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The Crystal Structure of Procaine Dihydrogen Orthophosphate

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The crystal structure of the dihydrogen phosphate salt of procaine was determined by use of three-dimensional X-ray diffractometer data. Crystals of the salt are triclinic, space group $P\bar{1}$, with $a = 8\cdot029$ (2), $b = 8\cdot384$ (1), $c = 13\cdot839$ (1) Å, $\alpha = 72\cdot37$ (3), $\beta = 83\cdot50$ (3) and $\gamma = 71\cdot94$ (3)°. The structure was solved by the heavy-atom method and refined by least-squares calculations. Difference Fourier maps suggest that there may be a partially substituted water site, and the refined occupancy of this site is $0\cdot050$ (4). The final R index, based upon 2793 reflections, is $0\cdot040$. The procaine conformation is like that found in crystal structures of other procaine salts, except for several large differences involving torsion angles within the diethylamino groups. Unlike other crystal structures of procaine salts, the carbonyl oxygen atom, O(7), is a hydrogen-bond acceptor. The procaine cation hydrogen-bonds to phosphate ions through its tertiary and *p*-amino groups, resulting in an arrangement similar to that postulated for the binding of procaine to the phospholipids of nerve membranes.

Introduction

Procaine, an ester of *p*-aminobenzoic acid, is a useful local anesthetic (Keys, 1945). Its exact mechanism of action is not known (Ritchie & Greengard, 1966), but there is evidence that the compound interacts with the membranes of nerve fibers (Toman, 1952; Skou, 1954; Shanes, 1958, 1963; Condouris, 1961, 1963; Buchi & Perlia, 1960; Shanes, Freygang, Grundfest & Amatniek, 1959; Thimann, 1943; Kuperman, Okamoto, Beyer & Volpert, 1969; Eckert, 1962*a,b*; Agin, 1965; Weidmann, 1955), thereby interfering with the ion-conduction processes required for nerve impulses (Skou, 1954; Shanes, 1958, 1963; Condouris, 1961, 1963). The biological effects of procaine, which forms reversible complexes with various phospholipids *in vitro* (Feinstein, 1964; Goldman, 1964), have been attributed to interactions between the anesthetic and the phospholipids of nerve membranes. One would expect the procaine cation to interact with the phosphate moieties of phospholipids. A model for the type of interaction that might occur has been postulated by Feinstein (1963, 1964). According to this model, procaine binds simultaneously to two phosphate groups from neighboring phospholipid molecules: to one through the terminal tertiary amino group, and to the other through the *p*-amino group of the phenyl moiety.

We determined the crystal structure of the dihydrogen phosphate salt of procaine to obtain information about the possible factors involved in procaine interactions with phosphates.

Experimental

Transparent plates of procaine phosphate were obtained by slowly evaporating an aqueous solution containing equimolar quantities of procaine and phosphoric acid. Weissenberg and oscillation photographs showed the unit cell to be triclinic, dictating space group $P1$ or $P\bar{1}$. A crystal fragment, with approximate dimensions of $0\cdot05 \times 0\cdot13 \times 0\cdot14$ mm, was cut from a larger plate and mounted on a Picker FACS-1 X-ray diffractometer with its *a* axis slightly inclined to the ϕ axis of the diffractometer. The angular settings for 12 high-angle (Cu $K\alpha_1$, $\lambda = 1\cdot54051$ Å) reflections were measured and the unit-cell parameters were obtained from a least-squares analysis of these measurements. Crystal data are listed in Table 1.

Table 1. Crystal data

Unit-cell parameters were measured at $25 \pm 2\,^{\circ}C$. The density was measured by flotation in a mixture of benzene and ethylene dibromide. The standard deviation in the measured density is that for the average value of 4 independent measurements. The calculated density is based upon 0·05 occupancy of the postulated water site. With water excluded and with full occupancy of the water site, the calculated density would be 1·315 and 1·386 g cm^{-3}, respectively.

Stoichiometry	$C_{13}H_{21}N_2O_2^+ \cdot H_2PO_4^- \cdot 0\cdot05H_2O$
Z	2
Space group	$P\bar{1}$
a	8·029 (2) Å
b	8·384 (1)
c	13·839 (1)
α	72·37 (3)°
β	83·50 (3)
γ	71·94 (3)
Cell volume	843·850 Å^3
ϱ(measured)	1·320 (1) g cm^{-3}
ϱ(calculated)	1·319 g cm^{-3}
μ(Cu $K\bar{\alpha}$)	17·1 cm^{-1}

Intensities of the 2793 symmetry-independent reflections with $2\theta \le 127\cdot5°$ were measured with the diffractometer, by use of nickel-filtered copper radiation, a θ-2θ scanning technique, and a scintillation counter. The scanning speed was 0·5° min^{-1}, and the background was counted for 20 s at each terminus of the scans. Those reflections below background level were given their net negative intensity values and were retained in all subsequent calculations. The intensities were assigned variances, $\sigma^2(I)$, based on the counting statistics plus a correctional term $(0\cdot03S)^2$, S being the scan count. Intensities and their variances were corrected for Lorentz and polarization factors, and absorp-

tion corrections were applied using the program *ORABS* (Wehe, Busing & Levy, 1962). The absorption correction factors ranged from 1·16 to 1·45. The first derivatives of the transmission factors, with respect to the absorption coefficient, were also computed for subsequent calculation of extinction corrections. Data were scaled by means of a Wilson (1942) plot.

A Howells, Phillips & Rogers (1950) plot indicated that the crystal structure is centrosymmetric. Therefore, we assumed the space group to be $P\bar{1}$; this assumption is corroborated by the structure analysis.

Determination and refinement of the structure

Trial coordinates for the phosphorus atom were obtained from a sharpened three-dimensional Patterson map, coordinates for the phosphate oxygen atoms were obtained from a Fourier map phased with the phosphorus atom, and a difference Fourier map then revealed the positions of the procaine heavy atoms. The trial structure was refined by full-matrix least-squares calculations using a modified version of the program *ORFLS* (Busing, Martin & Levy, 1962; Busing, 1971). The quantity minimized was $\sum w[F_o^2 - (1/k^2)F_c^2]^2$, where k is a scale factor and the weight w is equal to $1/\sigma^2(F_o^2)$. Scattering factors for the nonhydrogen atoms and the anomalous dispersion factors for phosphorus and oxygen were from *International Tables for X-ray Crystallography* (1962). The hydrogen atom scattering factors were from Stewart, Davidson & Simpson (1965). The hydrogen atoms on the procaine and phosphate ions were located in difference Fourier maps during the later stages of refinement. The later cycles

Table 2. Heavy-atom parameters and their standard deviations

Values for the phosphorus atom have been multiplied by 10^5, all other values by 10^4. The temperature factors are in the form exp $(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - 2\beta_{12}hk - 2\beta_{13}hl - 2\beta_{23}kl)$. The final value of the isotropic extinction parameter g is 0·047 (3). Parameters for the partially occupied water site are $x = 0\cdot788$ (3), $y = 0\cdot412$ (3), $z = 0\cdot233$ (2), $B = 4\cdot4$ (7) Å, and occupancy $= 0\cdot050$ (4).

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	04321 (6)	24259 (5)	48586 (3)	1552 (9)	901 (7)	387 (3)	−351 (6)	−58 (4)	−180 (3)
O(1)	−1176 (2)	4008 (2)	4400 (1)	189 (3)	119 (2)	76 (1)	−16 (2)	−46 (1)	−33 (1)
O(2)	−0186 (2)	1331 (2)	5888 (1)	241 (3)	141 (2)	41 (1)	−88 (2)	17 (1)	−30 (1)
O(3)	1806 (2)	3099 (1)	5116 (1)	153 (2)	109 (2)	54 (1)	−36 (2)	−15 (1)	−22 (1)
O(4)	1005 (2)	1354 (2)	4124 (1)	228 (3)	122 (2)	43 (1)	−73 (2)	14 (1)	−29 (1)
C(1)	2364 (3)	7569 (2)	0577 (1)	214 (4)	162 (4)	39 (1)	−45 (3)	−2 (2)	−24 (2)
C(2)	2353 (4)	6475 (3)	0004 (2)	451 (7)	194 (4)	37 (1)	−125 (5)	13 (2)	−26 (2)
C(3)	2119 (4)	4860 (3)	0451 (2)	509 (8)	186 (4)	44 (1)	−121 (5)	9 (3)	−37 (2)
C(4)	1857 (3)	4270 (2)	1500 (2)	269 (5)	140 (4)	45 (1)	−31 (3)	−2 (2)	−16 (2)
C(5)	1894 (3)	5364 (3)	2078 (1)	228 (4)	174 (4)	35 (1)	−38 (3)	1 (2)	−20 (2)
C(6)	2140 (3)	6966 (2)	1625 (1)	210 (4)	177 (4)	41 (1)	−46 (3)	−6 (2)	−31 (2)
N(4)	1554 (3)	2699 (2)	1934 (1)	489 (7)	155 (3)	46 (1)	−102 (4)	11 (2)	−21 (2)
C(7)	2572 (3)	9316 (3)	0132 (1)	211 (4)	172 (4)	40 (1)	−50 (3)	−1 (2)	−29 (2)
O(7)	2703 (2)	10273 (2)	0600 (1)	379 (4)	212 (3)	46 (1)	−127 (3)	2 (2)	−39 (1)
O(8)	2583 (2)	9799 (2)	−0888 (1)	319 (4)	162 (2)	35 (1)	−96 (2)	2 (1)	−20 (1)
C(9)	2742 (3)	11522 (2)	−1391 (1)	259 (5)	152 (4)	46 (1)	−77 (3)	4 (2)	−27 (2)
C(10)	2271 (2)	11996 (2)	−2481 (1)	182 (4)	132 (3)	46 (1)	−29 (3)	3 (2)	−23 (2)
N(11)	3550 (2)	11047 (2)	−3148 (1)	162 (3)	118 (2)	37 (1)	−22 (2)	−4 (1)	−14 (1)
C(12)	3633 (3)	9141 (2)	−2879 (2)	246 (4)	120 (3)	51 (1)	−32 (3)	−4 (2)	−14 (2)
C(13)	4286 (3)	8380 (3)	−3757 (2)	307 (6)	153 (4)	68 (2)	−29 (4)	9 (2)	−41 (2)
C(14)	5327 (2)	11316 (3)	−3232 (2)	155 (4)	180 (4)	57 (1)	17 (3)	−9 (2)	−26 (2)
C(15)	5281 (3)	13186 (3)	−3689 (2)	180 (4)	211 (4)	88 (2)	−80 (4)	−12 (2)	−7 (2)

of refinement included all positional parameters, along with anisotropic temperature factors for the heavy atoms, isotropic temperature factors for the hydrogen atoms, and Zachariasen's (1963) isotropic extinction parameter g (as formulated by Coppens & Hamilton, 1970).

The model refined to an R index $(\sum ||F_o| - |F_c||/\sum |F_o|)$ cf 0·043 and a goodness-of-fit $[\{\sum w(F_o^2 - F_c^2)^2/(m - s)\}^{1/2}$ where m is the number of reflections used and s is the number of parameters refined] of 2·06. A three-dimensional electron-density difference map calculated at this stage revealed one large peak of 0·52 e Å^{-3}; no other peaks or troughs exceeded 0·24 e Å^{-3} in magnitude. This large peak was within acceptable hydrogen-bonding distance to suitable hydrogen-bond donors and acceptors and was more than 3·1 Å from any other nonhydrogen atoms. Assuming that the peak corresponds to the partially occupied position of a water molecule, we assigned a partial-oxygen atom to this

position. Final cycles of least-squares refinement included the positional parameters, isotropic temperature factor, and occupancy factor of the partial-oxygen atom. The refined occupancy factor is 0·050 (4), a value that is consistent with the measured density of the crystals (Table 1). The final R index is 0·040 and the goodness-of-fit is 1·93. During the last cycle of refinement no parameter shifted more than 0·2 times its standard deviation. At the conclusion of refinement, a difference Fourier map showed residual troughs and peaks ranging from $-0·23$ to 0·21 e Å^{-3}.

The final heavy-atom parameters and their estimated standard deviations are listed in Table 2; the hydrogen-atom parameters and their estimated standard deviations are listed in Table 3. Observed and calculated structure factors are given in Table 4.

Results and discussion

Fig. 1 depicts the procaine and phosphate conformations, and the ellipsoids of thermal vibration. Bond

Table 3. *Hydrogen-atom parameters and their estimated standard deviations*

Positional parameters have been multiplied by 10^3.

|	x	y	z	B (Å^2)
H(O1)	-133 (3)	494 (3)	462 (2)	5·9 (6)
H(O2)	-055 (3)	036 (3)	583 (2)	6·0 (6)
H(C2)	254 (3)	684 (3)	-068 (2)	6·1 (5)
H(C3)	217 (3)	416 (3)	005 (2)	7·5 (6)
H(C5)	162 (3)	499 (3)	277 (2)	5·0 (5)
H(C6)	218 (3)	774 (3)	201 (2)	5·2 (5)
H(N4)	133 (3)	245 (3)	260 (2)	6·0 (5)
H'(N4)	159 (3)	202 (3)	155 (2)	6·1 (5)
H(C9)	198 (3)	1233 (3)	-109 (2)	4·9 (5)
H'(C9)	392 (2)	1155 (2)	-129 (1)	4·2 (4)
H(C10)	223 (2)	1324 (2)	-275 (1)	3·8 (4)
H'(C10)	116 (2)	1175 (2)	-251 (1)	4·6 (4)
H(N11)	302 (2)	1165 (3)	-385 (1)	4·4 (4)
H(C12)	237 (3)	910 (3)	-276 (2)	6·0 (5)
H'(C12)	439 (2)	858 (3)	-230 (1)	4·5 (4)
H(C13)	355 (3)	920 (4)	-436 (2)	8·4 (7)
H'(C13)	567 (4)	823 (4)	-392 (2)	8·4 (7)
H''(C13)	421 (3)	715 (3)	-356 (2)	7·3 (6)
H(C14)	597 (3)	1061 (3)	-366 (2)	5·3 (5)
H'(C14)	578 (3)	1085 (3)	-256 (2)	5·4 (5)
H(C15)	641 (3)	1324 (3)	-381 (2)	5·8 (5)
H'(C15)	465 (3)	1383 (3)	-319 (2)	6·3 (5)
H''(C15)	466 (3)	1358 (3)	-435 (2)	6·4 (6)
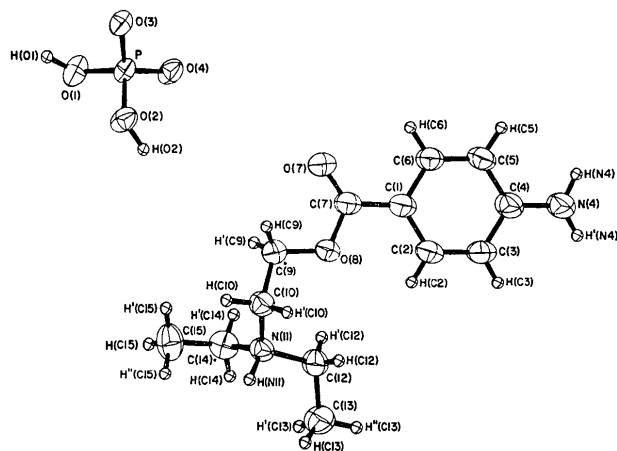
Fig. 1. Conformation of the procaine and phosphate ions. Nonhydrogen atoms are represented by thermal ellipsoids defined by the principal axes of thermal vibration and scaled to include 50 % probability. Hydrogen atoms are represented by spheres of 0·1 Å radius.
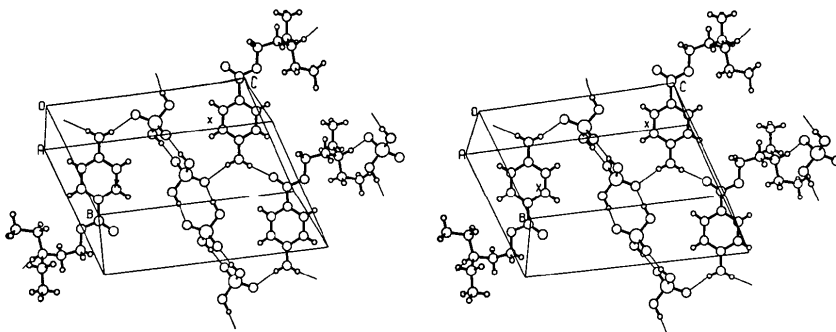

Fig. 2. Stereo drawing (Johnson, 1965) showing the crystal packing and hydrogen bonding as viewed perpendicular to the aromatic rings. Heavy lines represent covalent bonds and the narrower lines represent hydrogen bonds. The partially occupied water sites are represented by X's.

Table 4. *Observed and calculated structure factors*

From left to right, the columns contain values of *l*, 10*F_o*, 10|*F_c*|. Negative intensities have been given *F_o* values of 0·0.

lengths and angles involving nonhydrogen atoms are given in Table 5. The two O–H bond lengths are 0·89 and 0·98 Å, respectively; the N–H bond lengths range from 0·88 to 1·02 Å with an average value of 0·93 Å; and the C–H bond lengths range from 0·91 to 1·08 Å with an average value of 0·97 Å.

Table 5. *Bond lengths (Å) and angles (°) involving heavy atoms of procaine phosphate; standard deviations are given in parentheses*

P——O(1)	1·563 (1)	C(5)—C(6)	1·364 (3)
P——O(2)	1·565 (1)	C(7)—O(7)	1·206 (3)
P——O(3)	1·504 (2)	C(7)—O(8)	1·346 (2)
P——O(4)	1·498 (1)	O(8)—C(9)	1·440 (2)
C(1)–C(2)	1·386 (4)	C(9)—C(10)	1·499 (3)
C(1)–C(6)	1·394 (2)	C(10)–N(11)	1·505 (2)
C(1)–C(7)	1·461 (3)	N(11)–C(12)	1·509 (2)
C(2)–C(3)	1·370 (4)	N(11)–C(14)	1·498 (3)
C(3)–C(4)	1·400 (3)	C(12)–C(13)	1·508 (3)
C(4)–N(4)	1·357 (3)	C(14)–C(15)	1·493 (3)
C(4)–C(5)	1·395 (4)		
O(1)–P——O(2)	107·66 (7)	C(4)—C(5)—C(6)	120·7 (2)
O(1)–P——O(3)	109·17 (8)	C(5)—C(6)—C(1)	121·6 (2)
O(1)–P——O(4)	107·67 (8)	C(1)—C(7)—O(8)	112·7 (2)
O(2)–P——O(3)	106·21 (8)	C(1)—C(7)—O(7)	125·6 (2)
O(2)–P——O(4)	110·40 (7)	O(7)—C(7)—O(8)	121·7 (2)
O(3)–P——O(4)	115·49 (8)	C(7)—O(8)—C(9)	116·5 (2)
C(2)–C(1)–C(6)	117·8 (2)	O(8)—C(9)—C(10)	108·6 (2)
C(2)–C(1)–C(7)	123·0 (2)	C(9)—C(10)–N(11)	117·0 (1)
C(6)–C(1)–C(7)	119·2 (2)	C(10)–N(11)–C(12)	112·4 (1)
C(1)–C(2)–C(3)	121·1 (2)	C(10)–N(11)–C(14)	113·9 (2)
C(2)–C(3)–C(4)	121·1 (2)	C(12)–N(11)–C(14)	112·6 (1)
C(3)–C(4)–C(5)	117·7 (2)	N(11)–C(12)–C(13)	112·1 (2)
C(3)–C(4)–N(4)	120·8 (2)	N(11)–C(14)–-C(15)	112·8 (1)
C(5)–C(4)–N(4)	121·5 (2)		

Bond lengths and angles within the phosphate anion are in agreement with those in other crystal structures of dihydrogen phosphate salts (Aoki, Nagano & Iitaka, 1971). The geometry of the procaine cation in this structure can be compared with that found in the crystal structures of procaine bis-*p*-nitrophenyl phosphate (Sax, Pletcher & Gustaffson, 1971) and procaine hydrochloride (Dexter, 1972). Bond lengths and angles within the procaine cation do not differ significantly in these crystal structures. Table 6 compares the procaine torsion angles and some pertinent nonbonded intramolecular distances found for this structure with corresponding values of the two other procaine salts. Except for large differences in some of the torsion angles of the diethylamino group, the conformation of the procaine cation is similar for the three salts. In all three structures, the cation assumes a *trans* conformation about the O(8)–C(9) bond and a *gauche* conformation about the C(9)–C(10) bond. Beall, Herdklotz & Sass (1970) reviewed the intramolecular distances that are found in procaine and in several other related compounds that contain functional groups similar to the C(12)–N(11)–C(10)–C(9)–O(8) moiety of procaine. They showed that the conformations of these groups are generally such that O(8)···N(11) distances range from about 3·07 to 3·29 Å, and the O(8)···C(12) dis-

tances range from about 2·87 to 3·07 Å. As shown in Table 6 the intramolecular distances for procaine dihydrogen phosphate fall within these expected ranges.

Table 6. *Comparison of torsion angles and some intramolecular distances for procaine phosphate with those in crystal structures of other procaine salts*

	Procaine dihydrogen phos- phate	Procaine bis-*p*- nitrophenyl phosphate†	Procaine hydro- chloride‡
Torsion angles			
C(2)—C(1)—C(7)—-O(8)	5·9°	2·9°	−6·6°
C(2)—C(1)—-C(7)—O(7)	−175·0	−178·2	173·7
C(6)—C(1)—-C(7)—-O(8)	−173·2	−177·0	172·7
C(6)—C(1)—-C(7)—-O(7)	6·0	1·9	−7·0
C(1)—C(7)—-O(8)—-C(9)	178·6	176·1	−178·7
O(7)—-C(7)—-O(8)—-C(9)	−0·6	−2·8	1·0
C(7)—O(8)—C(9)—-C(10)	−165·6	−178·7	−172·7
O(8)—-C(9)—-C(10)–N(11)	−72·2	−65·1	−70·2
C(9)—C(10)–N(11)–C(12)	68·9	86·4	68·8
C(9)—C(10)–N(11)–C(14)	−60·8	*	−61·1
C(10)-N(11)–C(12)–C(13)	156·7	68·4	55·3
C(10)-N(11)–C(14)–C(15)	−61·5	*	−158·5
Intramolecular distances			
O(8)···C(2)	2·740 Å	2·797 Å	2·761 Å
O(8)···C(6)	3·620	3·650	3·643
O(8)···N(11)	3·074	2·982	3·069
O(8)···C(12)	2·952	3·087	2·992
O(8)···C(13)	4·435	3·992	3·316
O(8)···C(14)	3·823	*	3·789
O(8)···C(15)	4·799	*	5·136
C(2)···C(12)	4·130	4·439	4·225
C(2)···C(14)	5·899	*	5·951

* These angles involve disordered atoms and were not calculated.
† Sax, Pletcher & Gustaffson (1970).
‡ Dexter (1972).

Deviations from the least-squares plane through the phenyl ring are listed in Table 7. The *p*-amino group and the carboxyl group are tilted out of the phenyl plane by 4 and 6·6° respectively, compared with tilts of 2 and 2·5° for procaine bis-*p*-nitrophenyl phosphate, and 28 and 7·5° for procaine hydrochloride.

Table 7. *Distances (Å) of atoms from a least-squares plane through the aromatic ring*

C(1)	−0·006	*C(7)	−0·043
C(2)	0·000	*O(7)	0·036
C(3)	0·008	*O(8)	−0·198
C(4)	−0·010	*H(C2)	0·02
C(5)	0·003	*H(C3)	0·05
C(6)	0·004	*H(C5)	−0·09
*N(4)	−0·057	*H(C6)	0·02

* Atoms given zero weight in the least-squares calculation.

The crystal-packing and hydrogen-bonding schemes are depicted in Fig. 2. Hydrogen-bond distances and

angles are given in Table 8. As in many other crystal structures of dihydrogen phosphate salts, the phosphate ions are joined by hydrogen bonds, resulting in continuous phosphate columns. Within these columns, adjacent phosphate ions are connected by two short hydrogen bonds (donor–acceptor distances of 2·595 and 2·538 Å). The p-amino group of the phenyl ring and the protonated amino group both donate hydrogen bonds to phosphate ions. In addition, the p-amino group hydrogen-bonds to O(7), an atom that does not participate in hydrogen bonding in the other procaine crystal structures. The postulated partial water molecule forms two contacts that may involve hydrogen bonding: it is 2·88 Å from atom N(4) [2·70 Å from atom H(N4)], and 3·01 Å from phosphate oxygen atom O(1). The next-closest contact between the partially occupied water site and a nonhydrogen atom is an O(W)···C(12) contact of 3·18 Å. The water site also forms two short contacts with hydrogen atoms: a contact of 2·43 Å with H(C10) and a contact of 2·49 Å with atom H(C13).

Table 8. *Hydrogen-bond distances and angles*

Donor	Acceptor		D–A	H···A	D–H···A angle
O(1)—H(O1)····O(3)		a	2·595 Å	1·71 Å	171°
O(2)—H(O2)····O(4)		b	2·538	1·57	172
N(4)—H(N4)····O(4)			2·930	2·05	168
N(4)—H'(N4)···O(7)		c	3·021	2·19	159
N(11)–H(N11)···O(3)		d	2·730	1·74	165

Symmetry code

a	$-x$,	$1·0-y$,	$1·0-z$
b	$-x$,	$-y$,	$1·0-z$
c	x,	$-1·0+y$,	z
d	x,	$1·0+y$,	$-1·0+z$

A particularly interesting feature of the hydrogen-bonding scheme is the interaction between procaine and phosphate ions. As shown in the lower, right-hand portion of Fig. 2, the procaine cation bridges two symmetry-related phosphate anions, in an arrangement essentially like the one Feinstein (1964) postulated for the binding of procaine to the phospholipids of nerve membranes. This arrangement is similar to that found in the crystal structure of procaine bis-p-nitrophenyl phosphate, where the procaine cation also hydrogen-bonds to phosphate ions through its protonated and p-amino groups.

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