

Codeine dihydrogen phosphate  
hemihydrateChristoph Langes,<sup>a</sup> Thomas Gelbrich,<sup>a\*</sup> Ulrich J. Griesser<sup>a</sup>  
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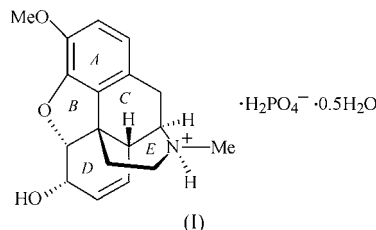
The cation of the title structure [systematic name: (5 $\alpha$ ,6 $\alpha$ )-6-hydroxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinanum dihydrogen phosphate hemihydrate], C<sub>18</sub>H<sub>22</sub>NO<sub>3</sub><sup>+</sup>·H<sub>2</sub>PO<sub>4</sub><sup>−</sup>·0.5H<sub>2</sub>O, has a T-shaped conformation. The dihydrogen phosphate anions are linked by O—H···O hydrogen bonds to give an extended ribbon chain. The codeine cations are linked together by O—H···O hydrogen bonds into a zigzag chain. There are also N—H···O bonds between the two types of hydrogen-bonded units. Additionally, they are connected to one another *via* O···H—O—H···O bridging water molecules. The asymmetric unit contains two codeine hydrogen cations, two dihydrogen phosphate anions and one water molecule. This study shows that the water molecules are firmly bound within a complex three-dimensional hydrogen-bonded framework.

## Comment

Codeine, a natural alkaloid of the opium poppy plant, is used as an analgesic for the treatment of mild to moderate pain, as an antitussive (cough depressant) and as an antidiarrhoeal agent (Eddy *et al.*, 1968, 1969; Atkinson *et al.*, 1943). Codeine is mainly produced from morphine in a semi-synthetic process. It is included in the WHO model list of essential drugs, and it is the most widely used narcotic drug in medical practice. The annual world production (2007) of codeine is 350 tons, and 45% of this amount is produced in the United Kingdom and the United States (International Narcotics Control Board, 2009). Codeine is a highly addictive substance because the human body metabolizes approximately 10% of administered codeine to form morphine. In fact, codeine cough remedies are among the most commonly abused pharmaceutical drugs.

The most important codeine salts are the phosphate, sulfate and hydrochloride salts. It is known that each of these salts, as well as the base, can exist in at least one hydrated form. In the case of the phosphate, a hemihydrate and a sesquihydrate are specified in individual monographs of the European Phar-

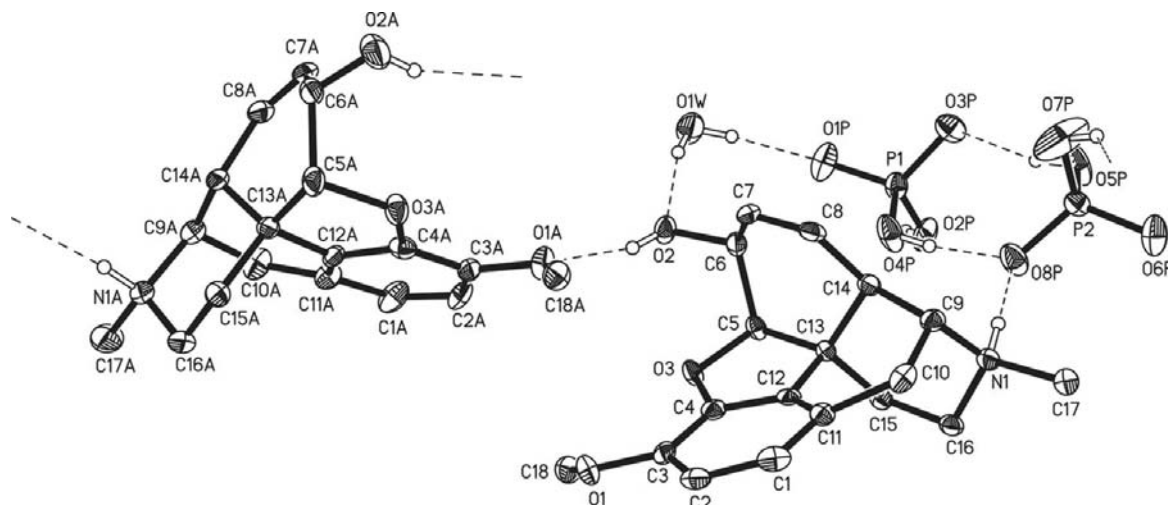
macopoeia (The European Pharmacopoeia, 2008*a,b*), and a hemihydrate is mentioned in the United States Pharmacopoeia, but a crystal structure of a codeine phosphate has not been reported so far. Single crystals of the title compound, (I), were produced as part of a comprehensive study of the solid-state properties of codeine.



The asymmetric unit of (I) is composed of two codeine hydrogen cations (*c*), two dihydrogen phosphate anions (*p*) and one water molecule (*w*) (see Fig. 1). A least-squares fit confirms that the two cations have the same geometry. They adopt the characteristic T conformation, which is known from related compounds of the opiate family, *e.g.* morphine monohydrate (Bye, 1976) and morphine derivatives, such as morphine monohydrate (Bye, 1976), salts (Mackay & Hodgkin, 1955; Gylbert, 1973; Wongweichintana *et al.*, 1984; Lutz & Spek, 1998) and derivatives (*e.g.* Canfield *et al.*, 1979; Deschamps *et al.*, 1996; Gathergood *et al.*, 2003; Balchin *et al.*, 2004) of morphine, the free base form of codeine (Canfield *et al.*, 1987), codeine monohydrate (Bel'skii *et al.*, 1988), codeine hydrobromide dihydrate (Kantha *et al.*, 1962) and codeine derivatives (Grant *et al.*, 1993; Kolev *et al.*, 2006; Liebman *et al.*, 1978). Using the nomenclature commonly applied to opiates, the mean planes defined by the rings A/B/C and D/E (see the scheme) form angles of 89.36 (5) and 88.66 (5)° in the two independent cations of (I).

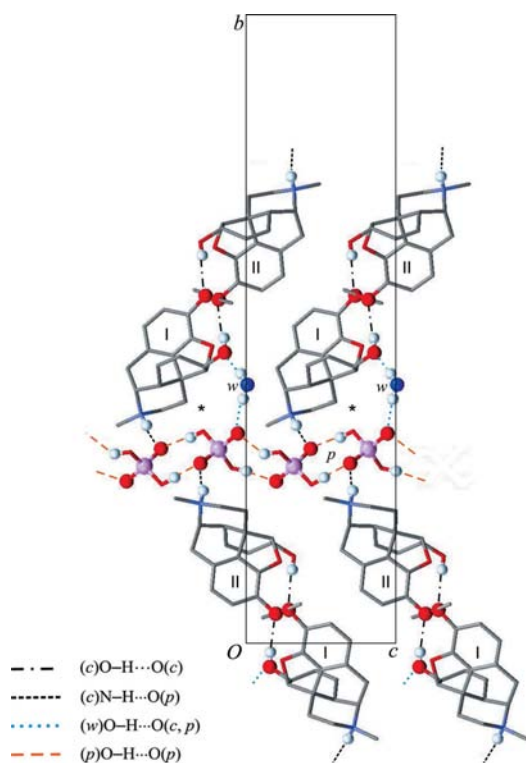
Adjacent dihydrogen phosphate anions of (I) are joined together by pairwise (*p*)O—H···O(*p*) hydrogen bonds to give an extended ribbon chain with an R<sub>2</sub><sup>2</sup>(8) ring motif (Bernstein *et al.*, 1995), as shown in Fig. 2. These phosphate chains run along the *c* axis. A systematic comparison with chemically related crystal structures reveals that this ring is the preferred supramolecular synthon in the aggregation of hydrogen phosphate anions. Furthermore, the ribbon chain motif of (I) is present in 34 of the 230 dihydrogen phosphate structures that are included in the current version of the Cambridge Structural Database [Version 5.30 (Allen, 2002), refcodes ACUXIG, BIDPEJ, CEXPAX, CLQUON01, CPAIMZ, DASNUH, DAYHOB, DUNHID, EDUQUP, EJEGAB, FEDMIL, FIJHEL, GEJYEA, GEXXAI, GOLTOQ, HEXRIM, ISUZIF, LELJOC, LELXII, MATKAT, MPAHZP, NELVUV, PAMRAX, PIFJAO, PROCPH, REZNEP, SASBIX, SEGGER, SEPHEB, SODCUJ, XAPRUC, MIKPUS, SIBMUM and SIBQEA]. Among the other R<sub>2</sub><sup>2</sup>(8)-based motifs is a second type of ribbon chain, which is topologically distinct from the chain observed in (I).

Independent codeine units are linked to one another through (*c*)O—H···O(*c*) hydrogen bonds by employing the hydrogen-bond donor and acceptor functions, respectively, of their hydroxy and methoxy groups. The resulting extended



### Figure 1

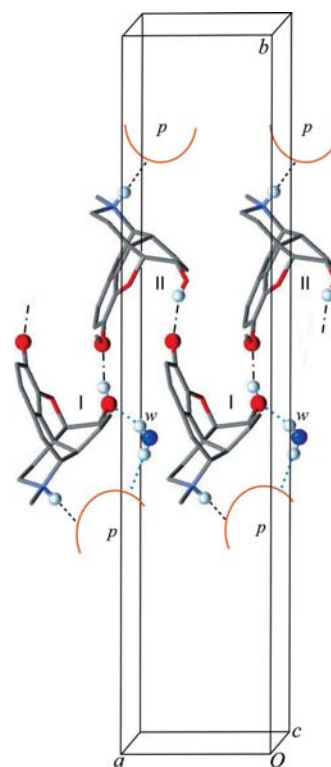
The asymmetric unit of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size. H atoms not involved in hydrogen bonding have been omitted for clarity and hydrogen bonds are represented by dashed lines.



### Figure 2

A portion of the complex three-dimensional hydrogen-bonded network of (I), viewed along the  $a$  axis. The central hydrogen-bonded phosphate ribbon chain (denoted  $p$ ) is additionally hydrogen bonded to four codeine chains. The two independent codeine cations are denoted I and II. The water molecules ( $w$ ) act as  $(c)O \cdots H-O-H \cdots O(p)$  bridges between the cation and anion chains. P atoms, water O atoms (dark) and all atoms directly engaged in hydrogen bonding are drawn as balls. Two  $R_4^3(16)$  rings are indicated by asterisks (\*).

zigzag chain of codeine molecules is depicted in Fig. 3. It propagates parallel to the *a* axis and lies approximately perpendicular to the hydrogen-bonded dihydrogen phosphate chains mentioned above. Fig. 3 also shows that these two chain types are (c)N—H...O(p) hydrogen bonded to one another



### Figure 3

A portion of the complex three-dimensional hydrogen-bonded network of (I), showing a single chain of hydrogen-bonded codeine cations and two bridging water molecules (*w*). The segments represent four phosphate (*p*) chains which are hydrogen bonded to the codeine chain. The line types and colour scheme used are the same as shown in the key in Fig. 2.

via the donor function of the protonated amino group of codeine. Thus, each hydrogen-bonded codeine chain is connected to a multitude of hydrogen-bonded phosphate chains and *vice versa*, to give a complex three-dimensional hydrogen-bonded network.

The water molecule acts as an additional (c)O...H—O—H...O(*p*) bridge between the hydroxy group of codeine and a

phosphate chain. Additional  $R_3^3(16)$  rings are formed due to these bonds (see Fig. 3), but only one independent codeine unit engages in this kind of interaction. Altogether, one unprotonated phosphate O atom accepts two hydrogen bonds, and the other accepts one hydrogen bond.

The crystal structure of (I) differs fundamentally from those of the free base, the monohydrate and the hydrobromide dihydrate of codeine in terms of molecular packing. This is presumably due to the very specific hydrogen-bonding capabilities of the dihydrogen phosphate anions. The observation that the water molecules of the hemihydrate are firmly bound within a hydrogen-bonded framework is in accordance with the experimentally observed hydration/dehydration behaviour (see below).

## Experimental

Codeine phosphate was provided by Siegfried Ltd (Zofingen, Switzerland). Suitable single crystals were obtained by slow evaporation from a dimethylformamide (DMF) solution of codeine phosphate on a watch glass. The hemihydrate displays a prismatic habit and forms druses (see Fig. 4 in the supplementary material). Thermogravimetric analysis of the hemihydrate showed that dehydration is very slow and proceeds over a wide temperature range, *viz.* between about 323 and 463 K. The measured total mass loss of about 2.3% confirms the presence of 0.5 equivalents of water per mol codeine dihydrogen phosphate. Gravimetric water vapour sorption experiments indicate that the hemihydrate is stable between 10 and 80% relative humidity (298 K). The crystals slowly release water when stored over desiccants. The formation of a dihydrate was observed above 90% relative humidity.

### Crystal data

$C_{18}H_{22}NO_3^+ \cdot H_2PO_4^- \cdot 0.5H_2O$	$V = 1838.74 (9) \text{ \AA}^3$
$M_r = 406.36$	$Z = 4$
Monoclinic, $P2_1$	Mo $K\alpha$ radiation
$a = 6.9113 (2) \text{ \AA}$	$\mu = 0.20 \text{ mm}^{-1}$
$b = 33.4470 (9) \text{ \AA}$	$T = 173 \text{ K}$
$c = 8.0716 (2) \text{ \AA}$	$0.32 \times 0.16 \times 0.16 \text{ mm}$
$\beta = 99.778 (3)^\circ$	

### Data collection

Oxford Diffraction Gemini-R Ultra diffractometer	5825 independent reflections
12119 measured reflections	5393 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.025$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.046$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.115$	$\Delta\rho_{\text{max}} = 0.52 \text{ e \AA}^{-3}$
$S = 1.02$	$\Delta\rho_{\text{min}} = -0.39 \text{ e \AA}^{-3}$
5825 reflections	Absolute structure: Flack (1983),
530 parameters	with 2341 Friedel pairs
12 restraints	Flack parameter: 0.10 (9)

All H atoms were identified in a difference map. Methyl H atoms were idealized and included as rigid groups that were allowed to rotate but not tip ( $C-H = 0.98 \text{ \AA}$ ) and refined with  $U_{\text{iso}}(H) = 1.5U_{\text{eq}}(C)$ . H atoms bonded to primary ( $C-H = 1.00 \text{ \AA}$ ), secondary ( $C-H = 0.99 \text{ \AA}$ ) and aromatic C atoms ( $C-H = 0.95 \text{ \AA}$ ) were positioned geometrically and refined with  $U_{\text{iso}}(H) = 1.2U_{\text{eq}}(C)$ . H

**Table 1**

Hydrogen-bond geometry ( $\text{\AA}$ ,  $^\circ$ ).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$O2-H2 \cdots O1A$	0.814 (19)	2.08 (2)	2.868 (3)	163 (4)
$N1-H1 \cdots O8P$	0.878 (19)	1.85 (2)	2.720 (4)	173 (4)
$O2A-H2' \cdots O1^i$	0.81 (2)	2.17 (3)	2.938 (4)	160 (5)
$N1A-H1' \cdots O3P^{ii}$	0.868 (19)	1.81 (2)	2.659 (4)	165 (4)
$O2P-H2P \cdots O6P^{iii}$	0.821 (19)	1.69 (2)	2.505 (3)	172 (5)
$O4P-H4P \cdots O8P$	0.829 (19)	1.78 (2)	2.601 (4)	170 (5)
$O5P-H5P \cdots O3P$	0.816 (19)	1.81 (2)	2.609 (4)	165 (5)
$O7P-H7P \cdots O1P^{iv}$	0.83 (2)	1.88 (5)	2.552 (4)	136 (6)
$O1W-H1W \cdots O1P$	0.825 (19)	1.98 (2)	2.798 (4)	172 (5)
$O1W-H2W \cdots O2$	0.817 (19)	2.06 (2)	2.862 (4)	167 (4)

Symmetry codes: (i)  $x-1, y, z$ ; (ii)  $-x, y+\frac{1}{2}, -z+2$ ; (iii)  $x, y, z+1$ ; (iv)  $x, y, z-1$ .

atoms attached to N and O atoms were refined with restrained distances [ $N-H = 0.86 (2) \text{ \AA}$  and  $O-H = 0.82 (2) \text{ \AA}$ ] and their  $U_{\text{iso}}$  parameters were refined freely. The absolute configuration of this structure was known prior to this study and was confirmed by the refined Flack (1983) parameter.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2003); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2003); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SIR2002* (Burla *et al.*, 2003); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 2008) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *publCIF* (Westrip, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG3114). Services for accessing these data are described at the back of the journal.

## References

- Allen, F. H. (2002). *Acta Cryst.* **B58**, 380–388.
- Atkinson, A. J., Adler, H. F. & Ivy, A. C. (1943). *J. Am. Med. Soc.* **121**, 646–652.
- Balchin, E., Malcolme-Lawes, D. J., Rowe, M. D., Smith, J. A. S., Bearpark, M. J., Steed, J. W., Wu, W., Horsewill, A. J. & Stephenson, D. (2004). *New J. Chem.* **28**, 1309–1314.
- Bel'skii, V. K., Babilev, F. V., Arzamastsev, A. P. & Simonova, L. L. (1988). *Khim. Farm. Zh.* **22**, 506–509.
- Bernstein, J., Davis, R. E., Shimon, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M., Macrae, C. F., McCabe, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst.* **B58**, 389–397.
- Burla, M. C., Camalli, M., Carrozzini, B., Cascarano, G. L., Giacovazzo, C., Polidori, G. & Spagna, R. (2003). *J. Appl. Cryst.* **36**, 1103.
- Bye, E. (1976). *Acta Chem. Scand. Ser. B*, **20**, 549–554.
- Canfield, D., Barrick, J. & Giessen, B. C. (1979). *Acta Cryst.* **B35**, 2806–2809.
- Canfield, D. V., Barrick, J. & Giessen, B. C. (1987). *Acta Cryst.* **C43**, 977–979.
- Deschamps, J. R., George, C. & Flippen-Anderson, J. L. (1996). *Acta Cryst.* **C52**, 698–700.
- Eddy, N. B., Friebel, H., Hahn, K.-J. & Halbach, H. (1968). *Bull. World Health Organ.* **38**, 673–741.
- Eddy, N. B., Friebel, H., Hahn, K.-J. & Halbach, H. (1969). *Bull. World Health Organ.* **40**, 425–454.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.

- Gathergood, N., Scammells, P. J. & Fallon, G. D. (2003). *Acta Cryst.* **E59**, o1918–o1919.
- Grant, A. D., Zacharias, D. E., Mascavage, L. M., Kemmerer, G. E. & Dalton, D. R. (1993). *J. Heterocycl. Chem.* **30**, 553–557.
- Gylbert, L. (1973). *Acta Cryst.* **B29**, 1630–1635.
- International Narcotics Control Board (2009). *Narcotic Drugs: Estimated World Requirements for 2009; Statistics for 2007*. Report E/INCB/2008/2. New York: United Nations.
- Kartha, G., Ahmed, F. R. & Barnes, W. H. (1962). *Acta Cryst.* **15**, 326–333.
- Kolev, T., Bakalska, R., Shivachev, B. & Petrova, R. (2006). *Acta Cryst.* **E62**, o255–o257.
- Liebman, A. A., Malarek, D. H., Blount, J. F., Nelson, N. R. & Delaney, C. M. (1978). *J. Org. Chem.* **43**, 737–739.
- Lutz, M. & Spek, A. L. (1998). *Acta Cryst.* **C54**, 1477–1479.
- Mackay, M. & Hodgkin, D. C. (1955). *J. Chem. Soc.* pp. 3261–3267.
- Oxford Diffraction (2003). *CrysAlis CCD* and *CrysAlis RED*. Versions 1.171. Oxford Diffraction Ltd, Abingdon, Oxfordshire, England.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- The European Pharmacopoeia (2008a). 6th edition, No. 0074 codeine hemihydrate. Council of Europe European – European Directorate for the Quality of Medicines.
- The European Pharmacopoeia (2008a). 6th edition, No. 0075 codeine sesquihydrate. Council of Europe European – European Directorate for the Quality of Medicines.
- Westrip, S. P. (2009). *publCIF*. In preparation.
- Wongweichintana, C., Holt, E. M. & Purdie, N. (1984). *Acta Cryst.* **C40**, 1486–1490.