysis describing a complex of the same anion with procaine has been published (Sax, Pletcher & Gustafsson, 1970). It is interesting to compare the two crystal structures, since both drugs form complexes with a variety of phosphodiesters despite their steric and chemical differences which are considerable.

Experimental

Crystals of phenacaine bis-*p*-nitrophenylphosphate monohydrate were prepared by the method of Feinstein & Paimre (1966). The space group was derived from Weissenberg photographs. Unit-cell dimensions

Table 1. *Crystal data for phenacaine bis-p-nitrophenylphosphate monohydrate.*

$(C_{18}H_{23}N_2O_2)^+(C_{12}H_8N_2PO_8)^- . H_2O$ M.W.656·585
m.p.80–84° (Feinstein & Paimre, 1966)
Monoclinic, space group $P2_1/c$ from systematic absences:
$h0l$ absent for l odd, $0k0$ absent for k odd.

$Z=4$
$V=3173{\cdot}5$ Å^3
$a=10{\cdot}703 \pm 0{\cdot}005$ Å
$\lambda(\text{Cu } K\alpha)=1{\cdot}5418$ Å
$b=28{\cdot}236 \pm 0{\cdot}006$
$\lambda(K\alpha_1)=1{\cdot}54051$
$c=15{\cdot}901 \pm 0{\cdot}005$
$\lambda(K\alpha_2)=1{\cdot}5443$
$\beta=138{\cdot}67 \pm 0{\cdot}05°$
$\mu(\text{Cu } K\alpha)=13{\cdot}12$ cm^{-1}
$d_x=1{\cdot}374$ g.cm^{-3}
$d_m=1{\cdot}376$ g.cm^{-3} by flotation in a carbon tetrachloride-benzene mixture.

were deduced from measuring axial reflections made on a Picker diffractometer. The crystal was mounted so that its b axis coincided with the φ axis of the full-circle crystal orienter. Cu $K\alpha$ radiation was used throughout the analysis. Table 1 lists the crystal data.

Integrated intensity measurements were made by scanning reflections in the θ:2θ mode at a rate of 2°/min over a 2θ range of 2°. The background was counted for 15 seconds at each of the scan limits. Seven reflections were chosen as standards, and at least a pair of these were monitored at intervals of approximately two hours. Examination of the standards during the data collection indicated no obvious systematic variation in reflection intensity.

A total of 5339 reflections was collected out of which 947 were less than $3\sigma(I)$, where $\sigma(I)$ is given by

$$[I_o+4(I_{B1}+I_{B2})]^{\frac{1}{2}} .$$

The total number of counts accumulated during the scan is and I_o both I_{B1} and I_{B2} are background counts. Intensities were corrected for Lorentz and polarization factors and were also corrected for absorption (Craven, 1963; Busing & Levy, 1957) at a later stage of refinement. In making the absorption correction, the crystal shape was approximated by ten bounding planes. Table 2 lists the coefficients of the equations defining these planes and the crystal's volume.

Table 2. *Crystal faces*

The x,y,z orthogonal axes are in the direction of $-a$, b^*, c^*, respectively and the unit is cm. Crystal volume $=1\cdot43\times10^{-5}$ cm^3. Crystal dimensions measured against an optical scale calibrated at 0·0095 cm/division. Coefficients in $Ax+By+Cz-D=0$.

A	*B*	*C*	*D*
−0·0000	−0·0000	1·0000	0·0095
0·9999	−0·0026	−0·0148	−0·0111
0·0020	0·9497	0·3131	0·0147
−0·0024	0·9138	−0·4061	0·0156
0·8873	0·0000	−0·4612	0·0158
0·8988	0·0000	0·4383	0·0140
0·7475	−0·6639	−0·0233	0·0173
−0·0229	0·9733	0·2282	−0·0175
0·0460	0·8594	−0·5092	−0·0156
0·0000	−0·0000	1·0000	−0·0095

Structure determination and refinement

The *X-ray* 67 system of programs (Stewart, 1967) was used to compute a scale and an overall temperature factor from a Wilson plot, to convert observed structure-factor amplitudes to E values, to determine the signs of 1000 reflections by the direct method, and to

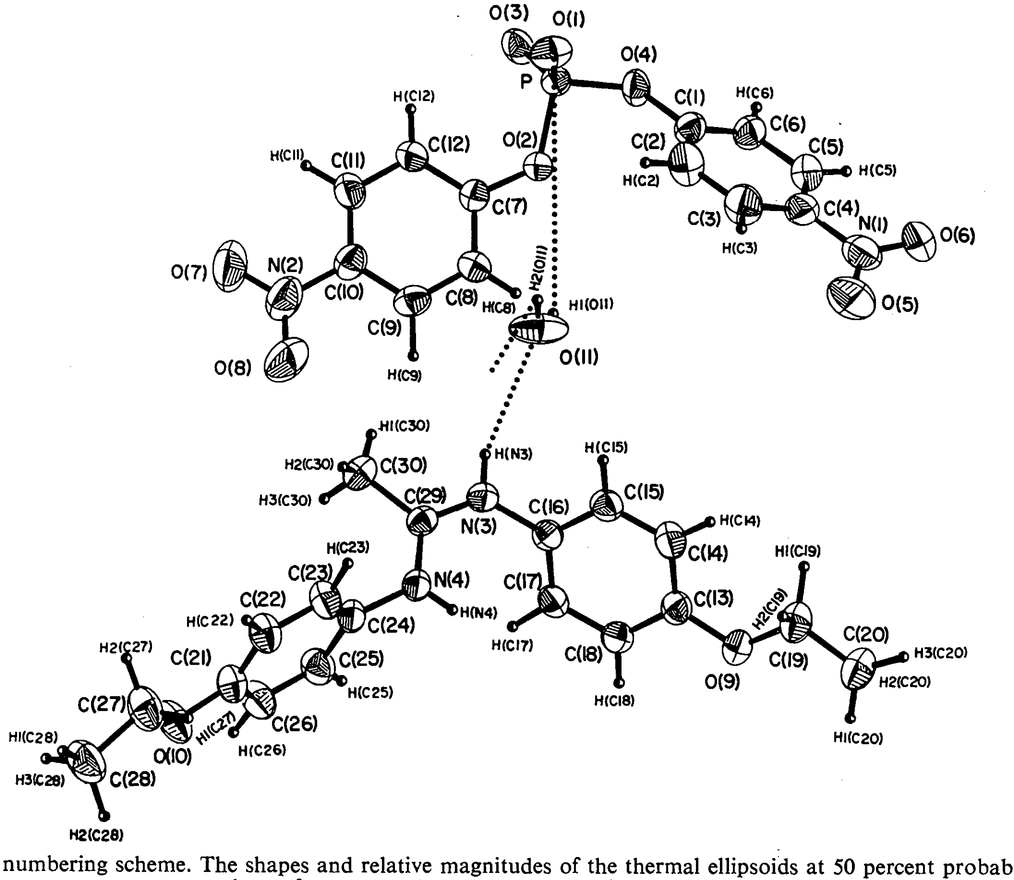


Fig. 1. Atomic numbering scheme. The shapes and relative magnitudes of the thermal ellipsoids at 50 percent probability level are shown for atoms other than hydrogen (Johnson, 1965).

synthesize an E map. Coordinates of 35 atoms were obtained from the E map. The remaining 11 atoms exclusive of the hydrogen atoms were located by an iterative routine, one cycle consisting of a difference Fourier synthesis followed by isotropic block-diagonal least-squares refinement. Parameters of the 46 atoms were then refined anisotropically by the full-matrix least-squares method. However, no more than 181 parameters were varied in any given cycle. The Hughes (1941) weighting scheme was employed with $\sigma = F/11$ if $F > 11$ and with $\sigma = 1$ if $F \leq 11$. The minimized function was $\sum w(|F_o| - K|F_c|)^2$ where K is a single scale factor. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1962), except for hydrogen, for which the data of Stewart, Davidson & Simpson (1965) were used. Hydrogen

Table 3. *Observed and calculated structure factors*

The columns within each group in order from left to right are the running index l, $10|F_o|$ and $10F_c$.

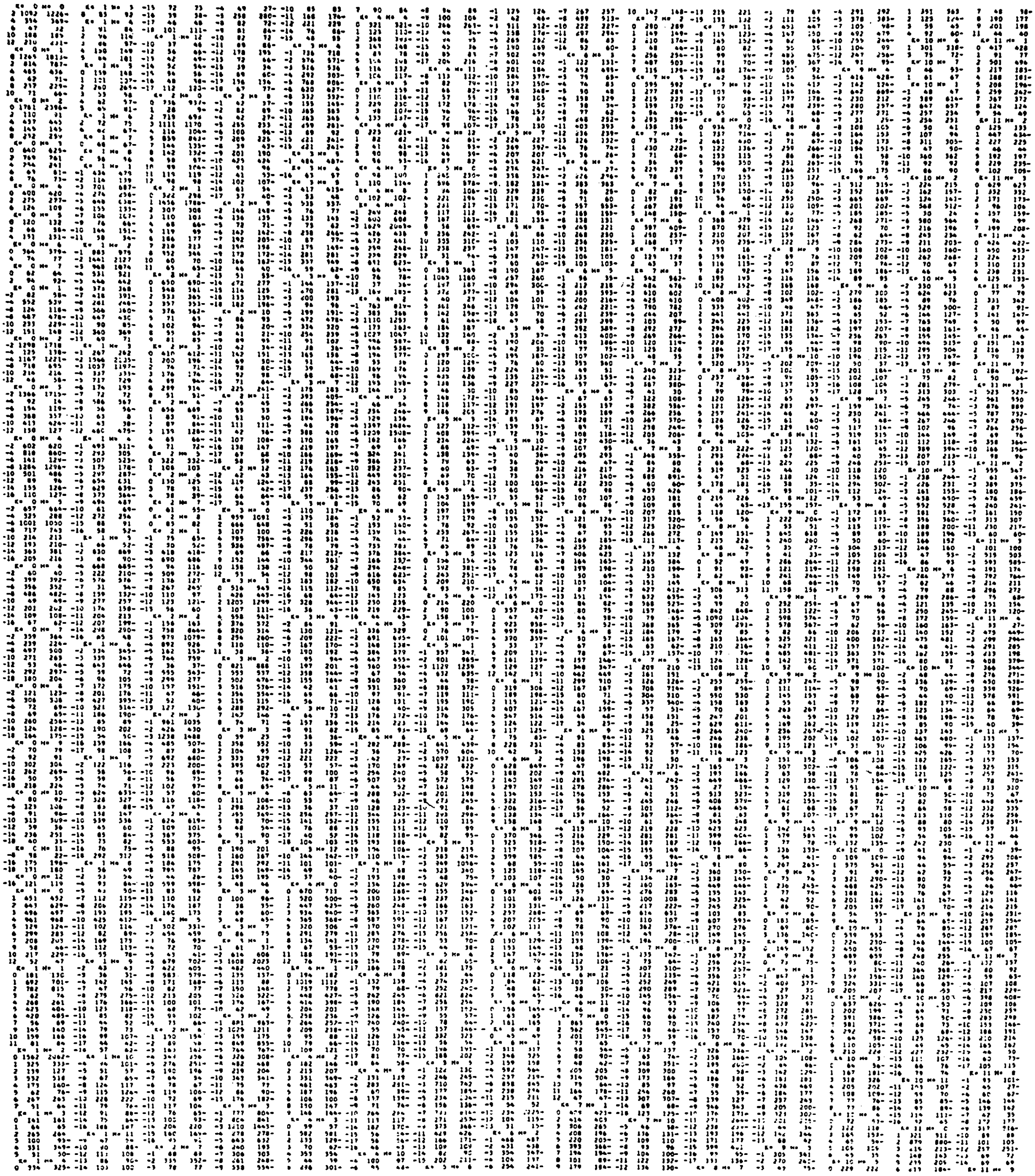
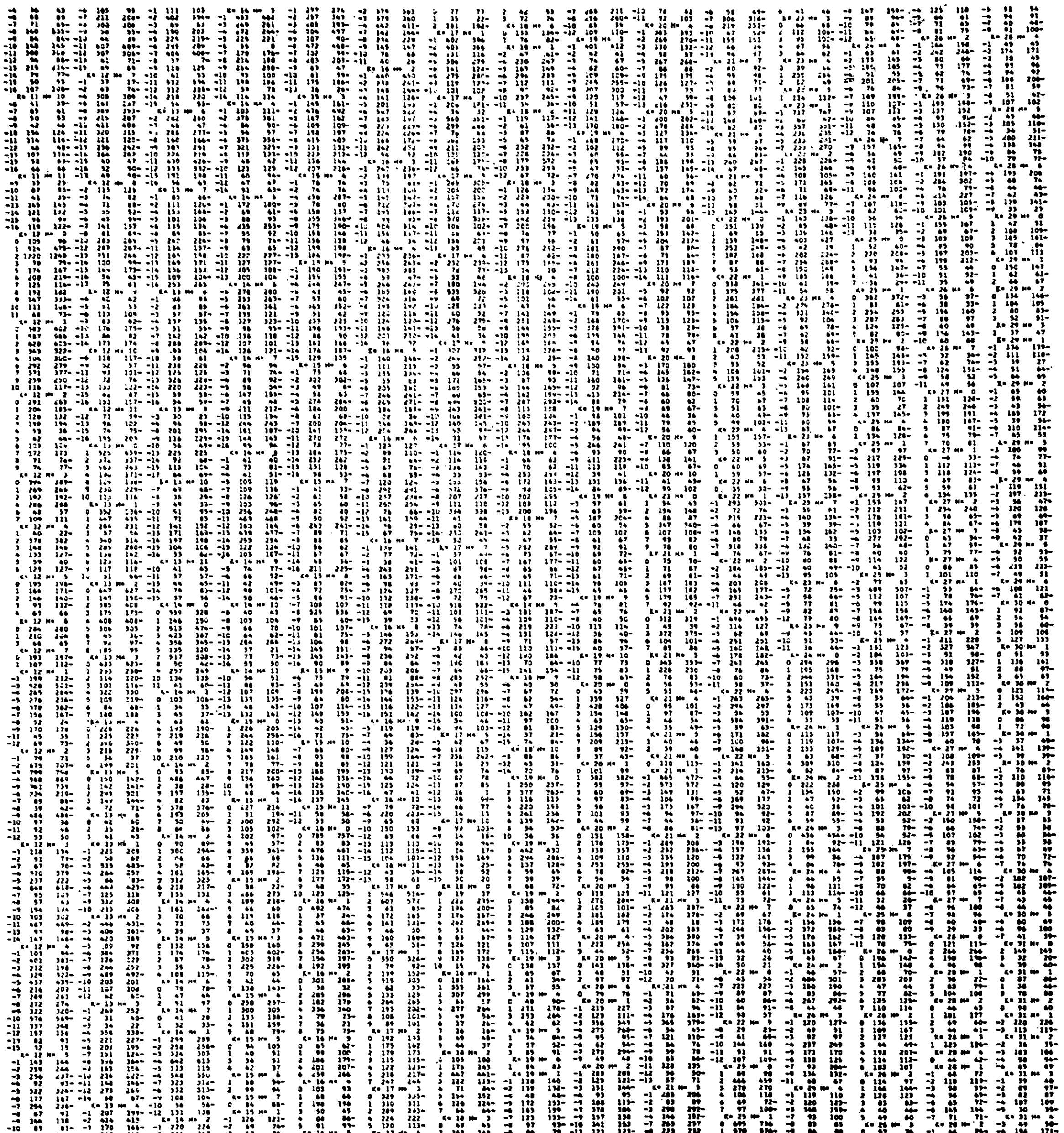


Table 3 (*cont.*)



coordinates were obtained from a difference synthesis calculated when the R value had been reduced to 0·09 near the end of the refinement. These were included as variables in the subsequent cycles of refinement. However, the hydrogen thermal parameters were not refined but were set equal to those of the atoms to which the hydrogen atoms were bonded. For the 4392 observed reflections (Table 3), the refinement converged to a conventional R index of 0·052. Atomic coordinates and thermal factors, and their estimated standard deviations are listed in Table 4. Fig. 1 shows the atomic numbering scheme and the molecular shape.

Discussion of the structure

The protonated phenacaine molecule in this complex is a substituted amidinium ion (Fig. 1) whose nitrogen atoms, N(3) and N(4), appear to be in very similar, if not identical, chemical bonding states. Each possesses a formal charge of $+\frac{1}{2}$ by virtue of the double bond resonating equally between C(29)–N(3) and C(29)–N(4). The equality of these two bonds (Table 5) and the coplanarity of atoms N(3), C(29), N(4) and C(30) (Table 6) are structural features attributable to the delocalized bond. Chemical substituents on N(3) are identical with those on N(4). Likewise, the bond distances and valency angles (Tables 5 and 7) involving N(3) do not differ significantly from the corresponding distances and angles at N(4), with possibly two exceptions. These are C(16)–N(3)–C(29) and C(24)–N(4)–C(29) which are $2\cdot3\sigma$ apart and C(30)–C(29)–N(4) and C(30)–C(29)–N(3) which differ by $2\cdot6\sigma$. These small differences may reflect the steric inequivalence in the milieu of N(3) and N(4). Thus, the C(29)–C(30) bond is *cis* with respect to N(4)–C(24), but it is *trans* relative to N(3)–C(16). The steric inequivalence extends to the orientations of the rings in the *p*-ethoxyphenyl groups, because the plane of C(13)–C(18) is rotated by 56·8° from coplanarity with atoms N(3), C(29), N(4) and C(30), whereas C(21)–C(26) is 78·1° from the N(3)–C(30) plane. Clearly, the rings are not favorably oriented to interact by resonance with the unsaturated bonds, N(3)–C(29) and N(4)–C(29). Moreover, the C(24)–N(4) and C(16)–N(3) bond lengths indicate no significant resonance of this kind. Accordingly, the N(3)–C(29)–N(4) π electrons can be treated as an independent bonding system, uninfluenced by the other π electrons in the molecule, at least to within limits delineated by

Table 4. *Fractional atomic coordinates* ($\times 10^4$ *for C, N, O, and P atoms and* $\times 10^3$ *for H atoms) and anisotropic thermal parameters* ($\times 10^4$).

Key to atomic numbering is given in Fig. 1. Thermal parameters are given in the form: $\exp[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})]$. Estimated standard deviations are shown in parentheses.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	5856 (2)	2833 (0)	1265 (1)	152 (2)	8(<1)	51 (1)	5(<1)	66 (1)	2(<1)
O(1)	7797 (5)	2796 (2)	1917 (4)	173 (8)	17 (1)	81 (4)	13 (2)	91 (5)	10 (1)
O(2)	5868 (5)	2720 (1)	2274 (3)	231 (8)	8(<1)	77 (3)	5(2)	112 (5)	2 (1)
O(3)	4278 (5)	2576 (1)	0071 (3)	202 (8)	10 (1)	60 (3)	1 (2)	74 (4)	−4 (1)
O(4)	5155 (5)	3372 (1)	0974 (3)	189 (8)	7(<1)	57 (3)	3 (1)	66 (4)	1 (1)
C(1)	5910 (7)	3738 (2)	1820 (4)	166 (10)	9 (1)	61 (4)	−5 (2)	73 (6)	−0 (1)
C(2)	7638 (8)	3716 (2)	3109 (5)	183 (11)	12 (1)	70 (5)	3 (2)	60 (7)	−0 (2)
C(3)	8203 (8)	4102 (2)	3867 (5)	208 (12)	14 (1)	69 (5)	−8 (3)	72 (7)	−5 (2)
C(4)	4802 (7)	4137 (2)	1297 (5)	194 (11)	10 (1)	66 (4)	3 (2)	81 (6)	3 (1)
C(5)	5391 (8)	4524 (2)	2053 (5)	231 (12)	9 (1)	97 (5)	4 (2)	116 (7)	1 (2)
C(6)	7077 (8)	4495 (2)	3338 (5)	229 (12)	11 (1)	84 (5)	−12 (2)	111 (7)	−7 (1)
N(1)	7683 (7)	4903 (2)	4146 (5)	291 (13)	15 (1)	123 (5)	−21 (2)	161 (8)	−15 (2)
O(5)	8883 (8)	4834 (2)	5296 (5)	358 (14)	22 (1)	94 (5)	−19 (3)	131 (7)	−17 (2)
O(6)	6984 (8)	5286 (2)	3648 (5)	432 (14)	11 (1)	161 (6)	−10 (2)	224 (9)	−11 (2)
C(7)	6355 (6)	2294 (2)	2871 (4)	138 (9)	8 (1)	63 (4)	0 (2)	69 (5)	1 (1)
C(8)	6769 (7)	2303 (2)	3921 (5)	166 (10)	11 (1)	67 (4)	−1 (2)	80 (6)	−3 (1)
C(9)	7182 (7)	1888 (2)	4563 (5)	173 (10)	13 (1)	60 (4)	−3 (2)	76 (6)	1 (1)
C(10)	6385 (8)	1870 (2)	2438 (5)	230 (12)	10 (1)	74 (5)	6 (2)	105 (7)	1 (1)
C(11)	6801 (8)	1454 (2)	3070 (5)	227 (12)	9 (1)	85 (5)	6 (2)	105 (7)	1 (1)
C(12)	7182 (7)	1469 (2)	4113 (5)	172 (10)	10 (1)	71 (5)	1 (2)	75 (6)	4 (1)
N(2)	7570 (8)	1027 (2)	4757 (5)	287 (13)	13 (1)	99 (5)	4 (2)	114 (7)	9 (2)
O(7)	7440 (11)	0657 (2)	4318 (6)	650 (24)	11 (1)	160 (7)	11 (3)	245 (11)	8 (2)
O(8)	8043 (12)	1047 (2)	5723 (6)	754 (27)	18 (1)	161 (7)	4 (4)	292 (13)	13 (2)
C(13)	1494 (7)	3756 (2)	7570 (4)	156 (9)	9 (1)	63 (4)	−7 (2)	70 (6)	−4 (1)
C(14)	2346 (7)	3709 (2)	7213 (5)	179 (11)	9 (1)	95 (5)	0 (2)	100 (7)	−2 (1)
C(15)	2354 (7)	3275 (2)	6821 (5)	173 (10)	10 (1)	85 (5)	−5 (2)	99 (6)	−4 (1)
C(16)	1528 (6)	2883 (2)	6775 (4)	130 (8)	9 (1)	52 (4)	−5 (2)	57 (5)	−3 (1)
C(17)	0617 (7)	2931 (2)	7088 (5)	173 (10)	9 (1)	73 (4)	−2 (2)	86 (6)	−4 (1)
C(18)	0619 (7)	3365 (2)	7491 (5)	185 (10)	10 (1)	79 (5)	−5 (2)	97 (6)	−3 (1)
C(19)	2518 (8)	4557 (2)	8223 (6)	216 (12)	10 (1)	108 (6)	6 (2)	114 (8)	6 (2)
C(20)	2145 (9)	4985 (2)	8568 (6)	250 (14)	11 (1)	117 (7)	6 (3)	128 (9)	9 (2)
O(9)	1423 (5)	4168 (1)	7982 (4)	213 (8)	8(<1)	95 (4)	−1 (2)	112 (5)	2 (1)
N(3)	1592 (6)	2442 (1)	6373 (4)	173 (8)	9 (1)	59 (3)	−2 (2)	77 (5)	−1 (1)
C(21)	5013 (7)	0785 (2)	10371 (5)	188 (11)	9 (1)	86 (5)	−5 (2)	93 (7)	−5 (1)
C(22)	3215 (8)	0964 (2)	9643 (6)	201 (11)	12 (1)	113 (6)	−6 (2)	120 (8)	−9 (2)
C(23)	2559 (8)	1360 (2)	3903 (5)	192 (11)	11 (1)	93 (5)	−9 (2)	103 (7)	−7 (2)
C(24)	3679 (7)	1580 (2)	8864 (5)	198 (11)	7 (1)	69 (4)	−2 (2)	88 (6)	−1 (1)
C(25)	5449 (8)	1402 (2)	9575 (5)	194 (11)	10 (1)	99 (5)	1 (2)	106 (7)	−4 (2)
C(26)	6127 (7)	1001 (2)	10328 (5)	176 (11)	10 (1)	95 (5)	−4 (2)	94 (7)	−5 (2)
C(27)	7382 (8)	0207 (2)	11884 (6)	209 (12)	12 (1)	115 (6)	−14 (2)	111 (8)	−13 (2)
C(28)	7668 (10)	−0179 (2)	12671 (7)	308 (17)	14 (1)	135 (8)	−20 (3)	158 (10)	−19 (2)
C(29)	2269 (6)	2040 (2)	7014 (4)	137 (9)	9 (1)	61 (4)	3 (2)	69 (5)	3 (1)
C(30)	2177 (8)	1613 (2)	6417 (5)	238 (13)	10 (1)	87 (5)	3 (2)	112 (7)	6 (2)
N(4)	3028 (6)	2012 (1)	8153 (4)	216 (9)	7 (1)	65 (4)	−3 (2)	91 (5)	−1 (1)
O(10)	5548 (6)	0403 (1)	11104 (4)	215 (9)	12 (1)	125 (5)	−15 (2)	125 (6)	−18 (1)
O(11)	0978 (6)	2516 (2)	4375 (4)	225 (10)	33 (1)	68 (4)	24 (3)	98 (6)	14 (2)

Table 4 (*cont*).

	x	*y*	*z*
H(C2)	385 (8)	344 (2)	346 (5)
H(C3)	941 (8)	409 (2)	476 (5)
H(C4)	362 (7)	418 (2)	040 (5)
H(C5)	472 (8)	479 (2)	169 (5)
H(C8)	666 (7)	258 (2)	418 (5)
H(C9)	735 (7)	190 (2)	530 (5)
H(C10)	609 (7)	186 (2)	174 (5)
H(C11)	682 (8)	116 (2)	279 (5)
H(C14)	295 (7)	397 (2)	729 (5)
H(C15)	277 (7)	325 (2)	649 (5)
H(C17)	006 (7)	266 (2)	711 (5)
H(C18)	008 (7)	338 (2)	775 (5)
H1(C19)	223 (8)	460 (2)	742 (6)
H2(C19)	381 (8)	447 (2)	881 (6)
H1(C20)	216 (9)	493 (2)	916 (6)
H2(C20)	279 (9)	529 (2)	874 (6)
H3(C20)	087 (9)	507 (2)	790 (6)
H(N3)	120 (7)	245 (2)	567 (5)
H(C22)	251 (8)	080 (2)	967 (5)
H(C23)	135 (8)	152 (2)	845 (5)
H(C25)	624 (7)	155 (2)	954 (5)
H(C26)	744 (7)	087 (2)	1084 (5)
H1(C27)	828 (8)	049 (2)	1244 (6)
H2(C27)	754 (8)	007 (2)	1137 (6)
H1(C28)	665 (9)	−045 (2)	1212 (6)
H2(C28)	746 (9)	−005 (2)	1321 (6)
H3(C28)	885 (9)	−033 (2)	1314 (6)
H1(C30)	165 (8)	168 (2)	569 (5)
H2(C30)	170 (8)	137 (2)	649 (5)
H3(C30)	349 (8)	149 (2)	702 (5)
H(N4)	316 (8)	226 (2)	850 (5)
H1(O11)	019 (9)	261 (3)	379 (6)
H2(O11)	196 (9)	250 (3)	453 (6)

the accuracy of this analysis. A molecular orbital calculation made with the usual simplifying assumptions (Wiberg, 1964) gives 0·69 for the π bond order in C(29)–N(3) and in C(29)–N(4). The respective lengths of these two bonds are 1·319 and 1·318 Å. Conformations of the terminal *p*-ethoxy groups in the phenacaine molecule are approximately *trans* planar (Table 6). Dihedral angles between the benzene rings and the planes of ethoxy groups are 11·2 and 5·6°.

Some interesting structural variations occur in the bis-*p*-nitrophenylphosphate ion in going from the phenacaine to the procaine complex. Thus, the valency angle between the esterified PO bonds is 97·2° in the former and 103·3° in the latter. Also, the internal rotation angles about the phosphate ester bonds differ in the two crystal structures. In the phenacaine complex the following values are observed: C(8)–C(7)–O(2)–P = +163·3, C(7)–O(2)–P–O(4) = +179·6, O(2)–P–O(4)–C(1) = 53·5, and P–O(4)–C(1)–C(2) = +10·1°. Here the four atomic symbols (*A*, *B*, *C* & *D*) signify the angle between bonds *BA* and *CD* when the complex is viewed in projection along the direction $B \rightarrow C$. The respective signs, + or −, denote the clockwise or the anticlockwise rotation required to bring *BA* into coincidence with *CD* when viewed along *BC*. The enantiomorphic conformer, whose angles are the negative of the four cited above, is also present in the unit cell. When the anion is complexed with procaine, the following internal rotation angles are observed about the phosphate ester bonds: C(20)–C(15)–O(3)–P = +105·0, C(15)–O(3)–P–O(2) = −77·4, O(3)–P–O(2)–C(6) = −82·3 and P–O(2)–C(6)–C(7) = 59·1°, where the atoms are numbered as in the original paper. Specified in the qualitatively descriptive nomenclature of Klyne & Prelog (1960), these conformations are *ap*, *sc* in the complex with phenacaine and -*sc*, -*sc* in the procaine adduct. They are the most commonly observed conformations in phosphate diesters, according to Shefter, Barlow, Sparks & Trueblood (1969). The dihedral angle between the two COP planes is 126·5° in the phenacaine and 101·1° in the procaine complex which agree with the values expected for these specific Klyne–Prelog conformations, as pointed out by Shefter, Barlow, Sparks & Trueblood (1969).

The torsion angle around the C–N bond connecting the phenyl ring and its nitro substituent in the bis-*p*-

Table 5. *Bond lengths and standard deviations*

i	*j*	D_{ij}	*i*	*j*	D_{ij}
P	O(1)	1·472 (6) Å	C(2)	H(C2)	0·92 (7) Å
P	O(2)	1·626 (5)	C(3)	H(C3)	0·96 (7)
P	O(3)	1·472 (5)	C(5)	H(C5)	0·88 (7)
P	O(4)	1·604 (5)	C(6)	H(C6)	0·97 (7)
O(4)	C(1)	1·378 (8)	C(8)	H(C8)	0·93 (7)
C(1)	C(2)	1·390 (10)	C(9)	H(C9)	1·04 (7)
C(2)	C(3)	1·383 (10)	C(11)	H(C11)	0·96 (7)
C(3)	C(4)	1·365 (10)	C(12)	H(C12)	0·90 (7)
C(4)	C(5)	1·379 (10)	C(14)	H(C14)	0·93 (7)
C(5)	C(6)	1·379 (10)	C(15)	H(C15)	0·91 (7)
C(6)	C(1)	1·372 (10)	C(17)	H(C17)	0·98 (7)
C(4)	N(1)	1·466 (10)	C(18)	H(C18)	0·93 (7)
N(1)	O(5)	1·226 (10)	C(19)	H1(C19)	1·07 (7)
N(1)	O(6)	1·210 (10)	C(19)	H2(C19)	0·95 (8)
O(2)	C(7)	1·369 (8)	C(20)	H1(C20)	0·93 (8)
C(7)	C(8)	1·384 (9)	C(20)	H2(C20)	1·00 (8)
C(8)	C(9)	1·383 (10)	C(20)	H3(C20)	0·93 (8)
C(9)	C(10)	1·381 (10)	N(3)	H(N3)	0·86 (7)
C(10)	C(11)	1·380 (10)	N(4)	H(N4)	0·82 (7)
C(11)	C(12)	1·385 (10)	C(30)	H1(C30)	0·84 (8)
C(12)	C(7)	1·392 (10)	C(30)	H2(C30)	0·91 (8)
C(10)	N(2)	1·462 (10)	C(30)	H3(C30)	0·99 (8)
N(2)	O(7)	1·205 (12)	C(22)	H(C22)	0·92 (7)
N(2)	O(8)	1·205 (12)	C(23)	H(C23)	1·00 (7)
C(13)	C(14)	1·395 (10)	C(25)	H(C25)	0·98 (7)
C(14)	C(15)	1·378 (10)	C(26)	H(C26)	1·02 (7)
C(15)	C(16)	1·383 (9)	C(27)	H1(C27)	1·04 (8)
C(16)	C(17)	1·394 (9)	C(27)	H2(C27)	1·02 (8)
C(17)	C(18)	1·381 (10)	C(28)	H1(C28)	1·04 (9)
C(18)	C(13)	1·392 (10)	C(28)	H2(C28)	1·09 (9)
C(13)	O(9)	1·365 (8)	C(28)	H3(C28)	0·97 (9)
O(9)	C(19)	1·433 (9)	O(11)	H1(O11)	0·68 (9)
C(19)	C(20)	1·497 (11)	O(11)	H2(O11)	0·88 (9)
N(3)	C(16)	1·424 (8)			
N(3)	C(29)	1·319 (8)			
C(29)	C(30)	1·492 (10)			
C(29)	N(4)	1·318 (8)			
N(4)	C(24)	1·437 (9)			
C(21)	C(22)	1·397 (11)			
C(22)	C(23)	1·374 (11)			
C(23)	C(24)	1·391 (10)			
C(24)	C(25)	1·379 (10)			
C(25)	C(26)	1·392 (10)			
C(26)	C(21)	1·386 (10)			
C(21)	O(10)	1·359 (9)			
O(10)	C(27)	1·428 (9)			
C(27)	C(28)	1·509 (12)			

nitrophenylphosphate ion also reflects the differences in the environment of this anion in the two crystal structures. These angles are 6·8 and 20·0° in phenacaine bis-*p*-nitrophenylphosphate monohydrate, whereas they are 4·0 and 6·9° in procaine bis-*p*-nitrophenylphosphate.

Shefter, Barlow, Sparks & Trueblood (1969) have tabulated the internal rotation angles around the PO bonds and the dihedral angles between the POC planes for all of the phosphate diesters and triesters for which parameters had been reported in the literature at the time. Among the compounds listed by them, L-α-glycerophosphorylcholine (Abrahamson & Pascher, 1966), vitamin B_{12} (Brink-Shoemaker, Cruickshank, Hodgkin, Kamper & Pilling, 1964; Hodgkin, Lindsey, Sparks, Trueblood & White, 1962; Lenhert, 1968), and the triphosphate salt $Na_5P_3O_{10}$ (Corbridge, 1960; Davies & Corbridge, 1958) were the only ones

Table 6. *Some least-squares planes through groups of atoms in the phenacaine-bis-p-nitrophenylphosphate monohydrate complex.*

Coefficients $\times 10^4$ in $AX+BY+CZ-D=0$, referred to the crystallographic axes (X, Y, Z in Å).

Plane*	No.	*A*	*B*	*C*	*D*
Benzene ring C(1) to C(6)	1	9110	3719	−8017	73755
Benzene ring C(7) to C(12)	2	7936	1284	−2029	53105
Benzene ring C(13) to C(18)	3	2273	2310	4542	54516
Benzene ring C(21) to C(26)	4	−2672	−5825	7077	−51888
N(3)–C(29)–C(30)–N(4)	5	8787	−2239	−3812	84502
C(13)–O(9)–C(19)–C(20)	6	606	−2798	5874	42248
C(21)–O(10)–C(27)–C(28)	7	−2210	6440	6497	109268

Plane No.	Displacement from the plane (Å × 10^3)
1	C(1) −8, C(2) 10, C(3) 0, C(4) −3, C(5) 13, C(6) −11, O(4) −50, N(1) −21, O(5) −389, O(6) 334.
2	C(7) −7, C(8) 5, C(9) 1, C(10) 4, C(11) 3, C(12) −5, O(2) −74, N(2) −43, O(7) −147, O(8) 53.
3	C(13) 12, C(14) −8, C(15) −6, C(16) 16, C(17) −12, C(18) −2, N(3) 29, O(9) 23, C(19) 211, C(20) 90.
4	C(21) 6, C(22) −4, C(23) 1, C(24) 0, C(25) 2, C(26) −5, N(4) 97, O(10) 50, C(27) 82, C(28) 250.
5	N(3) 1, C(29) −4, C(30) 1, N(4) 1, C(16) −23, C(24) −90, H(N3) 68, H(N4) 70.
6	C(13) −25, O(9) 29, C(19) 18, C(20) −22, H1(C19) −787, H2(C19) 719.
7	C(21) 29, O(10) −35, C(27) −18, C(28) 24, H1(C27) 863, H2(C27) −829.

* Hydrogen atoms were excluded from the least-squares calculations of all planes.

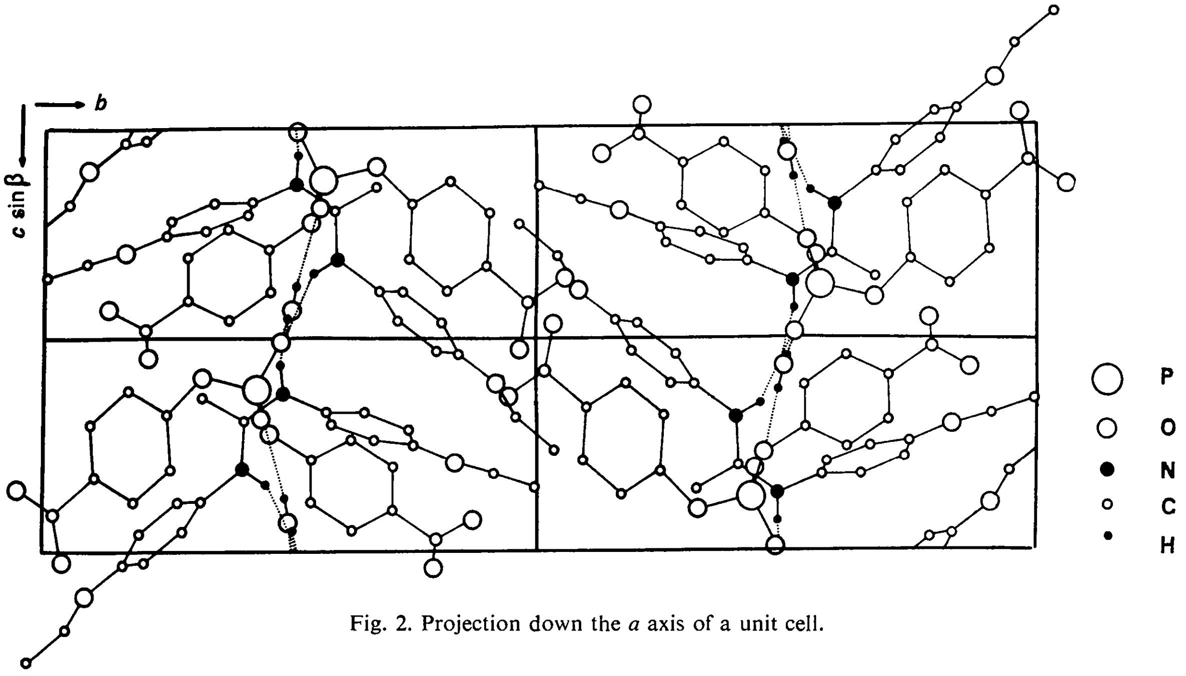


Fig. 2. Projection down the *a* axis of a unit cell.

observed in more than a single crystallographic environment. In none of these cases did the change in milieu alter the Klyne–Prelog classification of the relative phosphate diester conformation. Indeed, the variations observed in the conformational angles were small: they ranged from 4 to 17°. On the other hand the two Klyne–Prelog conformations found for bis-p-nitrophenylphosphate correspond to changes of 24 and 97° in the torsion angles. This conformational difference could be caused only by the dissimilar intermolecular packing forces acting on this anion in the two crystal environments. While it may not seem surprising that the conformational angles around bonds with low π character are sensitive to lattice forces, the changes of 6° produced in the OPO valency angle by the difference in lattice forces is unusually large. Indeed, 8 values of this angle that have been reported in various phosphate diesters (Table 8) range from 100 to 106·3° and average 102·7°. If these are normal values for phosphate diesters, then at 97·2° it is much smaller in phenacaine bis-p-nitrophenylphosphate monohydrate,

Table 7. *Bond angles and estimated standard deviations*

i	*j*	*k*	Angle (*ijk*)
O(1)	P	O(2)	109·3 (3)°
O(1)	P	O(3)	121·3 (3)
O(1)	P	O(4)	112·1 (3)
O(2)	P	O(3)	109·2 (3)
O(2)	P	O(4)	97·2 (2)
O(3)	P	O(4)	105·1 (3)
P	O(2)	C(7)	124·8 (4)
O(2)	C(7)	C(10)	123·4 (6)
O(2)	C(7)	C(8)	115·8 (6)
C(8)	C(7)	C(10)	120·8 (6)
C(7)	C(8)	C(9)	120·3 (6)
C(8)	C(9)	C(12)	118·3 (6)
C(9)	C(12)	N(2)	118·6 (6)
C(11)	C(12)	N(2)	119·1 (6)
C(12)	C(11)	C(10)	119·3 (7)
C(7)	C(10)	C(11)	119·1 (7)
C(12)	N(2)	O(7)	119·1 (8)
C(12)	N(2)	O(8)	118·6 (8)
O(7)	N(2)	O(8)	122·2 (9)
P	O(4)	C(1)	128·8 (4)
O(4)	C(1)	C(4)	114·7 (6)
O(4)	C(1)	C(2)	124·1 (6)
C(1)	C(2)	C(3)	118·5 (7)
C(2)	C(3)	C(6)	119·8 (7)
C(3)	C(6)	C(5)	122·0 (7)
C(3)	C(6)	N(1)	119·6 (7)
C(5)	C(6)	N(1)	118·4 (7)
C(6)	N(1)	O(6)	118·7 (7)
C(6)	N(1)	O(5)	117·4 (7)
O(5)	N(1)	O(6)	123·9 (8)
C(6)	C(5)	C(4)	118·5 (7)
C(1)	C(4)	C(5)	120·1 (7)
O(10)	C(27)	C(28)	106·9 (5)
C(21)	O(10)	C(27)	118·1 (6)
O(10)	C(21)	C(26)	124·6 (6)
C(21)	C(22)	C(23)	120·3 (7)
C(22)	C(23)	C(24)	119·9 (7)
C(23)	C(24)	C(25)	120·0 (7)
C(23)	C(24)	N(4)	119·3 (6)
C(25)	C(24)	N(4)	120·6 (6)
C(24)	C(25)	C(26)	120·6 (7)
C(21)	C(26)	C(25)	119·3 (7)
C(24)	N(4)	C(29)	124·5 (5)
N(3)	C(29)	C(30)	118·0 (6)
N(4)	C(29)	C(30)	120·2 (6)
N(4)	C(29)	N(3)	121·8 (6)
C(29)	N(3)	C(16)	126·1 (5)
C(15)	C(16)	C(17)	119·6 (6)
C(15)	C(16)	N(3)	118·6 (6)
C(17)	C(16)	N(3)	121·7 (6)
C(16)	C(17)	C(18)	119·6 (6)
C(13)	C(18)	C(17)	120·7 (6)
C(14)	C(13)	C(18)	119·3 (6)
C(14)	C(13)	O(9)	124·4 (6)
C(18)	C(13)	O(9)	116·3 (6)
C(13)	C(14)	C(15)	119·7 (6)
C(14)	C(15)	C(16)	120·9 (6)
C(13)	O(9)	C(19)	117·0 (5)
O(9)	C(19)	C(20)	109·1 (6)

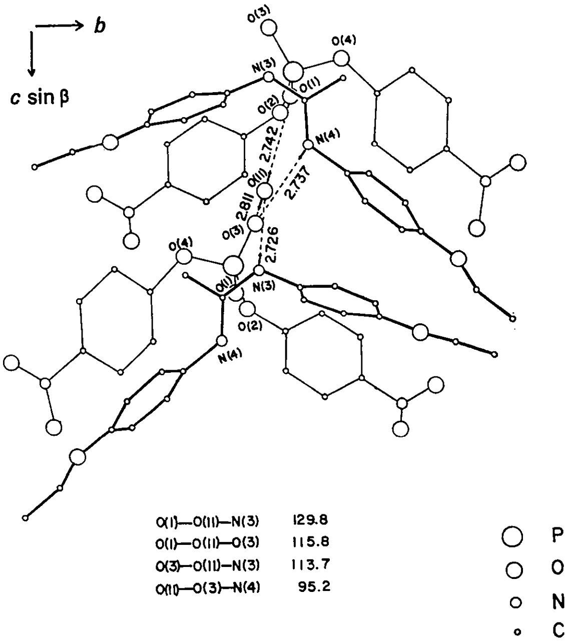


Fig. 3. Hydrogen bonding scheme of phenacaine bis-p-nitrophenylphosphate monohydrate.

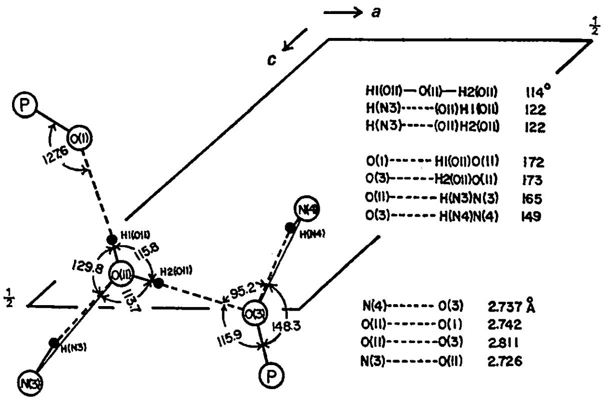


Fig. 4. Environment of the water molecule.

Table 8. *Phosphate diester angles.*

Substance	∠R–O–P–O–R′	Reference
Di-*p*-chlorophenyl hydrogen phosphate*	108·1 (0·5)°	Calleri & Speakman (1964)
Dibenzylphosphoric acid*	103·80 (0·21)	Dunitz & Rollett (1956)
β-Adenosine-2′-*β*-uridine-5′-phosphoric acid	102·8 (0·3)	Shefter, Barlow, Sparks & Trueblood (1969)
Barium diethylphosphate	103·5 (0·8)	Kyogoku & Iitaka (1966)
L-*α*-Glycerophosphorylcoholin I	104·02 (0·32)	Abrahamsson & Pascher (1966)
L-*α*-Glycerophosphorylcoholin II	102·22 (0·27)	
Air-dried crystals of vitamin B_{12}	102	Hodgkin, Lindsey, Sparks, Trueblood & White (1962)
Vitamin B_{12} coenzyme	100	Lenhert (1968)
Vitamin B_{12} grown from water and immersed in water	101	Brink-Shoemaker, Cruickshank, Hodgkin Kamper & Pilling (1964)
O-(L-*α*-Glycerylphosphoryl)-ethanolamine monohydrate	106·3	DeTitta & Craven (1970)

* Hydrogen is attached to the oxygen atom of phosphate group.

whereas its magnitude of 103·3° in the procaine complex seems normal.

The major feature distinguishing the molecular packing arrangements in the two crystal structures is the degree to which the phenyl rings on the phosphate diester intermingle with those of the local anesthetic. It is much more extensive when the local anesthetic is phenacine (Fig. 2). Significantly, in this molecule and in bis-*p*-nitrophenylphosphate, the ionic group is situated between two phenyl rings, whereas in the procaine molecule a central phenyl ring is flanked by two ionic groups. In the former case compatible molecular structures permit the phenyl rings on both cation and anion to intermingle and to pack neatly together while the ionic groups on each are maintained in close proximity. On the other hand, the ends of the procaine ion make contact with phosphate groups in separate anions, so that the local anesthetic cross-links the anions. The bridging procaine molecules are stacked in a column with adjacent anesthetic molecules oriented in opposite directions but with their phenyl rings overlapped (Sax, Pletcher, & Gustafsson, 1970). Clearly, the phenyl rings of the anesthetic are segregated from those of the diester to a much greater degree in procaine bis-*p*-nitrophenylphosphate. Furthermore, the disorder in the procaine complex may be indicative of an inferior molecular packing arrangement for the nonpolar groups. In phenacaine bis-*p*-nitrophenylphosphate monohydrate the intermolecular contacts occur at the normally expected van der Waals distances except those between hydrogen bonded atoms (Table 9). The details in the hydrogen bonding scheme appear in Table 9 and in Figs. 3 and 4. The average $\overset{(\frac{1}{2}+)}{\mathrm{N}}\cdots\mathrm{O}$ distance is 2·731 Å which is about 0·1 Å shorter than hydrogen bonds between neutral nitrogen and oxygen. There are only three hydrogen bonds to the water molecule. They form an almost trigonal planar arrangement and average 2·76 Å.

The formation of strong hydrogen bonds between the anesthetic molecule and the phosphate group is a characteristic of both the phenacaine and procaine complexes. The relevance of this structural feature with respect to the mode of action of local anesthetics

Table 9. *Some intermolecular and nonbonded intramolecular distances and angles*

In the hydrogen bonds	Distance (*ij*)	Angle(*ijk*)
H(N4)·····O(3)——P	2·00 Å	150°
O(3)·······H(N4)—N(4)		149
H(N3)·····O(11)——O(1)	1·89	126
O(11)······H(N3)—N(3)		165
H1(O11)···O(1)——P	2·06	127
O(1)·······H1(O11)–O(11)		172
H2(O11)···O(3)——P	1·93	118
O(3)·······H2(O11)–O(11)		173
In the amidinium moiety		
H(N3)···C(29)	1·89	
H(N3)···C(16)	1·95	
H(N3)···C(30)	2·50	
H(N3)···H(C15)	2·50	
H(N3)···H1(C30)	2·22	
H(N3)···H2(C30)	3·19	
H(N3)···H3(C30)	3·16	
H(N4)···C(24)	1·95	
H(N4)···C(29)	1·86	
H(N4)···H(C17)	2·49	
H(N4)···N(3)	2·45	
In the ethoxy group		
O(9)·······C(20)	2·388 Å	
O(9)····H1(C19)	2·05	
O(9)····H2(C19)	1·98	
O(10)···C(28)	2·360	
In nonhydrogen-bonded intermolecular contacts		
O(3)·······C(24)†	3·182	
N(1)·······O(5)*	3·153	
O(5)·······O(5)*	3·295	
O(5)·······C(19)*	3·197	
O(6)·······O(10)§	3·035	
O(6)·······H1(C19)′	2·42	
H1(C19)···O(5)″	2·55	

Symmetry code

*	$2-x$,	$1-y$,	$1-z$
†	x,	y,	$-1+z$
‡	$1+x$,	y,	z
§	$1-x$,	$\frac{1}{2}+y$,	$1\frac{1}{2}-z$
′	$1-x$,	$1-y$,	$1-z$
″	$-1+x$,	y,	z

has been presented in detail in a separate publication (Sax & Pletcher, 1969).

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The Crystal Structure of Bis-(*H*-pyrrole-2-aldimine)copper(II), $(C_5H_5N_2)_2$ Cu(II)

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The crystal structure of bis-(*H*-pyrrole-2-aldimine)copper(II) has been determined using three-dimensional data collected on a diffractometer equipped with a single-crystal orienter. The space group is $P2_1/c$ with $Z=2$; cell dimensions are $a=9{\cdot}845$ (2), $b=5{\cdot}562$ (3), $c=9{\cdot}604$ (3) Å and $\beta=103{\cdot}07$ (1)°. The Cu^{2+} ions occupy special positions (0,0,0) and $(0,\frac{1}{2},\frac{1}{2})$ and the molecule must lie on a centre of symmetry. The structure was elucidated by the heavy-atom method and was refined by the full-matrix least squares technique. The final R is 0·061. The Cu^{2+} ion is coordinated with four N atoms in a squareplanar arrangement; the two unique Cu–N distances are 1·97 (1) and 1·95 (1) Å. The molecule is essentially planar, the maximum deviation from the best least-squares plane being 0·06 Å.

Introduction

The preparation and chemical properties of pyrrole-2-aldimine chelates of copper have been reported by Enmart, Diehl & Collwitzer (1929) and Pfieffer, Hesse, Pfitzinger, Scholl & Theriot (1937). The electronic spectra of these chelates have been reported by Chakravorty & Kannan (1967). Stakleberg (1947) made