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Sodium mycophenolate

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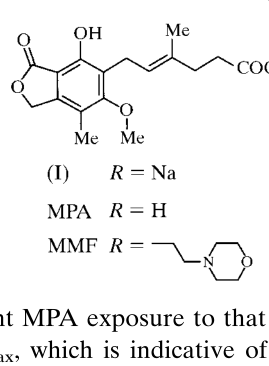
The title compound, sodium 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)-4-methylhex-4-enoate, $Na^+\cdot C_{17}H_{19}O_6^-$, is the sodium salt of the natural immunosuppressant compound mycophenolic acid. It consists of a phthalide moiety carrying four different substituents on the aromatic ring. The anion has no intramolecular hydrogen bonds, but a very strong intermolecular hydrogen bond links the phenolic hydroxy group to the carboxyl group of a neighbouring anion found in the same layer. Within a distance of 2.71 Å, the Na^+ ion is surrounded by five O atoms from four different anions, forming a distorted square pyramid. This Na—O network forms an infinite two-dimensional system running parallel to the *bc* plane.

Comment

Mycophenolic acid (MPA) is the pharmacologically active agent of the recently introduced immunosuppressive drug mycophenolate mofetil (MMF, CellCept™; Behrend, 1998). In fact, MMF has never been detected systemically due to its fast hydrolysis to MPA, which is responsible for the gastrointestinal side effects and leukocytopenia observed in transplant patients (Holt *et al.*, 1998). To alleviate the upper gastrointestinal tract problems, an enteric coated formulation of sodium mycophenolate, ERL080, (I), is currently in phase III clinical trials for the prophylaxis of transplant rejection. The phase I results demonstrated that, upon oral dosing, (I)



affords equivalent MPA exposure to that of MMF but with a longer mean T_{max}, which is indicative of the delivery of the drug in the small intestine (Schmouder *et al.*, 1999). Since the NMR conformation of (I) in water solution has been reported (Makara *et al.*, 1996), as well as that of MPA in the solid state (Harrison *et al.*, 1972), a crystal structure analysis of (I) was performed to determine its packing and to compare the resulting conformation with those in the above-mentioned reports.

In contrast with MPA, whose solid-state conformation was consistent with the solution NMR data for (I) (Makara *et al.*, 1996), the latter adopts a different conformation in the solid state. The discrepancies between MPA and (I) are solely due to changes in the conformation of the hexenoic acid chain. The most relevant differences in the torsion angles are: C10—C15—C16—C17 135.7 (2) [−120.8 (3)° in MPA], C16—C17—C18—C19 −98.9 (3) [−5.9 (5)° in MPA] and C18—C19—C20—O5 80.3 (3)° [−4.8 (5)° in MPA]. The close contact of 3.802 (3) Å between the two methyl groups C21 and C23 in (I) is remarkable compared with the values of 6.258 (5) Å in MPA and 5.67 Å in solution. For steric reasons, the C15—C16 bond of the alkyl side chain and the methoxy group lie at angles of 72.4 (2) and 87.5 (3)°, respectively, to the phenyl ring plane. The corresponding values in MPA are 82.3 (3) and 81.8 (3)°, respectively. In MPA and (I), atom C21 and the hexenoic side chain are on the same side of the phthalide ring system. An intramolecular O3—H···O2 hydrogen bond can be observed in MPA but not in (I). In spite of the various deviations, the data on the structure of MPA and (I) demonstrate that the hexenoic acid chain adopts an extended conformation, and not the bent conformation seen upon complexation of the molecule with its enzymatic target (Sintchak *et al.*, 1996).

The asymmetric unit with the adopted numbering scheme is shown in Fig. 1. The phthalide ring system is not completely planar, the dihedral angle between the plane of the five-membered ring and that of the aromatic ring being 4.0 (2)°. The Na^+ ion coordinated to O2 and O3 lies 0.807 (2) Å from the plane defined by the atoms O2/C7/C8/C9/O3.

The packing is illustrated in Fig. 2. The hydrophilic parts (O2, O3, O4 and O5) of neighbouring anions are directed towards each other and connected *via* Na^+ ions and hydrogen

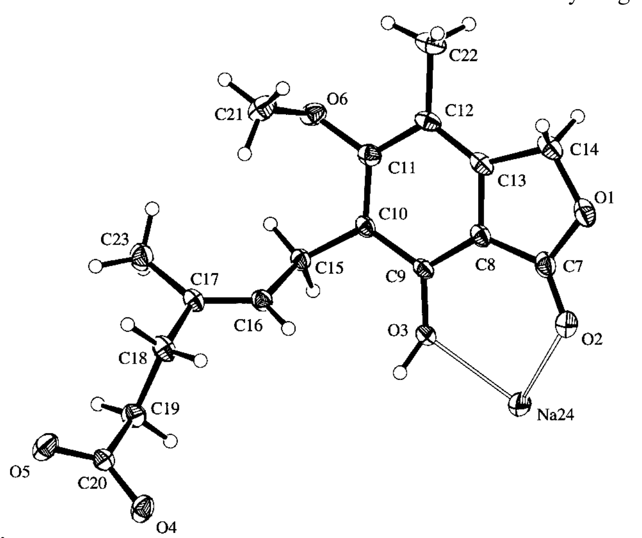


Figure 1
An *ORTEP*II (Johnson, 1976) plot of the asymmetric unit of (I) showing 50% probability ellipsoids.

bonds to form an infinite two-dimensional network which runs parallel to the *bc* plane. This kind of packing is probably the reason why the hexenoic acid chains adopt different conformations in the solid states of MPA and (I).

The environment of the Na^+ ion is a distorted square pyramid, with the longest Na—O bond [Na24—O2^{v} 2.699 (3) Å; symmetry code: (v) $x, y-1, z$] being in the apical position. The equatorial bond lengths fall into the range 2.249 (2)–2.423 (2) Å. Atoms O5 and O2 serve as bridging atoms between Na^+ ions. The four-membered ring [Na24/O5^{ii}/-Na24^{iv}/O5^{iii}; symmetry codes (ii) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (iii) $1-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $1-x, -y, 1-z$] lies on an inversion centre and is therefore planar. The Na24···Na24^{iv} distance across the inversion centre is 3.410 (2) Å.

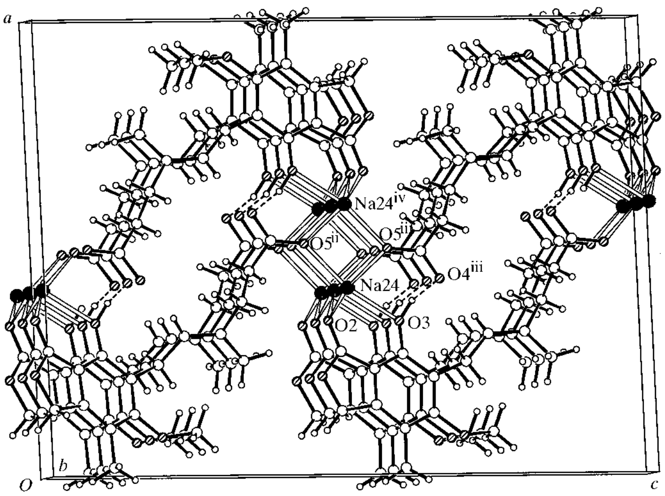


Figure 2
Packing diagram for (I) showing the Na—O network (broken lines indicate hydrogen bonds); the symmetry codes are as in Table 1.

Experimental

Compound (I) was obtained upon treatment of a methanolic solution of commercially available mycophenolic acid with one equivalent of sodium methanolate. After stirring for 1 h at room temperature, the solvent was evaporated to dryness *in vacuo* to afford the desired compound (m.p. 463 K). Single crystals were grown by evaporation and cooling of a water/ethyl acetate solution from about 323 K to room temperature.

Crystal data

$Na^+\cdot C_{17}H_{19}O_6^-$	D_x = 1.397 Mg m^{-3}
M_r = 342.31	Cu $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
a = 16.544 (4) Å	θ = 15–26°
b = 4.4770 (10) Å	μ = 1.107 mm^{-1}
c = 21.993 (3) Å	T = 293 (2) K
β = 92.140 (10)°	Prism, colourless
V = 1627.8 (6) Å^3	0.41 × 0.20 × 0.15 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 74.22°
$\omega/2\theta$ scans	$h = -20 \rightarrow 20$
3432 measured reflections	$k = 0 \rightarrow 5$
3334 independent reflections	$l = 0 \rightarrow 27$
2058 reflections with $I > 2\sigma(I)$	3 standard reflections frequency: 120 min
R_{int} = 0.058	intensity decay: 2%

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.048	$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.121	$(\Delta/\sigma)_{max} = -0.008$
S = 0.918	$\Delta\rho_{max}$ = 0.31 e Å^{-3}
2913 reflections	$\Delta\rho_{min}$ = −0.29 e Å^{-3}
217 parameters	

Table 1
Selected geometric parameters (Å, °).

O1—C7	1.364 (3)	O3—Na24	2.249 (2)
O1—C14	1.437 (3)	O4—C20	1.271 (3)
O2—C7	1.217 (3)	O5—C20	1.224 (3)
O2—Na24	2.423 (2)	Na24—O5^{ii}	2.259 (2)
O2—Na24^{i}	2.699 (3)	Na24—O5^{iii}	2.361 (2)
O3—C9	1.300 (2)	Na24—Na24^{iv}	3.410 (2)
O3—Na24—O5^{ii}	166.76 (8)	O5^{iii}—Na24—O2	152.69 (10)
O3—Na24—O5^{iii}	83.55 (7)	O3—Na24—O2^{v}	88.86 (8)
O5^{ii}—Na24—O5^{iii}	84.88 (7)	O5^{ii}—Na24—O2^{v}	95.58 (9)
O3—Na24—O2	81.55 (7)	O5^{iii}—Na24—O2^{v}	80.53 (9)
O5^{ii}—Na24—O2	106.36 (8)	O2—Na24—O2^{v}	121.77 (9)

Symmetry codes: (i) $x, 1+y, z$; (ii) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (iii) $1-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $1-x, -y, 1-z$; (v) $x, y-1, z$.

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O4^{iii}	0.88	1.73	2.464 (3)	139

Symmetry code: (iii) $1-x, y-\frac{1}{2}, \frac{3}{2}-z$.

All H atoms could be located from a difference Fourier map. The parameters of the H atom attached to O3 were kept fixed and the other H atoms were treated as riding.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ORTEP*II (Johnson, 1976) and *SCHAKAL*97 (Keller, 1997).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1094). Services for accessing these data are described at the back of the journal.

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