Acta Cryst. (1975). B31, 1354

The Crystal Structure of Lidocaine Bis-*p*-nitrophenylphosphate*

BY C. S. YOO, E. ABOLA, M. K. WOOD, M. SAX AND J. PLETCHER

Department of Crystallography, University of Pittsburgh, Pittsburgh, Pa. 15260, *U.S.A.*
and Biocrystallography Laboratory, Veterans Administration Hospital, Pittsburgh, Pa. 15240, *U.S.A.*

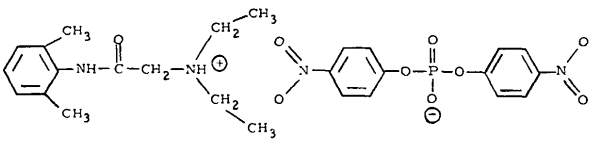
(*Received* 19 *August* 1974; *accepted* 16 *December* 1974)

The crystal and molecular structure of lidocaine bis-*p*-nitrophenylphosphate, $[C_{14}H_{23}N_2O]^+[C_{12}H_8N_2O_8P]^-$, has been determined from three-dimensional diffractometer data. Both the amino and the amide hydrogen atoms participate in hydrogen bonds to the phosphate group, with N···O distances of 2·690 and 2·801 Å. The conformations of the lidocaine cation and bis-*p*-nitrophenylphosphate (BPNP) anion are compared to those observed in the structures reported previously. The presence or absence of intramolecular hydrogen bonding is the chief cause for the conformational differences of lidocaine seen in three crystal structures. Accurate predictions of bond distances and valency angles in phosphate tetrahedra may be made using Baur's correlations with bond strength. Excessive discrepancies observed in phosphate esters are correlated with conformation. Indeed, from the conformational variations of the BPNP ion in four crystal structures, we find that the O–P–O angle is reduced by an average of 4·1° if the oxygen is *anti* to a substituent, and increased by an average of 1·4°, if they are *syn*-related. The compound crystallizes in the monoclinic space group $P2_1/c$, with four molecules in a unit cell of dimensions $a=14{\cdot}901$ (6), $b=7{\cdot}258$ (3), $c=27{\cdot}867$ (12) Å, $\beta=108{\cdot}65$ (2)°. The intensities of 4696 reflections were measured on a four-circle automated diffractometer using Cu $K\alpha$ radiation. The structure was refined by the full-matrix least-squares technique to a final R value of 0·067 for all reflections.

Introduction

The present investigation of lidocaine bis-*p*-nitrophenylphosphate (see Table 1) was undertaken in order to study the nature of the interaction between the constituents and to compare the common structural features of this salt to those found in other structures containing either ion. The crystal structures of lidocaine hydrohexafluoroarsenate and lidocaine hydrochloride monohydrate have been determined by Hanson (1972) and by Hanson & Röhrl (1972), respectively. The crystal structure of the bis-*p*-nitrophenylphosphate (BPNP) anion has also been observed as the salt of the following local anesthetics: procaine (Sax, Pletcher & Gustaffson, 1970), phenacaine (Sax, Pletcher, Yoo & Stewart, 1971) and benzocaine (Pletcher, Sax & Yoo, 1972).

Table 1. *Crystal data for lidocaine bis-p-nitrophenylphosphate*



$[C_{14}H_{23}N_2O]^+[C_{12}H_8N_2O_8P]^-$ M.W. 574·532
Monoclinic, space group $P2_1/c$, from systematic absences: $h0l$ absent for l odd, $0k0$ absent for k odd.

$a=14{\cdot}901$ (6) Å	$Z=4$
$b=7{\cdot}258$ (3)	λ(Cu $K\alpha$) = 1·5418 Å
$c=27{\cdot}867$ (12)	μ(Cu $K\alpha$) = 13·5 cm^{-1}
$\beta=108{\cdot}65$ (2)°	$F(000)=1208$
$V=2860{\cdot}6$ Å^3	

$d_o=1{\cdot}332$ g cm^{-3} by flotation in benzene–CCl_4 at 19°C
$d_c=1{\cdot}334$ g cm^{-3}
m.p. 152–154° (unc.) measured on a Thermolyne m.p. block.

Experimental

Transparent, needle-shaped crystals of the complex were prepared by mixing equimolar solutions of lidocaine and bis-*p*-nitrophenylphosphoric acid in absolute methanol and slowly evaporating the mixture at room temperature. The space group was determined from oscillation and Weissenberg photographs. The unit-cell dimensions were obtained from a least-squares analysis (Picker FACS-1 Disk Operating System, 1972) of 12 centered reflections using a Picker FACS-1 diffractometer. Graphite-monochromated Cu $K\alpha$ radiation was used throughout the analysis. The crystal data are given in Table 1. Integrated intensities were measured in the $\theta:2\theta$ scan mode with a speed of 1° min^{-1} over a 2θ range of 2°. The background was counted for 20 s at each of the scan limits. Three reflections, chosen as standards, were monitored after every 50 reflections. A reduction in the intensity of the standards exceeding 5% was used as a criterion for automatic realignment of the crystal.

4696 independent reflections were measured up to $2\theta=130°$. As the data were collected, each intensity was reduced to its structure amplitude by the appropriate Lorentz–polarization factor for graphite-monochromated ($2\theta_m=26{\cdot}16°$) radiation (Picker FACS-1 Disk Operating System, 1972). Of the independent re-

* Research supported by the U.S. Public Health Service, National Institutes of Health, Grant No. NS-09178.

flections 1319 were considered to be unobserved when $|F| \leq 6\sigma(F)$, where $|F|$ is the structure amplitude and $\sigma(F)$ is given by $[1/(2\mathrm{Lp}|F|)]\sigma(I)$; Lp is the Lorentz–polarization factor, $\sigma(I)=[I_t+K^2B]^{1/2}$, $I=I_t-B_t$, $B_t=KB$, $B=(b_1+b_2)$, $K=t_1/2t_2$, $I_t=(10S+5)$, $b_1=(10C_1+5)$, $b_2=(10C_2+5)$, S=the number of decacounts accumulated during the scan requiring time t_1, and C_1 and C_2=the background decacounts accumulated in time t_2 at either end of the scan range. Absorption corrections were not applied to the data.

Structure determination

The structure amplitudes were scaled and normalized to E values by means of a Wilson plot (Shiono, 1971*a*). The signs of 500 reflections with $E \geq 1{\cdot}62$ were determined by the direct method using the computer program *MULTAN* (Germain, Main & Woolfson, 1971). An E map calculated with these E factors revealed 30 of the non-hydrogen atomic positions in the complex, including those of the phosphate group. The remaining ten atoms, exclusive of the hydrogens, were located in a difference Fourier synthesis after a single cycle of block-diagonal least-squares refinement of the partial structure. The parameters of the 40 atoms were then refined anisotropically by the full-matrix least-squares method (Shiono, 1971*b*). The function minimized was $\sum w(|F_o|-K|F_c|)^2$, where K is a single scale factor and w is a weighting factor. Initially a weighting scheme suggested by Hughes (1941) was employed in which $w=1/\sigma(F)$ and $\sigma(F)=F/13{\cdot}0$ for $F>13{\cdot}0$ or $\sigma(F)=1{\cdot}0$ for $|F| \leq 13{\cdot}0$. The weighting scheme was changed at an $R=0{\cdot}08$ to one based on a plot of $|\Delta F|$ *vs* $|F_o|$, where $\Delta F=|F_o-F_c|$. The program *RESIG* (Wood, 1973) was used to find $\sigma(F)$ from this plot by linear interpolation after approximating the curve by three segments of a straight line. Atomic scattering factors for the non-hydrogen atoms were taken from Cromer & Waber (1965), while those for hydrogen atoms were taken from Stewart, Davidson & Simpson (1965). The final R index is 0·067 for all 4696 independent reflections and 0·052 for the 3377 reflections with $F>6\sigma(F)$. The

Table 2. *Atomic parameters and their e.s.d.'s for lidocaine bis-p-nitrophenylphosphate*

Fractional coordinates $\times 10^4$ for non-hydrogen atoms, $\times 10^3$ for hydrogen atoms. Thermal parameters $\times 10^4$ in the form: $\exp[-(h^2\beta_{11}+\ldots+2kl\beta_{23})]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	1731 (1)	−1636 (1)	833 (1)	38 (4)	174 (2)	10 (1)	7 (1)	3 (2)	−6 (4)
O(1)	1398 (2)	−2803 (4)	378 (1)	55 (1)	293 (7)	13 (0)	1 (2)	3 (1)	−21 (1)
O(2)	2242 (2)	−3052 (3)	1282 (1)	59 (1)	170 (5)	13 (0)	5 (2)	5 (1)	1 (1)
O(3)	1089 (2)	−375 (3)	979 (1)	52 (1)	241 (6)	16 (0)	27 (2)	7 (1)	−9 (1)
O(4)	2615 (2)	−360 (3)	818 (1)	53 (1)	195 (5)	18 (1)	−1 (2)	11 (1)	0 (1)
O(5)	6601 (3)	−992 (8)	561 (2)	69 (2)	817 (19)	36 (1)	−101 (5)	23 (1)	−58 (3)
O(6)	6073 (3)	−3665 (9)	306 (2)	77 (2)	632 (17)	41 (1)	29 (5)	25 (1)	−28 (4)
O(7)	3435 (3)	−1202 (8)	3592 (1)	143 (3)	689 (17)	14 (1)	1 (6)	12 (1)	−4 (2)
O(8)	4764 (3)	−862 (7)	3458 (1)	96 (3)	673 (17)	22 (1)	−10 (5)	−11 (1)	−28 (3)
O(9)	181 (2)	5318 (3)	1539 (1)	62 (1)	204 (6)	13 (1)	18 (2)	5 (1)	−7 (1)
N(1)	5995 (3)	−2170 (8)	474 (1)	56 (2)	574 (17)	16 (1)	−20 (5)	8 (1)	−14 (3)
N(2)	3921 (3)	−1199 (6)	3314 (1)	103 (3)	374 (11)	15 (1)	16 (5)	−2 (1)	0 (2)
N(3)	979 (2)	2610 (4)	1595 (1)	50 (1)	197 (6)	11 (0)	11 (3)	3 (1)	−8 (1)
N(4)	−996 (2)	4313 (4)	549 (1)	50 (1)	211 (7)	11 (0)	19 (3)	2 (1)	−7 (1)
C(1)	3424 (2)	−903 (5)	728 (1)	46 (1)	226 (7)	12 (0)	−1 (3)	5 (1)	4 (1)
C(2)	4105 (3)	478 (6)	783 (2)	69 (2)	257 (8)	18 (1)	−30 (3)	11 (1)	−9 (2)
C(3)	4950 (3)	67 (8)	701 (2)	60 (2)	412 (12)	18 (1)	−54 (4)	12 (1)	−9 (2)
C(4)	5099 (3)	−1715 (7)	565 (1)	43 (2)	420 (12)	13 (0)	−7 (4)	5 (1)	−4 (2)
C(5)	4446 (3)	−3073 (7)	516 (2)	60 (2)	313 (10)	20 (1)	12 (4)	10 (1)	−8 (2)
C(6)	3593 (3)	−2678 (6)	598 (2)	55 (2)	242 (7)	21 (1)	−4 (3)	13 (1)	−3 (2)
C(7)	2641 (2)	−2492 (5)	1781 (1)	53 (1)	152 (5)	12 (0)	5 (2)	5 (1)	5 (1)
C(8)	3614 (3)	−2381 (6)	1973 (1)	52 (2)	304 (9)	16 (1)	12 (3)	6 (1)	6 (2)
C(9)	4032 (3)	−1940 (7)	2479 (2)	54 (2)	355 (10)	17 (1)	5 (3)	0 (1)	4 (2)
C(10)	3470 (3)	−1634 (6)	2776 (1)	69 (2)	247 (8)	12 (0)	1 (3)	1 (1)	4 (1)
C(11)	2499 (3)	−1780 (6)	2586 (1)	69 (2)	265 (8)	14 (0)	−2 (3)	10 (0)	2 (2)
C(12)	2076 (2)	−2187 (5)	2079 (1)	52 (2)	230 (7)	14 (0)	−10 (3)	6 (1)	0 (1)
C(13)	1537 (3)	2792 (5)	2117 (1)	69 (2)	153 (6)	12 (0)	17 (3)	0 (1)	−2 (1)
C(14)	2516 (3)	2926 (5)	2233 (2)	64 (2)	173 (8)	21 (1)	18 (3)	−4 (1)	−7 (2)
C(15)	3056 (4)	3140 (7)	2735 (2)	99 (4)	300 (13)	23 (1)	35 (5)	−19 (2)	−16 (3)
C(16)	2635 (6)	3199 (9)	3110 (3)	155 (6)	376 (16)	17 (1)	62 (8)	−19 (2)	−11 (3)
C(17)	1664 (5)	3032 (8)	2990 (2)	164 (6)	358 (15)	13 (1)	66 (7)	9 (2)	8 (3)
C(18)	1090 (4)	2787 (6)	2488 (1)	106 (3)	217 (14)	13 (1)	22 (4)	10 (1)	4 (2)
C(19)	2983 (3)	2795 (6)	1831 (2)	50 (2)	253 (10)	29 (1)	11 (4)	3 (1)	−9 (3)
C(20)	39 (4)	2554 (7)	2357 (2)	120 (4)	297 (12)	21 (1)	7 (6)	29 (2)	11 (3)
C(21)	376 (2)	3927 (5)	1346 (1)	41 (2)	195 (7)	11 (0)	3 (3)	4 (1)	−4 (2)
C(22)	−40 (2)	3568 (6)	783 (1)	46 (2)	294 (10)	11 (1)	16 (3)	4 (1)	−10 (2)
C(23)	−904 (5)	6401 (6)	464 (2)	160 (6)	234 (10)	20 (1)	3 (6)	−8 (2)	−2 (2)
C(24)	−1613 (5)	7149 (7)	53 (2)	185 (5)	292 (12)	25 (1)	95 (6)	31 (2)	−32 (3)
C(25)	−1693 (3)	3858 (9)	799 (2)	59 (2)	594 (17)	20 (1)	−50 (5)	14 (1)	−32 (3)
C(26)	−1755 (6)	1811 (8)	843 (3)	191 (7)	641 (24)	35 (1)	−210 (11)	38 (2)	−14 (4)

Table 2 (*cont.*)

	x	*y*	*z*
H(C2)	394 (2)	177 (5)	88 (1)
H(C3)	547 (2)	114 (5)	75 (1)
H(C5)	449 (2)	−406 (6)	37 (1)
H(C6)	310 (2)	−359 (5)	59 (1)
H(C8)	403 (2)	−256 (5)	168 (1)
H(C9)	474 (2)	−174 (5)	263 (1)
H(C11)	204 (2)	−166 (5)	281 (1)
H(C12)	140 (2)	−242 (4)	193 (1)
H(C15)	381 (3)	315 (5)	280 (1)
H(C16)	293 (3)	292 (6)	350 (1)
H(C17)	137 (3)	307 (5)	331 (1)
H1(C19)	284 (2)	160 (5)	165 (1)
H2(C19)	259 (2)	340 (5)	154 (1)
H3(C19)	359 (2)	325 (5)	191 (1)
H1(C20)	−19 (3)	160 (5)	211 (1)
H2(C20)	−6 (3)	212 (5)	264 (1)
H3(C20)	−37 (3)	392 (5)	219 (1)
H1(C22)	39 (2)	418 (5)	63 (1)
H2(C22)	−13 (2)	238 (5)	68 (1)
H1(C23)	−96 (3)	696 (5)	76 (2)
H1(C24)	−176 (4)	634 (6)	−27 (2)
H2(C24)	−156 (4)	853 (6)	0 (2)
H1(C25)	−233 (3)	463 (6)	53 (1)
H2(C25)	−154 (3)	446 (7)	117 (2)
H1(C26)	−224 (3)	180 (7)	100 (2)
H(N3)	104 (2)	157 (4)	140 (1)
H(N4)	−117 (2)	387 (4)	24 (1)

final positional and thermal parameters and their estimated standard deviations are given in Table 2.*

A difference Fourier synthesis calculated when the *R* index had been reduced to 0·10 revealed the hydrogen atoms attached to the carbon and nitrogen atoms except for one each on C(23) and C(24) and two on C(26). Positional, but not thermal, parameters for the hydrogen atoms were refined in subsequent cycles. The thermal parameters were set equal to those of the atoms to which the hydrogens are bonded. Anomalous

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30838 (23 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Crystal structures containing either lidocaine or bis-p-nitrophenylphosphate*

(I)	Lidocaine bis-*p*-nitrophenylphosphate	This work
(II)	Lidocaine hydrochloride monohydrate	Hanson & Röhrl (1972)
(III)	Lidocaine hydrohexafluoroarsenate	Hanson (1972)
(IV)	Procaine bis-*p*-nitrophenylphosphate	Sax, Pletcher & Gustaffson (1970)
(V)	Phenacaine bis-*p*-nitrophenylphosphate monohydrate	Sax, Pletcher, Yoo & Stewart (1971)
(VI)	Benzocaine bis-*p*-nitrophenylphosphate	Pletcher, Sax & Yoo (1972)

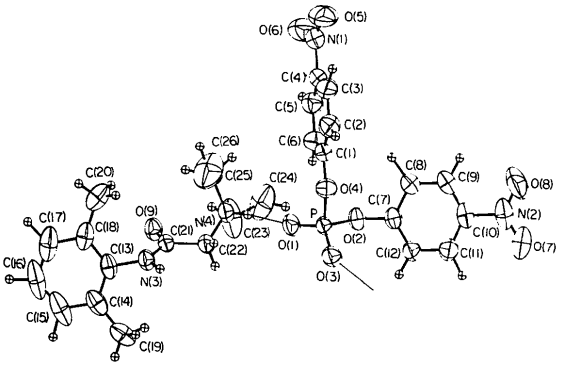


Fig. 1. A thermal-ellipsoid plot (Johnson, 1965) at 50% probability level of lidocaine bis-*p*-nitrophenylphosphate showing the numbering system of the atoms.

Table 4. *Torsion angles* (°)

The sign convention for the torsion angle is that of Klyne & Prelog (1960). The torsion angles in the other enantiomorph are opposite in sign. φ in (*a*) and (*b*) is the torsion angle about the specified bond. The other two atoms required to define the angle are attached to the ends of the bonds and are in the ring in question.

(*a*) Bis-*p*-nitrophenylphosphate (phenyl rings)

Ring *A*		Ring *B*	
Bond	φ	Bond	φ
C(1)–C(2)	0·7	C(7)—C(8)	−0·4
C(2)–C(3)	0·1	C(8)—C(9)	0·3
C(3)–C(4)	−0·8	C(9)—C(10)	0·9
C(4)–C(5)	0·8	C(10)–C(11)	−2·1
C(5)–C(6)	0·1	C(11)–C(12)	2·0
C(1)–C(6)	−0·8	C(12)–C(7)	−0·8

(*b*) Lidocaine (phenyl ring)

Bond	φ
C(13)–C(14)	−2·8
C(14)–C(15)	0·7
C(15)–C(16)	0·5
C(16)–C(17)	0·5
C(17)–C(18)	−2·4
C(18)–C(13)	3·6

(*c*) Extra-ring

	φ		φ
O(4)–C(1)–C(2)—C(3)	179·9	O(8)—N(2)—C(10)–C(9)	10·6
O(4)–C(1)–C(6)—C(5)	−179·9	N(2)—C(10)–C(9)—C(8)	179·0
O(5)–N(1)–C(4)—C(3)	5·7	N(2)—C(10)–C(11)–C(12)	179·9
O(6)–N(1)–C(4)—C(5)	8·1	C(19)–C(14)–C(13)–C(18)	175·6
N(1)–C(4)–C(5)—C(6)	−179·8	C(19)–C(14)–C(15)–C(16)	−177·8
N(1)–C(4)–C(3)—C(2)	179·7	C(19)–C(14)–C(13)–N(3)	−2·9
O(2)–C(7)–C(8)—C(9)	−175·9	C(20)–C(18)–C(13)–C(14)	−177·1
O(2)–C(7)–C(12)–C(11)	174·7	C(20)–C(18)–C(17)–C(16)	178·3
O(7)–N(2)–C(10)–C(11)	8·9	C(20)–C(18)–C(13)–N(3)	1·4

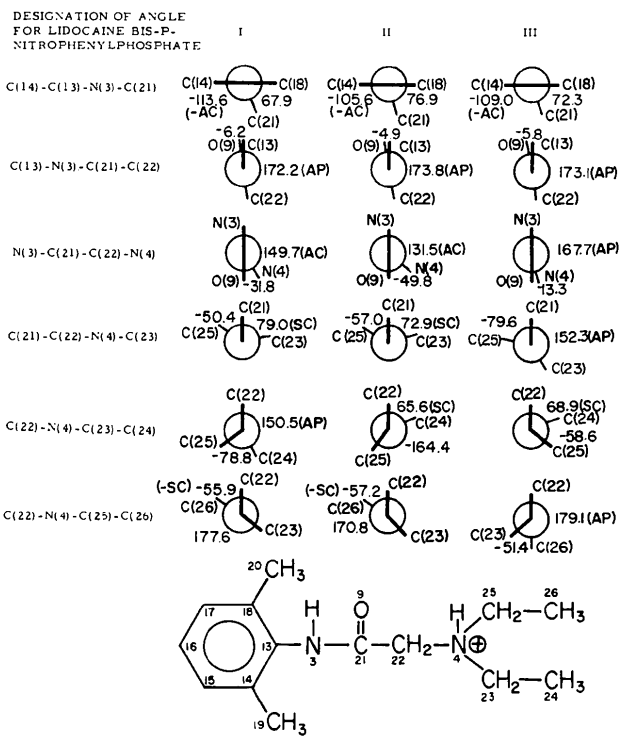


Fig. 2. The conformational details of the lidocaine cation in bis-*p*-nitrophenylphosphate (I), hydrochloride monohydrate (II), and hydrohexafluoroarsenate (III). The original numbering schemes for (II) and (III) are changed to correspond to that of (I).

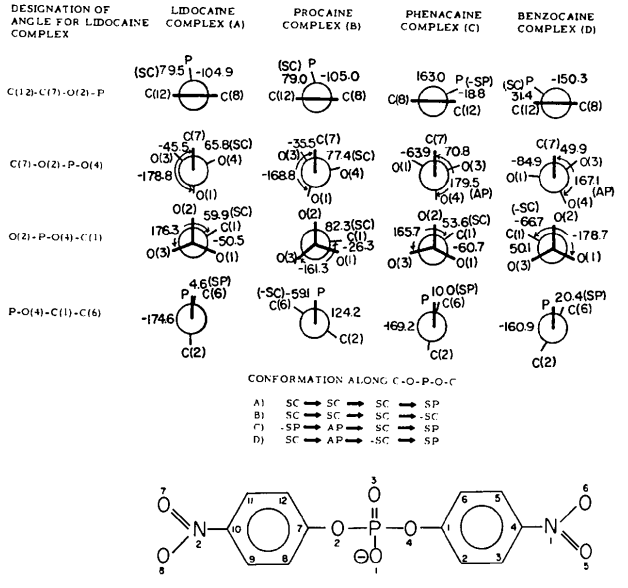


Fig. 3. The conformational details of the BPNP anion complexed with different local anesthetics. The original numbering schemes for (*B*), (*C*), and (*D*) are changed to correspond to that of (*A*).

peaks of maximum amplitude of 0·7 e $Å^{-3}$ appeared in the difference synthesis in the region between the two terminal ethyl groups. These peaks were closely examined at various stages during the refinement since the bond distances for N(4)–C(23) and C(23)–C(24) deviate considerably from expected values. Several disordered models for the terminal ethyl groups were tested, but a reasonable one was not found.

Discussion

The molecules in this complex are in their ionized forms (Fig. 1). The tertiary amine nitrogen atom N(4) in lidocaine is protonated by bis-*p*-nitrophenylphosphoric acid. The interesting features of the crystal structure include the conformation of the ions and the molecular packing scheme. Table 3 gives a list of six crystal structures in which either ion is found. The conformational details of the lidocaine cation in bis-*p*-nitrophenylphosphate (I), hydrochloride monohydrate (II) and hydrohexafluoroarsenate (III) are depicted in the Newman projections in Fig. 2. The qualitative description of the conformation for the lidocaine moiety in (I), viewed down the main chain [*i.e.* along C(13)–N(3)–C(21)–C(22)–N(4)], may be designated $-ac,ap$, ac,sc (Klyne & Prelog, 1960). In the latter two structures, the corresponding conformations are $-ac,ap$, ac,sc and $-ac,ap,ap,ap$, respectively. The values of the torsion angles show that the conformation of the lidocaine ion along the main chain is similar in (I) and (II) but is different in (III). The tertiary amine N(4) is synclinal to the carbonyl oxygen O(9) in both (I) and (II), but is very nearly eclipsed (*sp*) in (III). In the latter structure, the eclipsed conformation is stabilized by an intramolecular hydrogen bond N–H···O (Hanson, 1972), which obviously restricts rotation about two bonds, C(21)–C(22) and C(22)–N(4).

The dissimilarities in the conformations of the terminal ethyl groups for the three structures are most likely due to differences in their modes of packing. The amide groups in (I), (II) and (III) are essentially planar, making angles with the phenyl rings of 64, 71 and 66°, respectively. The phenyl ring of the cation is planar to within 0·02 Å and makes an angle of 9·4° with one of the nitrophenyl rings of the BPNP anion. The amount of distortion in the phenyl ring of the lidocaine ion is shown by the deviations of the torsion angles about C(13)–C(14) and C(13)–C(18) from 0·0° (Table 4). The angles about C(13)–C(14) and C(13)–C(18) are −2·8 and 3·6°, respectively. The deviations are presumably caused by steric interactions between the amide nitrogen N(3) and the methyl groups C(19) and C(20), which are 2·848 and 2·893 Å away from N(3).

In the Newman projections of Fig. 3, a comparison is made of the various conformations assumed by the BPNP anion in complexes with different local anesthetics. It is evident from the torsion angles that the conformation around the P–O ester bonds (*i.e.* along C–O–P–O–C) is similar in lidocaine and procaine

BPNP on the one hand and in benzocaine and phenacaine BPNP on the other hand. Likewise, the dihedral angles between the P–O–C planes in lidocaine and procaine BPNP are 92·8 and 101·1° respectively, which are normal values for *sc,sc* conformations (Shefter, Barlow, Sparks & Trueblood, 1969), while in phenacaine and benzocaine BPNP the respective dihedral angles are 126·5 and 110·0°, values expected for the *ap,sc* case. The nitrophenyl rings are essentially planar with e.s.d.'s from planarity of 0·005 and 0·008 Å. The nitro groups O(5)–N(1)–O(6) and O(7)–N(2)–O(8) are rotated 7·2 and 10·1° out of the planes of their respective phenyl rings.

The bond distances and valency angles with their associated standard deviations, exclusive of those involving C–H bonds, are shown in Fig. 4. The C–H bond distances lie in the interval between 0·84 and 1·08 Å. The e.s.d.'s of the distances range from 0·003 to 0·010 Å for the non-hydrogen atoms, while those for the valency angles range from 0·1 to 0·6°. The high thermal motion of the atoms in the lidocaine cation indicate, however, that the accuracy in these parameters may not be completely reflected in the e.s.d.'s. For instance, significant deviations from normal distances and valency angles are observed in the bonds involving atoms C(23), C(24), C(25) and C(26). All of these atoms have unusually high thermal motion. It is therefore not surprising that the distances C(23)–C(24) and C(25)–C(26) appear shorter than normal single bonds. However, the distance for C(23)–C(24) is much longer than would be expected from the differences in thermal parameters of N(4) and C(23). As discussed in the previous section, positional disorder may be present in the terminal ethyl group and may explain the long C(23)–N(3) distance.

Table 5. *Distances* (Å) *and valency angles* (°) *found for the phosphate of BPNP*

(i) Observed dimensions for (*A*) lidocaine, (*B*) procaine, (*C*) phenacaine and (*D*) benzocaine, $\Delta_1=[(a-b)_{obs}-(a-b)_{pre}]\times 10^3$, $\Delta_2=(\angle_{abc})_{obs}-(\angle_{abc})_{pre}$, $\Delta_{2c}=\Delta_2$–correction.

	a–b–c	$\angle_{abc}$	Δ_2	Δ_{2c}	*a–b*	Δ_1
(*A*)	O(2)–P–O(4)	101·4	1·8	−1·0	1·610	−6
	O(4)–P–O(1)	110·9	1·8	0·4	1·622	6
	O(1)–P–O(3)	121·8	0·6	0·6	1·472	7
	O(3)–P–O(2)	111·7	2·6	1·2	1·474	9
	O(2)–P–O(1)	104·3	−4·8	−0·7		
	O(4)–P–O(3)	104·9	−4·2	−0·1		
(*B*)	O(2)–P–O(3)	103·3	3·1	0·3	1·462	2
	O(3)–P–O(4)	110·8	1·0	−0·4	1·484	2
	O(4)–P–O(5)	123·3	3·1	3·1	1·603	−9
	O(5)–P–O(2)	109·5	1·1	−0·3	1·616	4
	O(2)–P–O(4)	105·9	−3·9	0·2		
	O(3)–P–O(5)	102·4	−6·0	−1·9		
(*C*)	O(4)–P–O(2)	97·2	−3·0	−0·3	1·472	12
	O(2)–P–O(1)	109·3	−0·5	−1·9	1·472	−10
	O(1)–P–O(3)	121·3	1·1	1·1	1·626	14
	O(3)–P–O(4)	105·1	−3·3	0·7	1·604	−8
	O(4)–P–O(1)	112·1	2·3	0·9		
	O(2)–P–O(3)	109·2	0·8	−0·6		
(*D*)	O(1)–P–O(3)	97·8	−2·4	0·3	1·459	−1
	O(3)–P–O(4)	111·3	1·5	0·1	1·490	8
	O(4)–P–O(2)	120·1	−0·1	−0·1	1·610	−2
	O(2)–P–O(1)	104·2	−4·2	−0·1	1·613	1
	O(1)–P–O(4)	111·9	2·1	0·7		
	O(3)–P–O(2)	109·1	0·7	−0·7		

Table 5 of valency angles for the phosphate group using the empirical equations suggested by Baur (1974). These equations are based upon a correlation between the P–O distances and the bond strengths received by the individual oxygen atoms and between the valency angle and the expected mean bond length of the two sides of the angle. The equations, however, do not take into account non-bonding interactions.

In Table 5, the discrepancies, Δ_1 and Δ_2, between the predicted and observed bond lengths and valency angles, respectively, are given following each observation. For his data base, Baur found these discrepancies to average, respectively, 0·010 Å and 1·5°. The agreement for the P–O bond lengths in these salts is satisfactory, the average Δ_1 being 0·007 Å. For each of these salts there are larger discrepancies than expected among the angles, the overall average Δ_2 being 2·3°. A correlation between conformation and bond-angle distortion has been proposed (Wood, Sax & Pletcher, 1975) such that the O–P–O angles of a substituted oxygen will be decreased with respect to oxygens *anti* to the substituent and increased with respect to oxygens *syn* to the substituent. A reasonable assumption is that steric repulsions (neglected in Baur's correlations) produce the effects. Using the limited amount of data available here, we estimate that the *anti* effect is approximately −4·1°, while the *syn* effect is approximately 1·4°. Incorporating these values into the predictions for these salts results in an average Δ_{2c} of 0·7°, a threefold improvement. These empirical values for the *cis* and *trans* effects should be generally valid for

Table 5 (*cont.*)

(ii) Dimensions predicted by Baur (1974) for phsophate having the configuration (*A*) found for BPNP in salts with procaine, phenacaine and benzocaine and (*B*) for lidocaine. The coordination of each oxygen is given in parentheses; '*C*' signifies an ester and '*H*' signifies a hydrogen bond. The oxygen atoms in (i) and (ii) are ordered identically with respect to the oxygen configuration.

(*A*)			(*B*)		
a–b–c	$\angle_{abc}$	*a–b*	*a–b–c*	$\angle_{abc}$	*a–b*
O(C)—P–O′(C)	100·2	1·612	O(C)—P–O′(C)	99·6	1·616
O′(C) –P–O(1H)	109·8	1·612	O′(C)—P–O(1H)	109·1	1·616
O(1H)–P–O(2H)	120·2	1·460	O(1H)–P–O′(1H)	121·2	1·465
O(2H)–P–O(C)	108·4	1·482	O′(1H)–P–O(C)	109·1	1·465
O(C)—P–O(1H)	109·8		C(C)—P–O(1H)	109·1	
O′(C) –P–O(2H)	108·4		O′(C)—P–O′(1H)	109·1	

phosphate esters and anhydrides although the estimation of their magnitudes should be improved by considering a larger number of structures.

The molecular-packing arrangement in this structure is influenced mainly by ionic interaction between the positively charged trialkylammonium group of the cation and the negatively charged phosphate group of BPNP, strong N–H···O hydrogen bonds, and non-polar interactions between the phenyl rings. Fig. 5

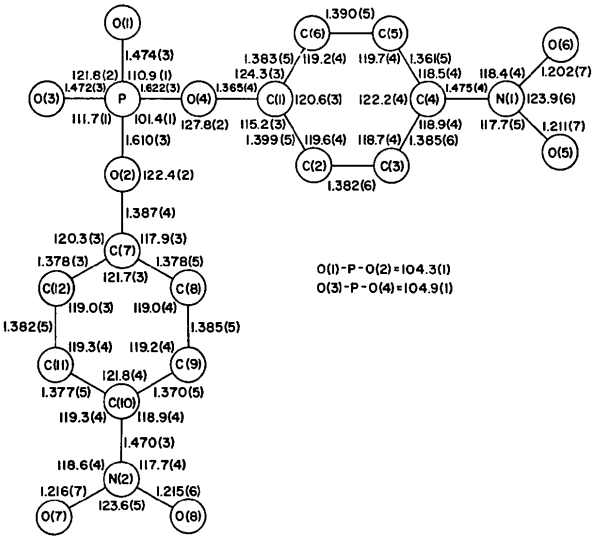


Fig. 4. The bond distances (Å) and valency angles (°) with their associated standard deviations. (*a*) BPNP, (*b*) lidocaine.

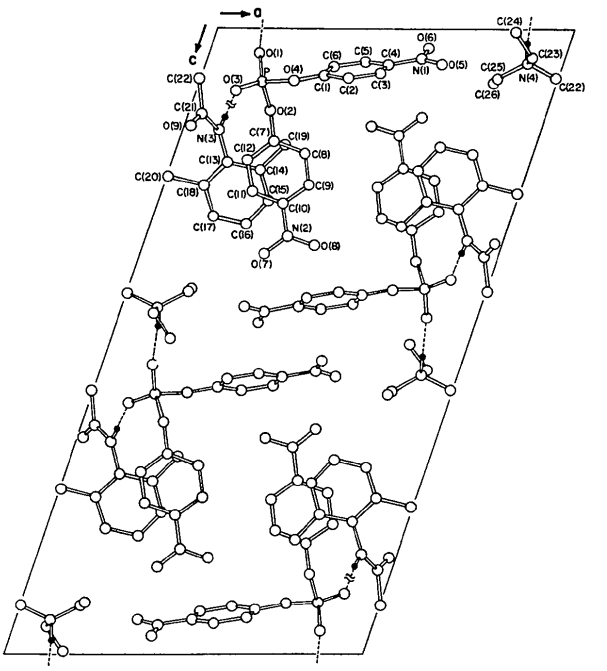


Fig. 5. Projection of one unit cell along the *b* axis. Hydrogen bonding is shown by dotted lines.

shows the contents of the unit cell projected down the *b* axis. As in structures (V) and (VI), there is considerable non-polar interaction between phenyl rings of the local anesthetic and the anion. The phenyl ring of the lidocaine ion lies between two nitrophenyl rings related to each other by translational symmetry along the *b* axis. The distances from these nitrophenyl rings to the phenyl ring of the cation average 3·552 and 3·643 Å,* with the nitrophenyl rings tilted about 9° relative to the phenyl ring of the cation. The other nitrophenyl ring of BPNP is partially overlapped by its symmetry-related counterpart, the ring across the inversion center

* The average distance is calculated by averaging over the distance of each atom from the least-squares plane defined for the phenyl ring of the cation.

Table 6. *Intermolecular distances and non-bonded contacts*

(*a*) Hydrogen bonds

i	*j*	*k*	*d*(*ij*)	*d*(*ik*)	*d*(*jk*)	∠(*ijk*)	∠(*jik*)
N(4)–H(N4)···O(1*a*)			0·87 Å	2·690 Å	1·82 Å	174°	4°
N(3)–H(N3)···O(3)			0·96	2·801	1·85	176	3

(*b*) Non-bonded contacts

O(1)–C(22*a*)	3·269 Å	C(12)–O(9*c*)	3·286 Å
O(3)–C(22)	3·276	O(5)—C(26*d*)	3·086
C(5)–O(6*b*)	3·212		

Symmetry code

None	x, y, z	*c*	$x, y-1, z$
a	$\bar{x}, \bar{y}, \bar{z}$	*d*	$1+x, y, z$
b	$\bar{x}, \bar{y}-1, \bar{z}$		

at $\frac{1}{2},\frac{1}{2},\frac{1}{2}$. The latter do not overlap to as large an extent as do the phenyl rings of lidocaine and BPNP. Besides the ring stacking, a close contact is observed between one of the terminal ethyl groups of lidocaine and a nitro group. Table 6 lists all of the intermolecular close contacts.

Figs. 5 and 6 show the hydrogen bonding between the lidocaine ion and the BPNP anion. Both the amide N(3) and the amino N(4) nitrogens are hydrogen bonded to the phosphoryl oxygens (Table 6).

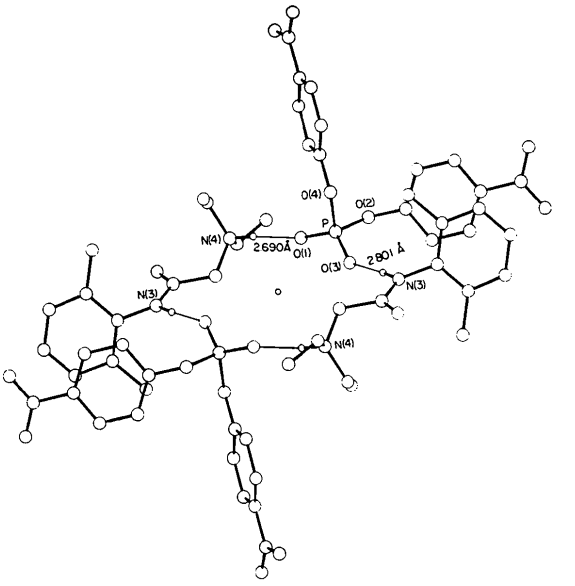


Fig. 6. Hydrogen bonding between the lidocaine cation and the BPNP anion.

References

BAUR, W. (1974). *Acta Cryst.* **B30**, 1185–1215.

CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* **18**, 104–109.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368–376.

HANSON, A. W. (1972). *Acta Cryst.* **B28**, 672–679.

HANSON, A. W. & RÖHRL, M. (1972). *Acta Cryst.* **B28**, 3567–3571.

HUGHES, E. W. (1941). *J. Amer. Chem. Soc.* **63**, 1737–1752.

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

KLYNE, W. & PRELOG, V. (1960). *Experientia* **16**, 521–523.

Picker FACS-1 Disk Operating System (1972). Picker Corporation, Cleveland, Ohio.

PLETCHER, J., SAX, M. & YOO, C. S. (1972). *Acta Cryst.* **B28**, 378–387.

SAX, M., PLETCHER, J. & GUSTAFFSON, B. (1970). *Acta Cryst.* **B26**, 114–124.

SAX, M., PLETCHER, J., YOO, C. S. & STEWART, J. M. (1971). *Acta Cryst.* **B27**, 1635–1644.

SHEFTER, E., BARLOW, M., SPARKS, R. A. & TRUEBLOOD, K. N. (1969). *Acta Cryst.* **B25**, 895–909.

SHIONO, R. (1971*a*). *Crystallographic Computing Programs for the IBM* 1130 *System*. Tech. Rep. No. 49, Department of Crystallography, Univ. of Pittsburgh, Pittsburgh, Pa.

SHIONO, R. (1971*b*). *Crystallographic Computing Programs for the IBM* 7090 *System*. Tech. Rep. No. 48, Department of Crystallography, Univ. of Pittsburgh, Pittsburgh, Pa.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

WOOD, M. K. (1973). *RESIG, Weighting Scheme Program*. Biocrystallography Laboratory, V. A. Hospital, Pittsburgh, Pa.

WOOD, M. K., SAX, M. & PLETCHER, J. (1975). *Acta Cryst.* **B31**, 76–85.