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Bis(nateglinide) hydronium chloride, and its unique self-assembly into extended polymeric arrays *via* O—H···O, N—H···Cl and O—H···Cl hydrogen bonds

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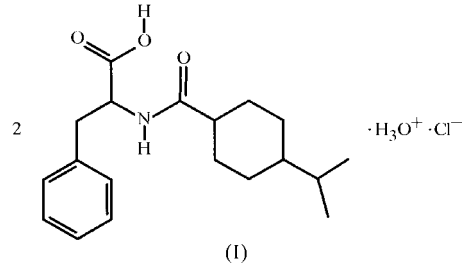
The title compound, bis[(−)-*N*-(*trans*-4-isopropylcyclohexanecarbonyl)-D-phenylalanine] hydronium chloride, $2C_{19}H_{27}NO_3\cdot H_3O^+\cdot Cl^-$, at 110 K contains four conformationally dissimilar moieties in the asymmetric unit, which are seemingly necessary in order to optimize the supramolecular association. The organic molecule forms O—H···O hydrogen-bonded carboxylic acid dimers, which are paired into six-component clusters *via* N—H···Cl hydrogen bonds through the two bridging chloride anions. These combined hexameric aggregates are further interlinked into extended two-dimensional network arrays *via* the hydronium ions by O—H···O and O—H···Cl hydrogen bonds. This study represents the first crystallographic report of nateglinide.

Comment

Nateglinide is an oral drug used to lower blood glucose levels in type 2 diabetes. It belongs to a class of drugs called meglitinides and gained FDA approval in December 2000. Nateglinide stimulates cells in the pancreas to produce insulin in a manner similar to the sulfonylurea insulin, although these two classes of insulin drugs are structurally unrelated. The first crystallographic determination of this pharmaceutically important material is described here; it could be crystallized only in the presence of dilute HCl. The title compound, (I), is a cocrystal of nateglinide and hydrated hydrochloric acid in a 2:1 stochiometric ratio. Incorporation of the latter into the crystal structure induces the formation of continuous hydrogen-bonding arrays, yielding a stable structure. Molecules of (I) are characterized by several degrees of conformational freedom, and the asymmetric unit consists of four organic species (labeled *A*, *B*, *C* and *D*) of different conformations (Table 1) and two hydrated HCl moieties (Fig. 1). Cocrystallization with HCl did not result (as is often observed) in protonation of the basic NH site in the drug. Rather, in the present structure, the hydrochloric acid, in the form of $H_3O^+\cdot Cl^-$, was found to act as a multiple hydrogen-bond donor and acceptor to direct the formation of supramolecular networks by bridging between the organic components. Nateglinide contains two proton donors (the –COOH and –NH sites) and two proton acceptors (the COOH and C=O sites), all of which effectively utilized. The hydrogen-bonding pattern can be best described in the following modular manner. Firstly, the organic molecules are paired by self-complementary O—H···O=C cyclic interactions through their carboxylic acid functions (Table 2). Then, two such self-assembled pairs are joined into a larger hydrogen-bonded assembly by two Cl^- ions, each attracting a H atom from the NH sites of two neighboring units (Fig. 2 and Table 2). These Cl-bridged oligomeric entities are further crosslinked by additional hydrogen bonding through the hydronium ions. The latter donate their H atoms to amide atoms O3 of adjacent species, as well as to chloride ions. This co-operative multiple hydrogen bonding leads to the formation of supramolecular networks, which are perpendicular to the *a* axis of the crystal and center around $x = 0$ and $x = \frac{1}{2}$ (Fig. 3 and Table 2). All the H-atom donating and accepting functions are embedded within these layers, while the hydrophobic isopropylcyclohexane and phenyl residues line the upper and lower surfaces of the layers.



(I)

Stacking of the hydrogen-bonded networks along (100) is thus stabilized by common van der Waals interactions between the hydrophobic surfaces (Fig. 4). The conformational flexibility of the nateglinide molecular framework, while preserving the chair conformation of the cyclohexyl residue, is demonstrated in Table 1 by the different torsion angles associated with the benzyl, isopropylcyclohexyl and carboxyl groups in the four independent molecules of the asymmetric unit. The four-molecule content of the asymmetric unit is seemingly required in order to optimize the inter-particle dispersive and multiple hydrogen-bonding interactions in the crystal structure.

All the bond lengths and angles are in the normal ranges, and the observed results distinguish clearly between the $C{=}O_{carbonyl}$ and $C{-}O_{hydroxy}$ bonds in the carboxylic acid groups. The short O—H···O hydrogen-bonding distances, within the range 2.454 (3)–2.530 (3) Å, involving atoms O4 and O5 are consistent with the positively charged hydronium identity of these species (Jeffrey, 1997). Evidently, the bifurcated $N{-}H\cdots Cl^-$ interactions are much weaker than the $H_3O^+\cdots Cl^-$ interactions (Table 2). The apparent optimization of the hydrogen-bonding scheme leads to a somewhat ineffi-

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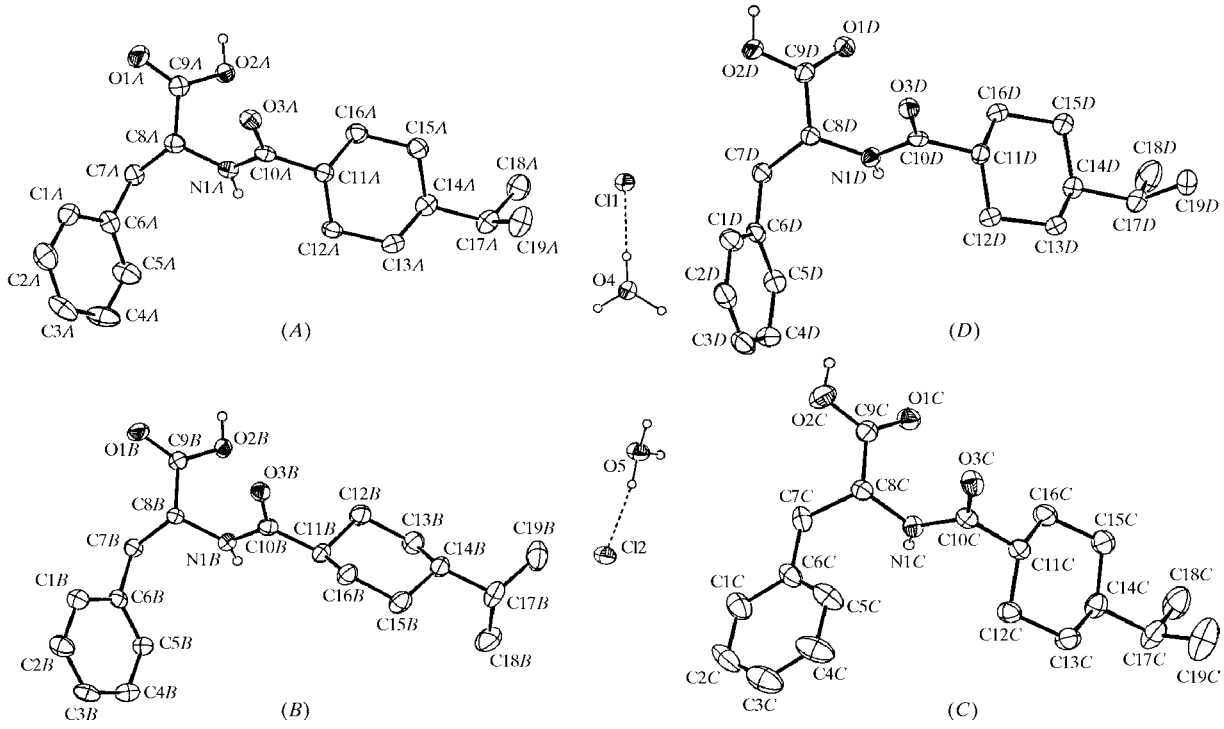

Figure 1
Compound (I), showing the atom-labeling scheme. Displacement ellipsoids are shown at the 50% probability level and H atoms bound to C atoms have been omitted. The four crystallographically independent molecules of nateglinide are denoted *A*–*D*.

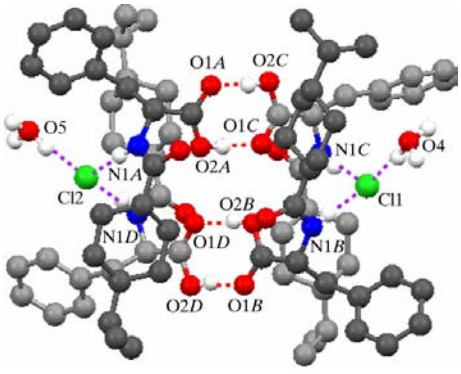

Figure 2
The self-assembled multicomponent asymmetric unit with hydrogen bonding through the COOH dimers and the two chloride ion bridges. For clarity, only H atoms that are involved in hydrogen bonds (dashed lines) are shown.

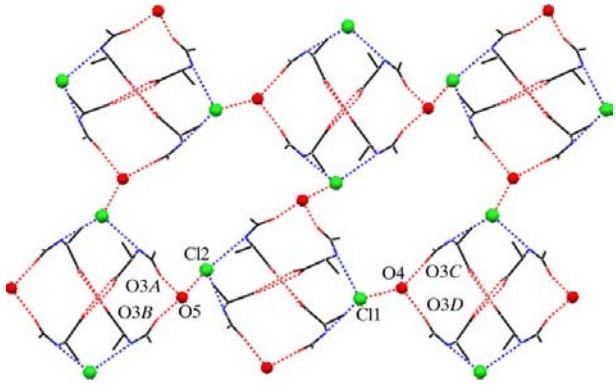

Figure 3
A face-on illustration of the continuous hydrogen-bonded networks normal to (100), showing further aggregation of the organic tetramers into two-dimensional arrays by crosslinking through the hydronium ions. For clarity, molecules are represented only by their central C—C(COOH)—NH—CO—C fragment; the hydronium and chloride ions are represented by small spheres.

cient crystal packing of relatively low density, which contains two solvent-accessible voids of *ca* 80 Å^3 that are centered along the interface between the hydrogen-bonded layers at (0.49, 0.22, 0.18) and (0.51, 0.72, 0.82). The terminal isopropyl groups that point into these voids reveal some disorder, reflected in the large-amplitude displacement ellipsoids of their respective atoms (particularly the C17*C*–C19*C* fragment). The total residual electron density in the void spaces was assessed to be ten electrons per unit cell (Spek, 2003), which is consistent with the rather minor conformational disorder in the structure. A survey of the Cambridge Structural Database (Allen, 2002) indicates that no structures of similar composition (cyclohexanecarbonyl and phenylalanine residues joined through an amide bond) and connectivity have been reported as yet. Multicomponent supramolecular assemblies sustained simultaneously by $(COOH)_2$ cyclic dimeric and N—H···Cl···H—N hydrogen bonds have not been found either, although separate appearances of these two synthons are quite abundant in organic crystals (Allen, 2002; Chang *et al.*, 1993; Chekmenev *et al.*, 2004).

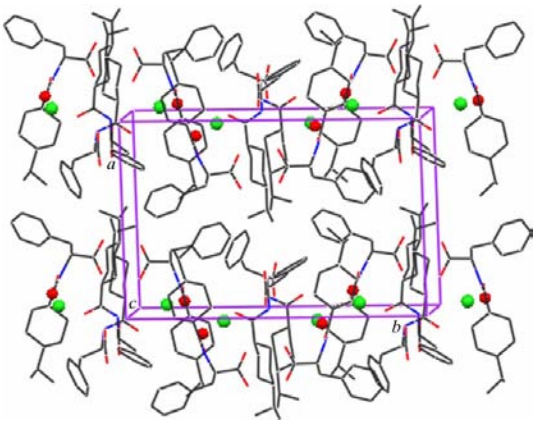

Figure 4
The crystal packing, viewed down (001), showing alternating hydrophilic (within the hydrogen-bonded layers) and hydrophobic zones (between the layers). A stick diagram is used to represent the nateglinide molecules, and the hydronium and chloride ions are represented by small spheres.

Experimental

Compound (I) was crystallized by dissolving nateglinide (0.0291 g) in 1.0 *M* HCl (4 ml) at 353 K, followed by slow cooling and evaporation.

Crystal data

$2C_{19}H_{27}NO_3\cdot H_3O^+\cdot Cl^-$
M_r = 689.31
Monoclinic, $P2_1$
a = 14.0121 (2) Å
b = 19.6631 (3) Å
c = 15.3773 (2) Å
β = 110.2998 (8)°
V = 3973.62 (10) Å^3
Z = 4
D_x = 1.152 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8475 reflections
θ = 1.6–27.9°
μ = 0.14 mm^{-1}
T = 110 (2) K
Prism, colorless
0.35 × 0.30 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
29123 measured reflections
15992 independent reflections
11365 reflections with $I > 2\sigma(I)$
R_{int} = 0.071
θ_{max} = 27.9°
$h = -18 \rightarrow 18$
$k = -25 \rightarrow 23$
$l = -20 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.055
$wR(F^2)$ = 0.115
S = 1.03
15992 reflections
931 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0461P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0041 (3)
Absolute structure: Flack (1983), 6258 Friedel pairs
Flack parameter: −0.01 (4)

Table 1
Selected torsion angles (°).

N1*A*—C8*A*—C9*A*—O1*A*	−166.8 (3)	N1*C*—C8*C*—C9*C*—O1*C*	−0.8 (4)
N1*A*—C8*A*—C9*A*—O2*A*	15.3 (4)	N1*C*—C8*C*—C9*C*—O2*C*	−179.9 (3)
N1*A*—C10*A*—C11*A*—C14*A*	36.5 (6)	N1*C*—C10*C*—C11*C*—C14*C*	32.0 (7)
C8*A*—N1*A*—C10*A*—O3*A*	7.5 (4)	C8*C*—N1*C*—C10*C*—O3*C*	8.0 (4)
N1*B*—C8*B*—C9*B*—O1*B*	−172.5 (3)	N1*D*—C8*D*—C9*D*—O1*D*	6.7 (4)
N1*B*—C8*B*—C9*B*—O2*B*	8.8 (3)	N1*D*—C8*D*—C9*D*—O2*D*	−174.3 (2)
N1*B*—C10*B*—C11*B*—C14*B*	163.5 (4)	N1*D*—C10*D*—C11*D*—C14*D*	21.8 (6)
C8*B*—N1*B*—C10*B*—O3*B*	6.6 (4)	C8*D*—N1*D*—C10*D*—O3*D*	8.9 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2*A*—HO2*A*···O1*C*	0.95 (2)	1.70 (2)	2.643 (3)	177 (5)
N1*A*—HN1*A*···Cl2	0.94 (2)	2.44 (2)	3.348 (3)	160 (3)
O2*B*—HO2*B*···O1*D*	0.95 (2)	1.72 (2)	2.653 (3)	168 (5)
N1*B*—HN1*B*···Cl1	0.91 (2)	2.34 (2)	3.237 (2)	173 (3)
O2*C*—HO2*C*···O1*A*	0.91 (2)	1.70 (2)	2.609 (3)	174 (4)
N1*C*—HN1*C*···Cl1	0.93 (2)	2.40 (2)	3.300 (3)	163 (3)
O2*D*—HO2*D*···O1*B*	0.94 (2)	1.64 (2)	2.569 (3)	168 (4)
N1*D*—HN1*D*···Cl2	0.92 (2)	2.37 (2)	3.262 (2)	163 (3)
O4—HO4*A*···O3*C*^{i}	0.96 (2)	1.58 (2)	2.530 (3)	172 (4)
O4—HO4*B*···O3*D*^{i}	0.96 (2)	1.51 (2)	2.454 (3)	166 (6)
O4—HO4*C*···Cl1	0.97 (2)	2.05 (2)	3.008 (2)	171 (4)
O5—HO5*A*···Cl2	0.96 (2)	2.00 (2)	2.959 (2)	172 (3)
O5—HO5*C*···O3*A*^{ii}	0.97 (2)	1.49 (2)	2.459 (3)	178 (4)
O5—HO5*B*···O3*B*^{ii}	0.96 (2)	1.57 (2)	2.506 (3)	165 (5)

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

H atoms bound to C atoms were located in idealized positions (C—H = 0.95–1.00 Å) and were refined with fixed displacement parameters [U_{iso}(H) = 1.2U_{eq}(C) or 1.5 U_{eq}(C)] using a riding model. H atoms attached to O and N atoms were located reliably in difference Fourier maps and included in the refinement with isotropic displacement parameters and distance restraints imposed on the O—H and N—H bonds. The minor disorder apparent in some of the isopropyl fragments could not be resolved.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1291). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Altomare, A., Burla, M. C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A. & Polidori, G. (1994). *J. Appl. Cryst.* **27**, 435.
Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M., Macrae, C. F., McCabe, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst.* B**58**, 389–397.
Burnett, M. N. & Johnson, C. K. (1996). *ORTEPIII*. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee, USA.
Chang, Y.-L., West, M.-A., Fowler, F. W. & Lauher, J. W. (1993). *J. Am. Chem. Soc.* **115**, 5991–6000.
Chekmenev, E. Y., Zhang, Q., Waddell, K. W., Mashuta, M. S. & Witterbort, R. J. (2004). *J. Am. Chem. Soc.* **126**, 379–384.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Jeffrey, G. A. (1997). In *An Introduction to Hydrogen Bonding*. Oxford University Press.
Nonius (1999). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.