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The Crystal Structure of 4-Carbethoxyanilinium Bis-*p*-nitrophenylphosphate

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The crystal structure of a 1:1 complex between 4-aminobenzoic acid ethyl ester and bis-*p*-nitrophenylphosphate has been determined. Crystals are orthorhombic, $Pna2_1$, $a=12\cdot273$ (4), $b=27\cdot357$ (4), $c=7\cdot114$ (4) Å, $Z=4$. The intensities of 2221 reflections were measured with a four-circle automated diffractometer using Cu $K\alpha$ radiation. The structure was refined to an R of 0·049 over all the reflections. In the complex the 4-amino group is protonated. All three of the amino hydrogen atoms participate in hydrogen bonds to the phosphate group with N---O distances of 2·754, 2·780, and 2·838 Å. The bis-*p*-nitrophenylphosphate ion, which is also found in crystalline complexes with phenacaine and procaine, has a CO–P–OC valency angle of 97·8°. This structural feature, along with the torsion angles about the phosphate ester bonds, shows greater similarity to that in the phenacaine complex. The molecular packing indicates that the nonpolar interactions between the components of the complex are more extensive than was observed in the procaine complex. This aspect was also apparent in the structure of the phenacaine complex, although not to the same extent as in the present structure.

Introduction

On the basis of studies with model systems (Feinstein, 1964; Feinstein & Paimre, 1966), Feinstein and Paimre suggested that local anesthetics block nerve conduction by complexing with phospholipids in the neural membrane. Their studies demonstrated that the local anesthetics would precipitate phospholipids or phosphodiester compounds in general. In fact, the reaction with a simple phosphodiester, bis-*p*-nitrophenylphosphate, resulted in the precipitation of a crystalline complex. To examine the nature of this interaction, we determined the crystal structures of several of these complexes (Sax, Pletcher & Gustaffson, 1970; Sax, Pletcher, Yoo & Stewart, 1971). The results of these structure analyses, along with other experimental observations, led to the suggestion that the hydrogen-bond donor capability of local anesthetics was an important aspect in the anesthetics' mode of action (Sax & Pletcher, 1969). In exploring this idea further, we attempted to prepare a complex with a neutral, nonionizable local anesthetic. Benzocaine, which is 4-aminobenzoic acid ethyl ester, was selected for this purpose as it is normally regarded as a neutral, nonionizable drug. Contrary to expectation that the benzocaine complex with bis-*p*-nitrophenylphosphoric acid would exist in the uncharged or neutral form, crystal-structure analysis shows that the complex crystallizes in the ionized form.

Experimental

Crystals of the complex were prepared by mixing equimolar solutions of bis-*p*-nitrophenylphosphoric acid* and benzocaine† in absolute methanol. White needle-shaped crystals of the complex were obtained

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* In partial fulfillment of the requirement for the Ph.D. degree.

* Aldrich Chemical Company.
† Eastman Organic Chemicals.

by slowly evaporating the mixture at room temperature. The crystal data for the compound are summarized in Table 1. Systematic absences are consistent with both space groups $Pna2_1$ and $Pnam$. The latter of these two possible space groups was eliminated on the basis of structural considerations and the requirement that the unit cell must contain four molecules of the complex as indicated by the density. The centric space group $Pnam$ requires the molecular complex to be located on a mirror plane. The molecular conformations imposed by this restriction seemed highly improbable. The solution of the structure confirmed the choice of space group $Pna2_1$.

Table 1. *Crystal data*

4-Carbethoxyanilinium bis-*p*-nitrophenylphosphate

$(C_9H_{12}O_2N)^+.(C_{12}H_8O_8N_2P)^-$		M.W. 505·38
a = 12·273 (4) Å	measured at 24 °C.	$\lambda_{Cu\ K\alpha}$ = 1·5418 Å
b = 27·357 (4)		α_1 = 1·5405
c = 7·114 (4)		α_2 = 1·5443
V = 2388·5 Å		Z = 4
ϱ_o = 1·403 g.cm^{-3} by flotation in benzene-CCl_4 at 19 °C		
ϱ_c = 1·405 g.cm^{-3}		
$\mu_{Cu\ K\alpha}$ = 15·6 cm^{-1}		$F(000)$ = 1048

m.p. 138–140 °C (unc.) measured on a Thermolyne m.p. Block.
Space group:
$Pna2_1$ from systematic absences $0kl$ for $k+l=2n+1$,
$h0l$ for $h=2n+1$.

A crystal, 0·08 by 0·10 mm in cross section and 0·72 mm long, was mounted on a Picker four-circle automated diffractometer with its c axis parallel to φ. Since freshly prepared crystals tended to be unstable when exposed to the atmosphere, the crystal was spray-coated with Krylon after it was mounted on a glass fiber. The intensity data were collected using $\theta/2\theta$ scans over a range of 2° in 2θ at a scan rate of 2° min^{-1}, with Ni-filtered Cu $K\alpha$ radiation and a thallium-activated sodium iodide scintillation detector. Background was counted for 15 sec at both limits of the scan range. Five reflections were chosen as standards. At least two of these were monitored at approximately two-hour intervals, and all five were measured at least once every 12 hours. During the data collection, the intensities of the standard reflections gradually decreased by an average of 5%. Scale factors, based on the variation of the standard reflections, were applied to the intensity data to compensate for this time-dependent decrease. The intensities of 2221 reflections, with $\sin\theta \leq 0·906$, were measured of which 269 were less than $3\sigma(I)$, where $\sigma(I)$ is given by $[I_o + 4(I_{B1}+I_{B2})]^{1/2}$; I_o is the total number of counts accumulated during the scan, and I_{B1} and I_{B2} are the accumulated background counts. Intensities were corrected in the usual manner by Lorentz and polarization factors, but they were not corrected for absorption.

Structure determination and refinement

After the structure amplitudes were scaled and normalized to E values by means of a Wilson plot, a three-dimensional, sharpened, origin-removed Patterson function was synthesized with (E^2-1) as coefficients, using the 1952 observed reflections. On the Harker section, $P(uv\frac{1}{2})$, a set of peaks attributed to phosphorus–phosphorus interactions was consistent with the location of a phosphorus atom at $x=0·695$ and $y=0·543$. In $Pna2_1$ the origin is not fixed along the c axis direction; therefore, the fractional z parameter for phosphorus was arbitrarily assigned a value of 0·3. Based on these trial parameters, the phases of 415 strong reflections were calculated, and these reflections were used to compute an electron-density Fourier synthesis. The resulting map contained plausible positions for the oxygen atoms in the phosphate group. A structure-factor calculation, based only on the phosphate group, gave an R value of 0·51 for 2221 reflections. A three-dimensional Fourier synthesis computed with these phases contained 14 additional peaks, with heights nearly equal to those expected for carbon, nitrogen, and oxygen atoms in bis-*p*-nitrophenylphosphate. The remaining 16 atoms, exclusive of the hydrogen atoms were located by an iterative routine, one cycle con-

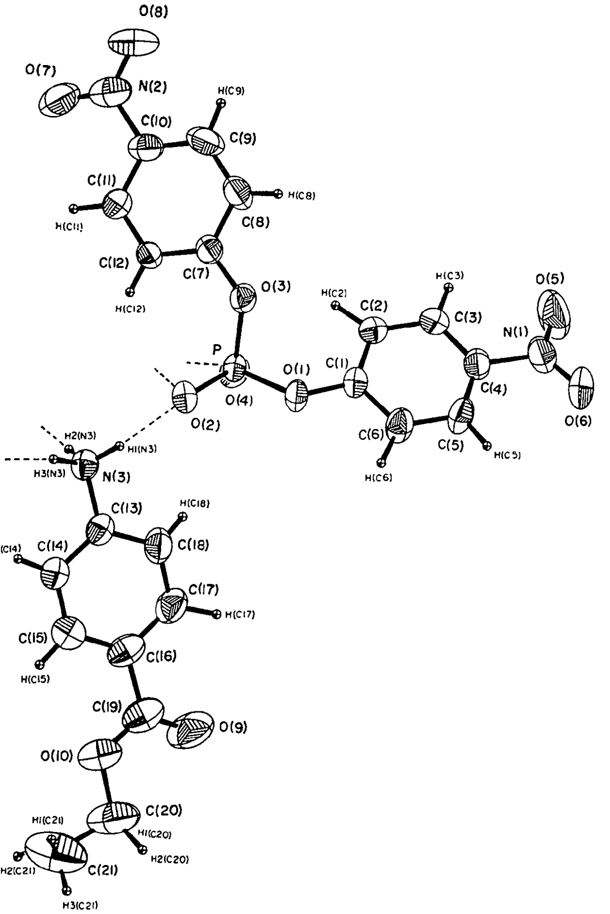

Fig. 1. A thermal-ellipsoid plot (Johnson, 1965) at 50% probability level of benzocaine bis-*p*-nitrophenylphosphate showing the numbering system of the atoms.

sisting of a difference Fourier synthesis followed by isotropic block-diagonal least-squares refinement. Parameters of the 35 atoms were then refined anisotropically by the full-matrix least-squares method. However, not more than 181 parameters were varied in any given cycle. The Hughes (1941) weighting scheme was employed, with $\sigma = F/3{\cdot}4$ for $F > 3{\cdot}4$, $\sigma = 1$ for $F \leq 3{\cdot}4$, and zero weight for unobserved reflections. The function minimized was $\sum w(|F_o| - K|F_c|)^2$ where K is a single scale factor. Atomic form factors for P, O, N,

Table 2. *Observed and calculated structure factors for* 4-*carbethoxyanilinium bis-p-nitrophenylphosphate*

Columns are: index, $|10F_{\text{obs}}|$, $|10F_{\text{calc}}|$. Asterisks indicate unobserved reflections.

[illegible]

Table 3. *Atomic parameters and their e.s.d.'s.*

	Fractional coordinates × 10^4			Thermal parameters × 10^4 in the form: exp $[-(h^2\beta_{11}+\cdots 2kl\beta_{23})]$					
	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	6958 (1)	5450 (< 1)	3004	34 (< 1)	11 (< 1)	131 (2)	1(< 1)	−1(< 1)	−3(< 1)
O(1)	8093 (2)	5264 (1)	3886 (4)	34 (2)	14 (< 1)	172 (6)	0 (1)	0 (2)	12 (1)
O(2)	6111 (2)	5188 (1)	4117 (4)	41 (2)	14 (< 1)	189 (6)	−3 (1)	3 (3)	−1 (1)
O(3)	7023 (2)	6010 (1)	3708 (4)	45 (2)	11 (< 1)	193 (6)	0 (1)	−8 (3)	−10 (1)
O(4)	6956 (2)	5420 (1)	0956 (4)	56 (2)	14 (< 1)	139 (5)	5 (1)	−8 (3)	−3 (1)
C(1)	9125 (3)	5405 (1)	3371 (5)	39 (2)	12 (< 1)	135 (8)	0 (1)	−1 (3)	−2 (1)
C(2)	9369 (3)	5832 (1)	2411 (6)	53 (2)	10 (< 1)	195 (9)	1 (1)	4 (4)	3 (2)
C(3)	10436 (3)	5939 (1)	2005 (8)	58 (2)	10 (< 1)	264 (10)	−2 (1)	9 (5)	−1 (2)
C(4)	11247 (3)	5623 (1)	2577 (6)	45 (2)	13 (1)	201 (10)	−2 (1)	4 (4)	−8 (2)
C(5)	11030 (3)	5204 (2)	3546 (7)	41 (2)	18 (1)	200 (9)	6 (1)	−4 (4)	13 (2)
C(6)	9960 (3)	5089 (2)	3917 (7)	50 (2)	17 (1)	212 (10)	3 (1)	−1 (4)	24 (2)
N(1)	12372 (3)	5734 (1)	2069 (7)	55 (2)	17 (1)	315 (10)	−7 (1)	7 (5)	−8 (2)
O(5)	12527 (3)	6059 (2)	0899 (8)	73 (3)	31 (1)	521 (15)	−15 (1)	17 (6)	60 (3)
O(6)	13104 (2)	5492 (1)	2795 (7)	40 (2)	24 (1)	390 (12)	−1 (1)	−17 (4)	1 (2)
C(7)	6355 (3)	6378 (1)	3062 (6)	49 (2)	11 (< 1)	167 (8)	−1 (1)	17 (4)	−10 (2)
C(8)	6792 (3)	6846 (1)	3054 (8)	60 (3)	14 (1)	279 (11)	−9 (1)	7 (5)	−9 (3)
C(9)	6148 (4)	7234 (1)	2517 (8)	98 (4)	10 (1)	325 (15)	−8 (1)	26 (6)	−4 (2)
C(10)	5101 (3)	7151 (1)	1949 (7)	83 (3)	9 (< 1)	215 (9)	2 (1)	31 (5)	0 (2)
C(11)	4662 (3)	6684 (1)	1926 (7)	56 (2)	12 (< 1)	211 (9)	2 (1)	12 (5)	−3 (2)
C(12)	5299 (3)	6298 (1)	2494 (6)	45 (2)	9 (< 1)	199 (9)	−3 (1)	15 (4)	−5 (2)
N(2)	4401 (3)	7563 (1)	1346 (7)	118 (4)	12 (1)	267 (11)	6 (1)	39 (5)	3 (2)
O(7)	3513 (3)	7469 (1)	0612 (7)	104 (3)	15 (< 1)	369 (12)	15 (1)	14 (5)	7 (2)
O(8)	4750 (4)	7970 (1)	1599 (8)	171 (5)	9 (< 1)	475 (16)	3 (1)	−1 (7)	7 (2)
N(3)	4422 (2)	4589 (1)	2902 (6)	48 (2)	13 (< 1)	157 (6)	0 (1)	−3 (4)	−4 (2)
C(13)	4777 (3)	4083 (1)	2612 (5)	53 (2)	13 (< 1)	142 (8)	3 (1)	−8 (3)	−4 (2)
C(14)	4033 (3)	3711 (1)	2788 (7)	53 (2)	14 (1)	181 (9)	1 (1)	3 (4)	−1 (2)
C(15)	4354 (3)	3241 (2)	2436 (6)	78 (3)	14 (1)	183 (9)	−2 (1)	−1 (4)	1 (2)
C(16)	5395 (4)	3135 (1)	1898 (7)	90 (3)	15 (1)	178 (8)	10 (1)	0 (5)	−3 (2)
C(17)	6147 (4)	3518 (2)	1715 (7)	64 (3)	17 (1)	255 (11)	7 (1)	25 (5)	−9 (2)
C(18)	5831 (3)	3989 (2)	2072 (7)	51 (3)	17 (1)	256 (11)	0 (1)	10 (5)	−7 (2)
C(19)	5785 (4)	2631 (2)	1455 (7)	111 (4)	16 (1)	239 (12)	13 (2)	9 (6)	−6 (2)
O(9)	6646 (4)	2540 (1)	0732 (8)	141 (4)	19 (1)	453 (15)	18 (1)	87 (7)	−13 (3)
O(10)	5063 (3)	2294 (1)	1927 (7)	125 (3)	13 (< 1)	313 (9)	9 (1)	6 (5)	−3 (2)
C(20)	5384 (8)	1793 (2)	1574 (15)	183 (8)	15 (1)	457 (28)	12 (2)	48 (12)	−2 (4)
C(21)	4409 (11)	1486 (3)	1817 (17)	261 (13)	22 (1)	395 (25)	−15 (3)	37 (16)	−11 (5)

Table 3 (*cont.*)

	Fractional coordinates × 10^3		
	x	y	z
H(C2)	867 (3)	601 (1)	176 (6)
H(C3)	1064 (3)	622 (1)	103 (7)
H(C5)	1153 (3)	498 (2)	411 (7)
H(C6)	969 (3)	478 (2)	447 (7)
H(C8)	750 (3)	686 (2)	362 (7)
H(C9)	637 (3)	754 (1)	254 (8)
H(C11)	390 (3)	662 (1)	165 (7)
H(C12)	500 (3)	599 (1)	252 (6)
H1(N3)	502 (3)	476 (1)	332 (7)
H2(N3)	412 (3)	470 (1)	170 (7)
H3(N3)	386 (3)	461 (1)	419 (6)
H(C14)	336 (3)	380 (1)	318 (7)
H(C15)	388 (3)	297 (2)	260 (7)
H(C17)	696 (3)	348 (2)	153 (7)
H(C18)	623 (3)	423 (2)	223 (8)
H1(C20)	562 (6)	174 (3)	001 (13)
H2(C20)	594 (6)	155 (2)	259 (13)
H1(C21)	431 (8)	159 (3)	295 (13)
H2(C21)	373 (8)	143 (3)	102 (13)
H3(C21)	465 (8)	118 (3)	187 (13)

and C were taken from *International Tables for X-ray Crystallography* (1962) and hydrogen scattering factors were those of Stewart, Davidson & Simpson (1965). The hydrogen coordinates were obtained from a difference synthesis when the *R* value had been reduced to 0·10. These were included as variables in 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. The refinement converged to a conventional *R* index of 0·049 for all the reflections and 0·040 for the 1952 observed reflections. The final structure factors are listed in Table 2. The atomic coordinates, thermal factors, and their estimated standard deviations are listed in Table 3. The thermal-ellipsoid representation of the molecular components, with the assigned atomic numbering scheme, is shown in Fig. 1.

The computer programs used in this analysis are the Shiono (1965) version of *ORFLS* (Busing, Martin & Levy, 1962), a modification of the Zalkin Fourier Synthesis (Shiono, 1967), the *ORTEP* program (Johnson, 1965), and a number of programs of Shiono *et al.* (1963–8).

Discussion

Intramolecular bond distances and angles with their associated e.s.d.'s, are listed in Table 4. It is apparent from Fig. 1 that molecules in the complex are in their ionized forms as a result of the amino group of benzocaine having been protonated by the bis-*p*-nitrophenylphosphoric acid. Since the anesthetic molecule is also ionized in this structure, it is not possible to examine the hydrogen-bonding interactions in the absence of the ionic charges, which was the original purpose for investigating the structure. However, several features are of interest when they are compared with features of the other anesthetic complexes.

Table 4. *Bond lengths and angles for* 4-*carbethoxyanilinium bis-p-nitrophenylphosphate and their e.s.d.'s.*

i j k	D_{ij}	Angle (*ijk*)	*i j k*	D_{ij}	Angle(*ik*)
O(1)—P——O(2)	1·610 (3) Å	104·2 (2)°	C(12)–C(7)—O(3)	1·374 (5) Å	122·8 (3)°
O(2)—P——O(3)	1·490 (3)	109·1 (2)	C(8)—C(7)—C(12)	1·388 (5)	120·7 (3)
O(3)—P——O(1)	1·613 (3)	97·8 (1)	C(7)—C(8)—C(9)		119·3 (4)
O(4)—P——O(1)	1·459 (3)	111·9 (2)	C(8)—C(9)—C(10)	1·377 (6)	119·6 (4)
O(2)—P——O(4)		120·1 (2)	C(9)—C(10)–C(11)	1·366 (6)	121·6 (4)
O(3)—P——O(4)		111·3 (2)	C(10)–C(11)–C(12)	1·384 (5)	118·9 (3)
P——O(1)—C(1)		127·3 (2)	C(11)–C(12)–C(7)	1·376 (5)	119·9 (3)
O(1)—C(1)—C(2)	1·372 (4)	124·6 (3)	N(3)—C(13)–C(14)	1·464 (5)	119·3 (3)
C(6)—C(1)—O(1)	1·394 (6)	115·5 (3)	C(18)–C(13)–N(3)	1·373 (6)	119·8 (3)
C(2)—C(1)—C(6)	1·387 (5)	120·0 (3)	C(14)–C(13)–C(18)	1·374 (5)	120·8 (3)
C(1)—C(2)—C(3)		119·3 (3)	C(13)–C(14)–C(15)		119·3 (4)
C(2)—C(3)—C(4)	1·371 (5)	119·6 (4)	C(14)–C(15)–C(16)	1·367 (6)	121·3 (4)
C(3)—C(4)—C(5)	1·379 (5)	122·3 (4)	C(15)–C(16)–C(17)	1·364 (6)	119·1 (4)
C(4)—C(5)—C(6)	1·366 (6)	118·3 (4)	C(16)–C(17)–C(18)	1·400 (7)	120·0 (5)
C(5)—C(6)—C(1)	1·375 (7)	120·6 (4)	C(17)–C(18)–C(13)	1·370 (7)	119·6 (4)
N(1)—C(4)—C(3)	1·458 (5)	118·7 (3)	C(15)–C(16)–C(19)		123·6 (4)
N(1)—C(4)—C(5)		119·0 (4)	C(17)–C(16)–C(19)		117·3 (4)
C(4)—N(1)—O(5)		117·6 (4)	C(16)–C(19)–O(9)	1·495 (7)	124·2 (5)
O(6)—N(1)—C(4)	1·229 (5)	118·4 (4)	C(16)–C(19)–O(10)		112·1 (4)
O(5)—N(1)—O(6)	1·232 (6)	124·0 (4)	O(9)—C(19)–O(10)	1·201 (7)	123·7 (5)
C(7)—O(3)—P	1·378 (4)	124·1 (2)	C(19)–O(10)–C(20)	1·322 (6)	115·7 (5)
O(3)—C(7)—C(8)		116·4 (3)	O(10)–C(20)–C(21)	1·447 (9)	107·3 (7)
N(2)—C(10)–C(9)	1·481 (5)	120·3 (4)	O(8)—N(2)—C(10)	1·206 (6)	117·0 (4)
C(11)–C(10)–N(2)		118·2 (3)	O(7)—N(2)—O(8)		124·5 (4)
O(7)—N(2)—C(10)	1·236 (5)	118·4 (4)	C(20)–C(21)	1·471 (4)	

Bond lengths involving H atoms. $X-H \equiv H(X)$ Å

H(*X*)	*D*	H(*X*)	*D*	H(*X*)	*D*	H(*X*)	*D*
H(C2)	1·09 (4) Å	H(C9)	0·89 (4) Å	H3(N3)	1·15 (4) Å	H1(C20)	1·16 (8) Å
H(C3)	1·06 (4)	H(C11)	0·97 (4)	H(C14)	0·91 (4)	H2(C20)	1·19 (7)
H(C5)	0·96 (5)	H(C12)	0·91 (4)	H(C15)	0·94 (5)	H1(C21)	0·86 (9)
H(C6)	0·99 (5)	H1(N3)	0·92 (4)	H(C17)	1·02 (5)	H2(C21)	1·02 (9)
H(C8)	0·96 (5)	H2(N3)	0·98 (4)	H(C18)	0·84 (5)	H3(C21)	0·89 (9)

Table 5. *Some least-squares planes through groups of atoms in the benzocaine molecule and for the phenyl rings of the phosphodiester*

Coefficient × 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 in benzocaine	1	2607	−1106	9591	20730
Carboxyl group + C(16), C(20), C(21)	2	3749	−938	9223	29410
Benzene ring C(1) to C(6)	3	733	4915	8678	101680
Benzene ring C(7) to C(12)	4	−3119	1232	9421	17646

Plane no.	Displacement from the plane (Å × 10^3)
1	C(13) 2, C(14) −3, C(15) 2, C(16) 0, C(17) −1, C(18) 0, N(3) −66, C(19) −26, O(9) −216, O(10) 168, C(20) 181, C(21) 128, H1(N3) 360, H2(N3) −1019, H3(N3) 625, H1(C20) −796, H2(C20) 1122, H1(C21) 840, H2(C21) −618, H3(C21) 337.
2	C(19) 0, O(9) −55, O(10) 65, C(16) −18, C(20) 109, C(21) −101, H1(C20) −795, H2(C20) 1091, H1(C21) 572, H2(C21) −925, H3(C21) 126.
3	C(1) 2, C(2) 6, C(3) −5, C(4) −3, C(5) 11, C(6) −10, N(1) −67, O(5) −338, O(6) 122.
4	C(7) 5, C(8) −10, C(9) 7, C(10) 0, C(11) −5, C(12) 2, N(2) 3, O(7) −181, O(8) 176.

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

Benzocaine is structurally related to procaine in that both compounds are esters of *p*-aminobenzoic acid. The former is simply the ethyl ester, while the latter is the *N,N*-diethylaminoethyl ester. Although common features in the complexes of these anesthetics are generally similar, several significant differences do exist. For example, in the procaine complex (Sax *et al.*, 1970) the *p*-aminobenzoate group, plus the first two carbon atoms of the diethylaminoethyl group, all practically lie in a common plane. In the present structure the atoms of the ethyl carboxylate group exhibit greater deviations from the plane of the benzene ring as shown by the least-squares planes calculations in Table 5. The decreased planarity of the ring substituents in benzocaine is the result of small conformational variations in the side chain. For example, the carboxyl group is rotated about the C(19)–C(16) bond by 9·4° as compared with 2·5° for procaine. Another conformational variation involves the torsion angle about the carboxylate ester bond, which is expressed in terms of the right-hand rule of Klyne & Prelog (1960) for the sequence C(19), O(10), C(20), C(21) as −168·6°. The corresponding value for procaine is 178·8°. For both compounds this conformation is qualitatively described as *antiperiplanar*. These quantitative variations in conformation most likely result from the different mode of packing in the two structures.

The differences that are observed in the bond lengths of the *p*-aminobenzoate group (Table 6) result from the protonation of the amino substituent in the benzocaine molecule. In procaine the trialkylamino group in the ester side chain is much more basic than the amino substituent on the ring; hence it is protonated first, leaving the *p*-amino group unprotonated. In procaine the *p*-aminobenzoate moiety exhibits the quinoidal character which results from resonance contribution by the conjugated amino group. The NH_3^+ as found in the benzocaine structure cannot be conjugated with the aromatic ring. The observed N(3)–C(13) distance of 1·464 Å, the C(16)–C(19) distance of 1·495 Å, and the nearly equal bond lengths within the benzene ring are consistent with expected values. In the structure of *o*-aminophenol hydrochloride (Cesur & Richards, 1965), the C–NH_3^+ bond was found to be 1·474 (9) Å and in *p*-phenylenediamine dihydrochloride (Chandrasekaran, 1969) a value of 1·490 (13) Å was observed for this bond. The remaining distances and angles in the ethyl ester group are all normal except for C(20)–C(21) which is considerably shorter than normal. The reason for this apparently short distance is not clear, although it is most probably the result of the larger thermal motion for these atoms. The final difference Fourier synthesis does not give any indications of positional disorder associated with C(21).

In the crystal structures of three anesthetic complexes the anionic component of the complex has always been the same, namely, bis-*p*-nitrophenylphosphate. Because of the differences in modes of interaction with the anesthetics, it is of interest to compare the structural features of bis-*p*-nitrophenylphosphate in the three crystals. The pertinent conformational details are summarized in Table 7. The torsion angles of the P–O ester bonds and the dihedral angle between the C–O–P planes are within the ranges observed for phosphodiesters (Shefter, Barlow, Sparks & Trueblood, 1969). It is evident from the tabulated values that the phosphodiester conformation in the benzocaine complex more closely resembles the one in the phenacaine complex, even though the anesthetic molecule shows greater apparent similarity to procaine. The O(3)–P–O(1) bond angle is of particular interest since valency angles are generally less sensitive than torsion angles to lattice forces. Yet this angle is observed to be significantly smaller in the benzocaine and phenacaine complexes than the average of 102·7°, which is found in other phosphate diesters (Sax *et al.*, 1971).

It was previously suggested that the differences be

Table 6. *Comparison of molecular dimensions for p-aminobenzoate group and carboxylate group in benzocaine bis-p-nitrophenylphosphate* (I), *procaine bis-p-nitrophenyl phosphate* (II)* *and p-aminobenzoic acid* (III)†

	I	II	III
p-Aminobenzoate group			
Exocyclic C–N	1·464 Å	1·377 Å	1·380 Å
Exocyclic C–C	1·495	1·461	1·460
Average value of central-bond distance in benzene ring	1·369	1·375	1·375
Average value of remaining ring C–C distances	1·373	1·399	1·399
Average valency angle at the carbon atoms defining the *para* position within the ring	120·0°	118·4°	118·8°
Average value of the other four endocyclic angles within the ring	120·1	120·8	120·6
Carboxylate group			
Carbonyl C–O	1·201 Å	1·212 Å	1·242 Å
Ester C–O	1·322	1·364	1·304

*Sax *et al.* (1970).
† Lai & Marsh (1967).

Table 7. *Comparison of conformational details in bis-p-nitrophenylphosphate for three different crystal structures*

Designation of angle for benzocaine complex	Values observed Benzocaine complex	 Phenacaine complex*	 Procaine complex†
Torsion angles			
C(8)–C(7)–O(3)–P	−150·2°	163·3°	105·0°
C(7)–O(3)–P–O(1)	167·1 (+ap)	179·6 (+ap)	−77·4 (−sc)
O(3)–P–O(1)–C(1)	−66·7 (−sc)	53·5 (+sc)	−82·3 (−sc)
P–O(1)–C(1)–C(2)	20·4	10·1	59·1
Bond angle O(3)–P–O(1)	97·8	97·2	103·3
Dihedral angle between planes C(1)–O(1)–P and C(7)–O(3)–P	111·0	126·5	101·1
Rotation of nitro groups with planes of benzene ring	12·9; 10·3	20·0; 6·8	6·9; 4·0

* Sax *et al* (1971).
† Sax *et al.* (1970).

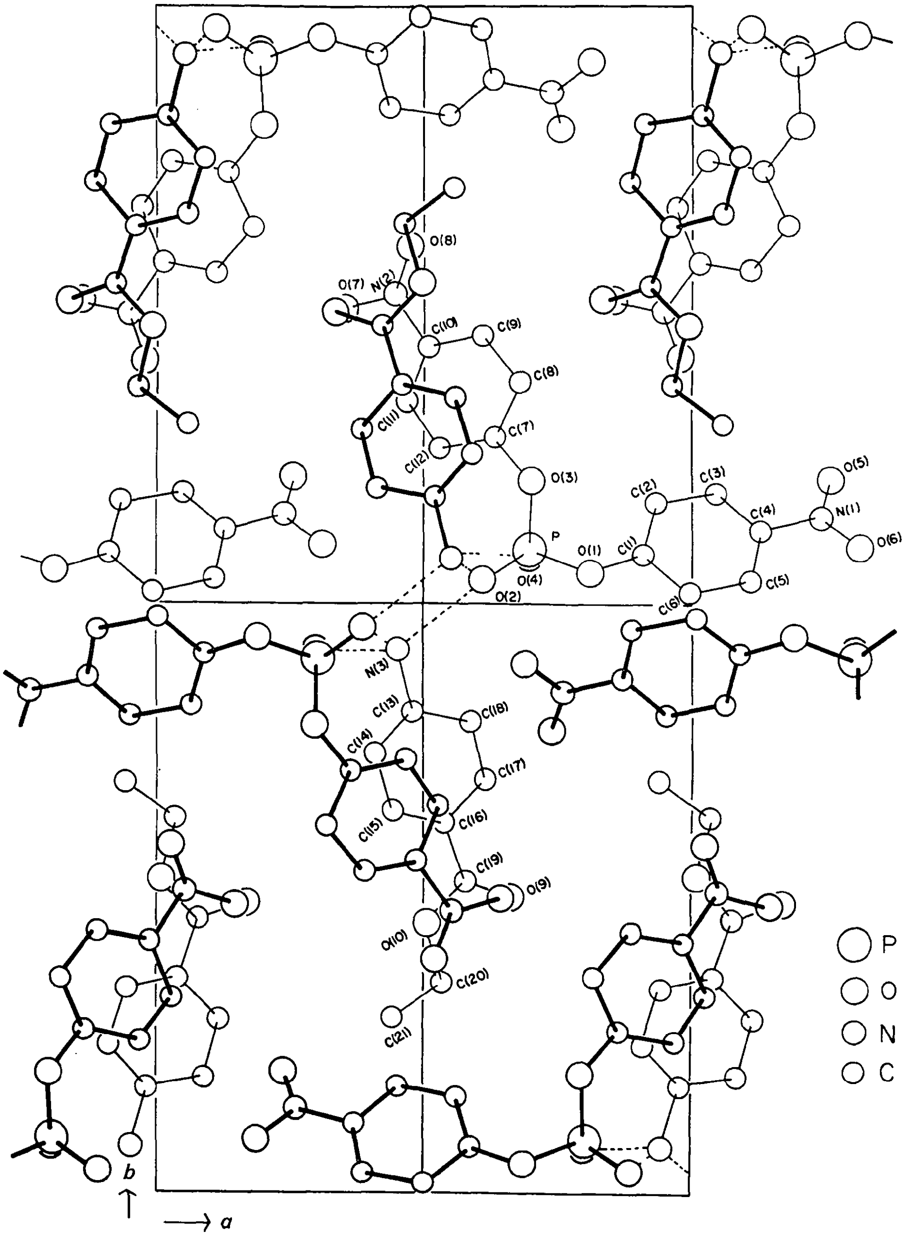

Fig. 2. Projection of one unit cell along the *c* axis. Hydrogen bonding is shown by dotted lines.

tween the phosphodiester conformation in the phenacaine and procaine complexes resulted from additional nonpolar interactions between phenacaine and the phosphodiester. In this structure nonpolar interactions between benzocaine and the phosphodiester are even more favorable, while still maintaining the strong hydrogen-bonding interactions. The overlap of the benzoate ester and the nitrophenyl ring is shown very clearly in the packing diagram (Fig. 2). The two overlapping rings are very nearly parallel and are separated by a distance of 3·37 and 3·39 Å,* which is just double the half-thickness of a benzene ring. The intermolecular contact distances in Table 8 indicate that the ethyl ester group and the nitrophenyl ring are within normal contact distances. In the procaine complex (Sax *et al.*, 1970) the polar groups at the two ends of the anesthetic molecule form strong hydrogen bonds with the phosphate, while only limited nonpolar interactions between the two components occur. Instead, the benzene rings in the middle of the procaine molecule are stacked through the center of the unit cell, while the nitrophenyl groups of the phosphate ester are in association along the two edges of the cell. On the contrary, benzocaine, which has a polar group at one end of the molecule, exhibits the tendency to form nonpolar interactions as well as hydrogen bonds with the phosphodiester. This observation is consistent with the suggestion that the protonation of procaine interferes with its membrane lipid interaction (Sax & Pletcher, 1969). This suggestion was offered to account for the anomalous anesthetic activity of procaine, which shows a greater potency in its un-ionized form (Ritchie & Ritchie, 1968). The anesthetic activity of benzocaine is intermediate to the neutral and cationic forms of procaine.

The hydrogen bonding between the anesthetic and the phosphate is a common feature in the structures of the anesthetic complexes. In benzocaine the three hydrogen atoms on the protonated amino group all participate in hydrogen bonding; H1(N3) is bonded across the screw axis at $(\frac{1}{2},\frac{1}{2},0)$ to O(2), H2(N3) is bonded to O(2) of the 'screw-related' phosphate which is stacked below the anesthetic, and

Table 8. *Intermolecular bonds and nonbonded contact distances*

(*a*) Hydrogen bonds

i	*j*	*k*	D_{ik}	D_{jk}	(*ijk*)
N(3)	H1(N3)	O(2)	2·780 Å	1·87 Å	172°
N(3)	H2(N3)	O(2*a*)	2·838	1·88	163
N(3)	H3(N3)	O(4*b*)	2·754	1·61	173
C(13)	N(3)	O(2)			112·3
C(13)	N(3)	O(2*a*)			98·0
C(13)	N(3)	O(4*b*)			106·6
P	O(2)	N(3)			129·7
P	O(2)	N(3*b*)			124·1
P	O(4)	N(3*a*)			142·1

(*b*) Contact distances

i	*j*	D_{ij}
between parallel nitrophenyl rings and anesthetic*		
O(3)	C(14*b*)	3·269
C(10)	C(19*b*)	3·437
N(2)	C(19*b*)	3·680
O(8)	C(20*b*)	3·602
N(2)	C(19*a*)	3·527
O(8)	C(20*a*)	3·636
N(2)	O(10*a*)	3·236
O(7)	C(19*a*)	3·093
O(7)	O(10*a*)	3·217
O(7)	O(9*a*)	3·477
O(8)	O(10*a*)	3·408
involving the second nitrophenyl ring		
C(6)	C(6*c*,*d*)	3·592
C(6)	C(4*d*)	3·575
C(6)	C(5*d*)	3·601
C(6)	C(3*d*)	3·603
C(6)	C(1*d*)	3·624
C(6)	C(2*d*)	3·635
C(2)	O(8*e*)	3·360
C(3)	O(8*e*)	3·114
C(1)	O(5*c*)	3·819
C(2)	C(21*f*)	3·909
C(2)	C(20*f*)	3·972
C(3)	C(21*f*)	3·741
C(3)	C(21*h*)	3·988
O(5)	C(11*g*)	3·213
O(5)	C(12*g*)	3·645
O(5)	C(18*c*)	3·390
O(5)	C(17*c*)	3·585
O(6)	N(3*g*)	2·955
O(6)	C(12*g*)	3·487
O(6)	C(18*d*)	3·602
miscellaneous		
C(8)	O(9*f*)	3·303
C(8)	O(7*e*)	3·314
C(9)	O(7*e*)	3·304

Symmetry code:

–	*x*, *y*, *z*
a	$1-x,\ 1-y,\ -\frac{1}{2}+z$
b	$1-x,\ 1-y,\ \frac{1}{2}+z$
c	$2-x,\ 1-y,\ -\frac{1}{2}+z$
d	$2-x,\ 1-y,\ \frac{1}{2}+z$
e	$\frac{1}{2}+x,\ 1\frac{1}{2}-y,\ z$
f	$1\frac{1}{2}-x,\ \frac{1}{2}+y,\ \frac{1}{2}+z$
g	$1+x,\ y,\ z$
h	$1\frac{1}{2}-x,\ \frac{1}{2}+y,\ -\frac{1}{2}+z$

* Does not include any contact distance between atoms in both rings, since the inter-ring separation is described in text.

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* The distance between the rings was determined by calculating the perpendicular displacements from the least-squares planes. From the benzene ring of the anasthetic to atoms of the phenyl ring above, distances range from 3·498 to 3·357 Å, and to the ring below they range from 3·465 to 3·325 Å. The three atoms that overlap the anesthetic ring, C(7), C(11), and C(12), are separated by an average of 3·427 Å above and 3·396 Å below. If the plane of the phenyl ring of the phosphate immediately above the anesthetic is considered as the starting point, then the distances to the atoms of the anesthetic ring below range from 3·411 to 3·256 Å, and to the ring above they range from 3·446 to 3·291 Å. For the three atoms that overlap the phenyl ring, C(14), C(15), C(16), the average distance to the ring is 3·356 Å from below and 3·346 Å from above. By averaging these two sets, the separation between the anesthetic and the ring above is 3·392 Å, and to the ring below the separation is 3·371 Å.

H3(N3) is bonded to O(4) of the 'screw-related' phosphate which is stacked above. This bonding scheme (Figs. 2 and 3) produces continuous spirals about the screw axes at $(\frac{1}{2},\frac{1}{2},0)$, $(0,0,0)$, $(1,0,0)$, $(0,1,0)$, and $(1,1,0)$. The hydrogen-bonded chains that run parallel to the *c* axis are held together in the crystal along the **a** and **b** axial directions, primarily by van der Waals forces. All of the principal intermolecular contact distances are listed in Table 8. The nitrophenyl group, which is not associated with the anesthetic, does form several other intermolecular contacts. These rings are related by screw axes at $(1,\frac{1}{2},0)$, $(\frac{1}{2},0,0)$, $(0,\frac{1}{2},0)$, and $(\frac{1}{2},1,0)$, with C(6) nearly on the screw axis. Since the planes of the ring are nearly at right angles, C(6) is approximately equidistant from all atoms in the ring of the 'screw-related' molecule, with an average separation of 3·62 Å. On the other side of the ring, C(2) and C(3) are in contact with the terminal methyl, C(21), of the '*n*-glide related' benzocaine and with O(8) of the '*a*-glide related' nitrophenyl. The nitro group oxygen atom, O(6), is directed towards the amino nitrogen atom, N(3), of the molecule having a unit translation along the **a** axial direction at a distance of 2·96 Å. This oxygen atom is situated nearly along the center line between the three tetrahedrally bonded hydrogen atoms.

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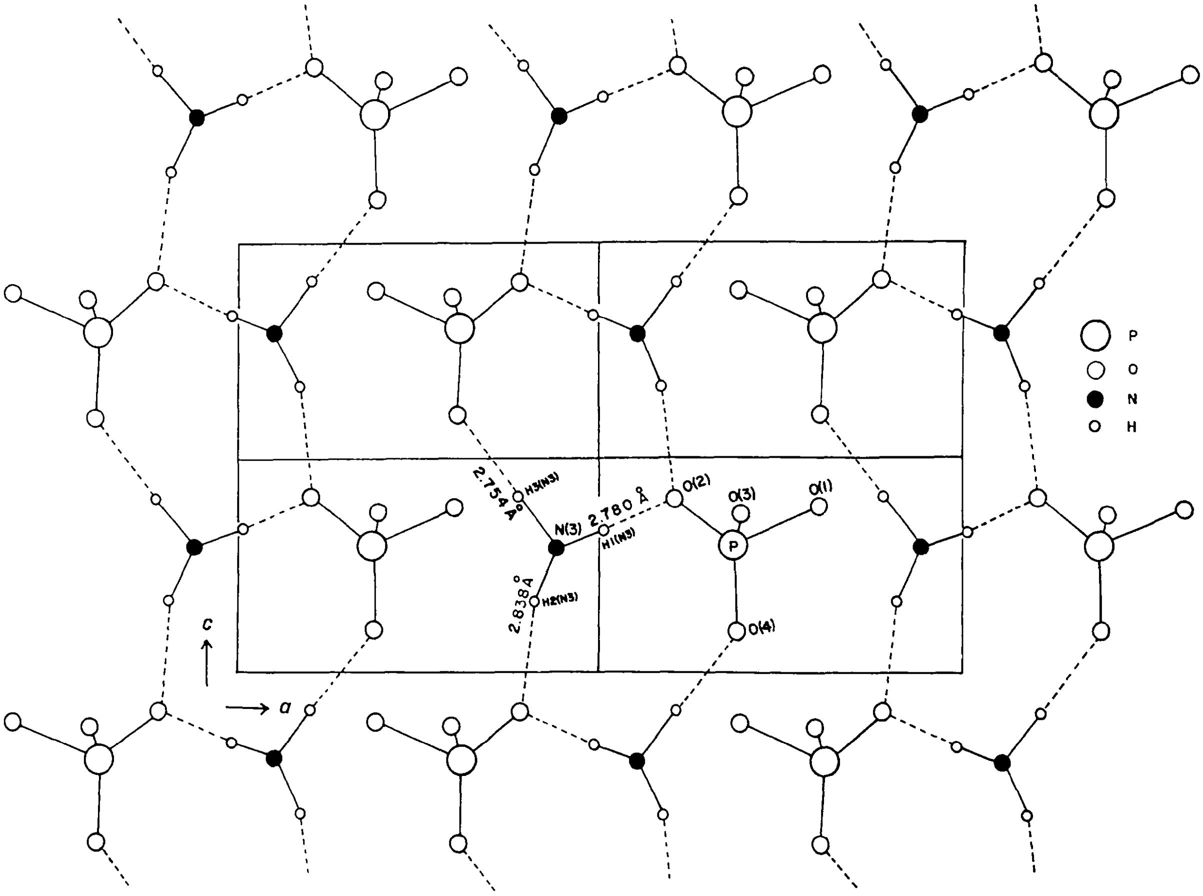

Fig. 3. Hydrogen-bonding scheme viewed along the *b* axis. Only protonated *p*-amino groups and phosphate groups are shown in this projection.

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The Crystal Strucure of Bisthiourea Pyridinium Bromide

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The adduct of pyridinium bromide with two molecules of thiourea gives orthorhombic crystals, $a=14{\cdot}756$ (2), $b=10{\cdot}893$ (1), $c=8{\cdot}363$ (1) Å and space group *Cmcm*. There are four formula units per cell. Full-matrix least-squares refinement on 893 observations gave an R value of 0·043. Anisotropic vibration was allowed for atoms other than hydrogen. For the hydrogen atoms of thiourea isotropic vibration parameters were refined; it was not possible to locate those on the pyridinium ion. The thiourea molecules lie on the mirror planes at $z=\frac{1}{4}$ and $\frac{3}{4}$ with the N···N vector along **c** in which direction N–H···S hydrogen bonds hold the molecules in columns. The pyridinium ions occupy spaces formed by eight sulphur atoms; each sulphur atom has four cation neighbours. Disorder of the pyridinium ions yields the $2/m$ symmetry required by the space group but parameter interaction precludes mathematical distinction between two types of disorder, $\frac{1}{6}$ nitrogen, $\frac{5}{6}$ carbon in each site or $\frac{1}{2}$ nitrogen, $\frac{1}{2}$ carbon in only two sites; however, the latter arrangement gives more chemically reasonable bond lengths. These two sites are at 3·642 (9) Å from the bromide ions. Each bromide ion has two such contacts, subtending an angle of 58·4°; on its other side are 4 hydrogen atoms each at 2·50 Å; they are bonded to nitrogen atoms of 4 thiourea molecules and the N–H···Br distance is 3·467 Å.

Introduction

Thiourea forms complexes with halides of nearly all metals from large univalent ones, *e.g.* caesium, to small transition metals, *e.g.* nickel. It also forms complexes with salts of the pyridinium and *N*-methylpyridinium ions, (Phillips, 1967), of stoichiometry pyrH^+X^-,bisthiourea where X may be a halide, nitrate, or sulphate. Our original interest in these compounds was to study the interaction of thiourea with a non-spherical cation. Of the isomorphous series with X=Cl, Br or I we chose the bromide for a full structure analysis.

Experimental

Crystal data

Pyridinium bromide–bisthiourea, $C_7H_{13}BrN_5S_2$, $M=311{\cdot}26$; orthorhombic, $a=14{\cdot}756$ (2), $b=10{\cdot}893$ (1), $c=8{\cdot}363$ (1) Å, $U=1341$ Å^3, $D_m=1{\cdot}57$ g.cm^{-3}, $Z=4$, $D_c=1{\cdot}536$ g.cm^{-3}. Systematic absences, hkl with $h+k$ odd, $h0l$ with l odd. $F(000)=628$. Zr-filtered Mo $K\alpha$ radiation. $\lambda(\text{Mo } K\alpha_1)=0{\cdot}7093$ Å, $\mu(\text{Mo } K\alpha)=35{\cdot}3$ cm^{-1}. Absorption correction applied. Space group *Cmcm*, established by structure analysis.

A crystal 0·5 × 0·3 × 0·3 mm was mounted in Araldite on a rigid support* on the Picker diffractometer. Optimization of 23 reflexions centred on Mo $K\alpha_1$ radiation gave the orientation matrix and cell dimensions. Observations were collected for hkl and $hk\bar{l}$ to allow for possible significant differences caused by anomalous dispersion if the space group were non-centric. Shells of reciprocal space were measured from $2\theta=3°$ to $2\theta=60°$, when the crystal suddenly started to decompose rapidly. The θ–2θ scan mode was used from 0·7° below 2θ for Mo $K\alpha_1$ to 0·8° above 2θ for Mo $K\alpha_2$ at $\frac{1}{2}$°.min^{-1}. Backgrounds were measured for 20 sec at each end of the scan. Three reference reflexions 004,

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* On a support designed by R. H. B. Mais and P. G. Owston, Imperial Chemical Industries Ltd.