Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Similarity in structures of racemic and enantiomeric ibuprofen sodium dihydrates

Yuegang Zhang and David J. W. Grant*

Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Weaver–Densford Hall, 308 Harvard Street SE, Minneapolis, MN 55455-0343, USA
Correspondence e-mail: grant001@umn.edu

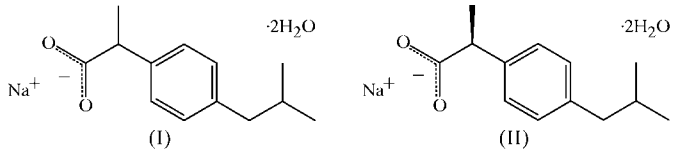
Received 22 June 2005
Accepted 3 August 2005
Online 31 August 2005

The crystal structures of two ibuprofen sodium dihydrates, racemic sodium (*RS*)-2-(4-isobutylphenyl)propanoate dihydrate or (*RS*)-NaIBDH, $Na^+\cdot C_{13}H_{17}O_2^-\cdot 2H_2O$, and enantiomeric sodium (*S*)-2-(4-isobutylphenyl)propanoate dihydrate or (*S*)-NaIBDH, $Na^+\cdot C_{13}H_{17}O_2^-\cdot 2H_2O$, have been determined in the space groups $P\overline{1}$ and *P*1, respectively. The unit cells of the two triclinic structures have similar lattice parameters and cell volumes. The constituent ions have similar coordination environments, but differ slightly in their hydrogen-bonding interactions. The dominance of the interactions between the O atoms and the Na^+ cations explains the structural similarity of these two structures, despite the fact that one is heterochiral while the other is homochiral.

Comment

Ibuprofen [α-methyl-4-(isobutyl)phenylacetic acid] is a chiral non-steroidal anti-inflammatory drug (NSAID). The racemic compound, (*RS*)-ibuprofen, is usually formulated as tablets or suspensions, which may be purchased without a prescription. The sodium salt of racemic ibuprofen is much more water-soluble than the free acid (Gaikar & Latha, 1997), and crystallizes from water as a dihydrate. Recent publications have described the pharmacokinetics (Soergel *et al.*, 2005), while recent patents have disclosed the formulation of ibuprofen sodium dihydrate (Gruber, 2003; Armitage *et al.*, 1992). This paper compares the crystal structures of racemic [(*RS*)-NaIBDH] and enantiomeric [(*S*)-NaIBDH] ibuprofen sodium dihydrates, (I) and (II), respectively, and explains their similarity.

The ibuprofen sodium dihydrate phase is stable under ambient conditions, while the anhydrous phase is highly hygroscopic. Differential scanning carlorimetry (DSC) and thermogravimetric analysis (TGA) indicate that both structures lose two water molecules in one step. (*RS*)-NaIBDH loses 13.5% of weight (theoretical value 13.6%) between 317 and 365 K. The anhydrous *RS* salt melts at 474 K. (*S*)-NaIBDH loses 13.1% of weight (theoretical value 13.6%) between 314 and 362 K and the anhydrous *S* salt then melts at 507 K.



The two dihydrate structures are triclinic, with similar lattice parameters and cell volumes. For comparison, the non-reduced cell is shown here for the (*S*)-NaIBDH structure, while the CIF file with the structure in the reduced cell is provided in the supplementary material [lattice parameters: a = 5.7767 (5), b = 6.0797 (5) and c = 23.880 (2) Å, α = 93.499 (1), β = 93.518 (1) and γ = 118.322 (1)°, and V = 733.01 (11) Å^3]. The space group of (*RS*)-NaIBDH is $P\overline{1}$, while that of (*S*)-NaIBDH is *P*1. These two structures are very similar in their packing styles, due to the similarity of the coordination interactions. In the (*RS*)-NaIBDH structure, two paired *R* and *S* ibuprofen anions are related by a center of symmetry. The two *S* ibuprofen anions, the two Na^+ cations and the four water molecules in the asymmetric unit of (*S*)-NaIBDH are related by a pseudo-twofold screw axis along the *a* direction. However, the ring formed by the Na^+ cations, the water molecules and the carboxylate groups gives the impression of a pseudo-center of symmetry. The two structures are shown in Figs. 1 and 2.

The structures clearly show hydrophilic and hydrophobic regions. The hydrophilic regions are formed by the network of water molecules, Na^+ cations and carboxylate groups. The carboxylate groups on the ibuprofen molecules are bridged by the Na^+ cations to form a one-dimensional infinite chain. In the (*RS*)-NaIBDH structure, each of the two chains contains only *R* or *S* molecules, respectively. Two such chains are linked by the water molecules bridging the Na^+ cations to form a one-dimensional infinite zipper along the *a* direction, approximately parallel to the $(0\overline{1}2)$ crystallographic plane. Such zippers stack along the *b* direction and interact by hydrogen bonding to form wafers, the thickness of which is the same as the length of the *c* dimension, parallel to the *ab* plane. The two sides of the thick wafers consist of the disordered isobutyl

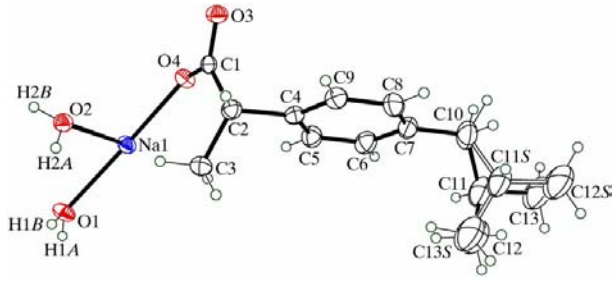


Figure 1
A plot of the asymmetric unit of (*RS*)-ibuprofen sodium dihydrate, (I). Displacement ellipsoids are drawn at the 50% probability level. The disordered fragment with shaded bonds consists of atoms C11, C12 and C13, while that with unshaded bonds consists of atoms C11*S*, C12*S* and C13*S*.

 DOI: 10.1107/S0108270105024807

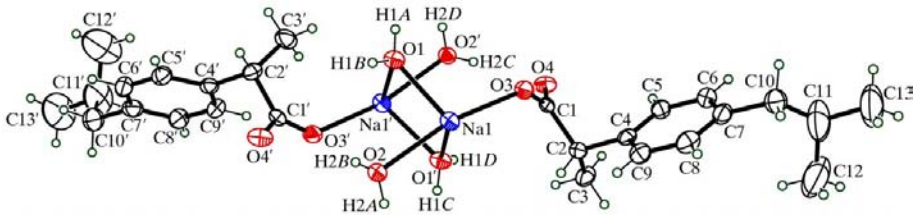


Figure 2
A plot of the asymmetric unit of (*S*)-ibuprofen sodium dihydrate, (II). Displacement ellipsoids are drawn at the 50% probability level.

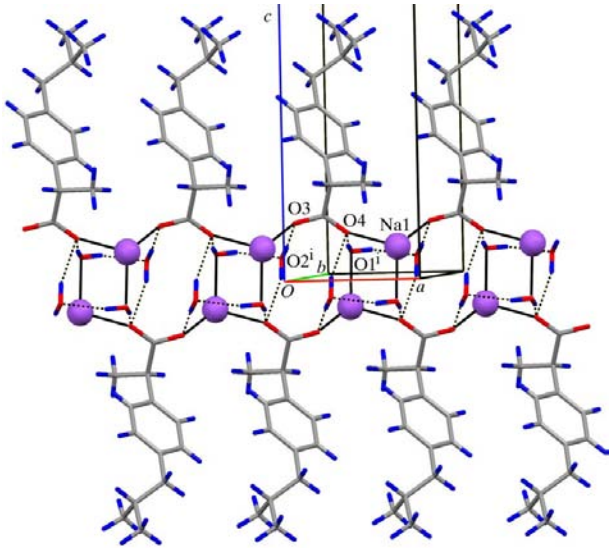


Figure 3
Interactions in the (*RS*)-ibuprofen sodium dihydrate crystal. The disordered fragment has been truncated for clarity. [Symmetry code: (i) $x-1, y+1, z$.]

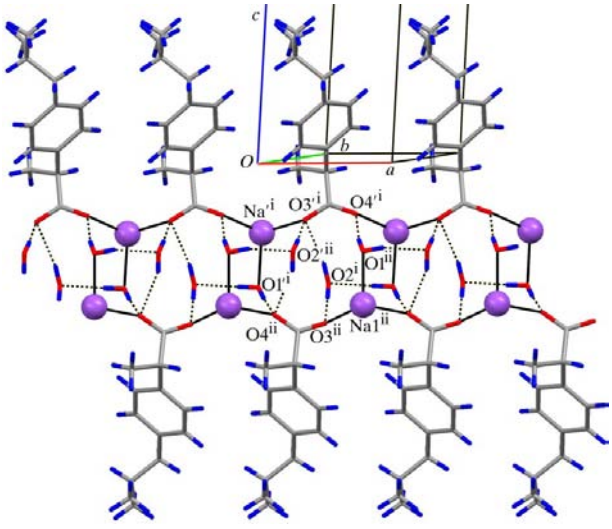


Figure 4
Interactions in the (*S*)-ibuprofen sodium dihydrate crystal. [Symmetry codes: (i) $x-1, y, z-1$; (ii) $x, y-1, z-1$.]

groups and form the hydrophobic regions. The thick wafers stack to form the whole crystal *via* weak van der Waals interactions.

The water molecule bridging the two Na^+ cations donates two lone pairs of electrons, and also donates two H atoms to form hydrogen bonds. The other water molecule donates one lone pair of electrons to an Na^+ cation and two H atoms for hydrogen bonding. The interactions surrounding this latter water molecule are strong enough to hinder its loss on a par with the doubly coordinated water molecule, as indicated by the dehydration behavior seen in the TGA. The relatively high stability of the dihydrate phases also explains the hygroscopicity of anhydrous ibuprofen sodium. From the point of view of the hydrogen bonding, two pairs of ibuprofen anions are bridged by two water molecules to form a ring; the rings are bridged by a third water molecule to form a one-dimensional column along the *a* direction. In (*RS*)-NaIBDH, the ring has a centrosymmetric chair conformation, while in (*S*)-NaIBDH, the ring is not centrosymmetric due to the O2—H2*B*···O3′ hydrogen bonding (Figs. 3 and 4). The hydrogen-bonding geometries of the two structures are provided in Tables 1 and 2.

Each Na^+ cation has close contact with three O atoms of the water molecules and two O atoms of two carboxylate groups to form a pyramidal coordination. Two neighboring Na^+ cations are bridged by a pair of water O atoms to form a square plane. The Na^+ cations are linked by carboxylate groups to form one-dimensional chains. Each carboxylate group coordinates to two Na^+ cations and also acts as the proton acceptor for H atoms of three water molecules.

The similarities between the racemic and enantiomeric crystal structures have been observed for other organic molecules, as summarized in Table 3. Comparison shows that one type of structure has two molecules in the asymmetric unit of the enantiomeric structure, which is similar to one pair of asymmetric units in the centrosymmetric structure. In the other type, the unit cell is doubled in the racemic structure and both structures have two molecules in their asymmetric units. Although these structures are similar in packing style, differences arise from the chirality.

This research demonstrates that the dominant interaction for the packing of ibuprofen sodium dihydrate structures is the cation coordination, although the influence of chirality is also seen in the hydrogen-bonding interactions.

Experimental

(*RS*)-Ibuprofen sodium was purchased from Sigma (Saint Louis, Missouri). Enantiomeric (*S*)-ibuprofen sodium anhydrate was

prepared according to the method of Zhang *et al.* (2003). The respective dihydrate crystals of diffraction quality crystallized as thin plates by slow evaporation of a solution of the corresponding anhydrous sodium salt in water–acetonitrile (2:1 *v*/*v*). For (*RS*)-NaIBDH, an equimolar amount of D-maltose was added to obtain satisfactory crystals. The crystals obtained were stored in contact with their mother liquor.

Compound (I)

Crystal data

$Na^+\cdot C_{13}H_{17}O_2^-\cdot 2H_2O$
M_r = 264.29
Triclinic, $P\overline{1}$
a = 5.7396 (4) Å
b = 6.0284 (4) Å
c = 23.8301 (17) Å
α = 83.457 (1)°
β = 89.241 (1)°
γ = 63.154 (1)°
V = 730.20 (9) Å^3
Z = 2
D_x = 1.202 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2507 reflections
θ = 1.8–27.0°
μ = 0.11 mm^{-1}
T = 173 (2) K
Plate, colorless
0.40 × 0.30 × 0.10 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
Oscillation photo scans around ω at four φ
Absorption correction: empirical (using intensity measurements) based on ΔI (*SADABS*; Bruker, 2000)
T_{min} = 0.791, T_{max} = 1.000
8727 measured reflections
3317 independent reflections
2610 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 27.6°
$h = -7 \rightarrow 7$
$k = -7 \rightarrow 7$
$l = -30 \rightarrow 30$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.135
S = 1.05
3317 reflections
185 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0626P)^2 + 0.4067P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.49 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2A···O3^{i}	0.83 (2)	1.86 (2)	2.6907 (17)	176 (3)
O1—H1B···O4^{i}	0.83 (2)	1.98 (2)	2.7998 (17)	172 (3)
O1—H1A···O2^{ii}	0.82 (2)	1.95 (2)	2.7507 (17)	166 (3)
O2—H2B···O4^{iii}	0.83 (2)	2.04 (2)	2.8438 (18)	162 (3)

Symmetry codes: (i) $x+1, y-1, z$; (ii) $x+1, y, z$; (iii) $-x+1, -y, -z$.

Compound (II)

Crystal data

$Na^+\cdot C_{13}H_{17}O_2^-\cdot 2H_2O$
M_r = 264.29
Triclinic, $P1$
a = 5.7767 (5) Å
b = 6.0835 (5) Å
c = 23.880 (2) Å
α = 83.151 (1)°
β = 86.482 (1)°
γ = 61.612 (1)°
V = 733.00 (11) Å^3
Z = 2
D_x = 1.197 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3725 reflections
θ = 1.9–27.0°
μ = 0.11 mm^{-1}
T = 173 (2) K
Plate, colorless
0.30 × 0.30 × 0.10 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
Oscillation photo scans around ω at four φ
Absorption correction: empirical (using intensity measurements) based on ΔI (*SADABS*; Bruker, 2000)
T_{min} = 0.822, T_{max} = 1.000
7383 measured reflections
2589 independent reflections
2350 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 25.0°
$h = -6 \rightarrow 6$
$k = -7 \rightarrow 7$
$l = -28 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.113
S = 1.07
2589 reflections
356 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0737P)^2 + 0.1763P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.57 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2B···O3′	0.85 (2)	2.15 (2)	2.990 (4)	170 (6)
O2′—H2D···O3′^{i}	0.85 (2)	1.88 (2)	2.723 (4)	173 (7)
O1—H1A···O4′^{i}	0.85 (2)	1.92 (2)	2.766 (4)	171 (6)
O1′—H1C···O4^{ii}	0.85 (2)	1.96 (2)	2.806 (4)	172 (6)
O1′—H1D···O2^{iii}	0.85 (2)	1.92 (2)	2.771 (4)	177 (6)
O2′—H2C···O4	0.85 (2)	2.14 (3)	2.940 (4)	158 (6)
O2—H2A···O3^{ii}	0.85 (2)	1.84 (2)	2.688 (4)	176 (6)
O1—H1B···O2′^{iv}	0.85 (2)	1.93 (3)	2.753 (4)	162 (6)

Symmetry codes: (i) $x-1, y+1, z$; (ii) $x+1, y-1, z$; (iii) $x-1, y, z$; (iv) $x+1, y, z$.

The absolute configuration was known for (*S*)-NaIBDH from the synthesis. This experiment did not attempt to determine the absolute structure. Friedel pairs were merged before refinement. The disordered isobutyl group in (*RS*)-NaIBDH was modeled as two fragments, while that in (*S*)-NaIBDH was modeled as one fragment, due to the instability of the restrained refinement as two fragments. The CH_2–CH_3 C—C distances in the isobutyl group were restrained to be identical. The displacement parameters of all H atoms were restrained to be identical in each structure. Water H atoms were restrained to have O—H bond distances within ±0.005 Å in each structure. All other H atoms were refined using a riding model, with idealized geometry (C—H = 0.93–1.00 Å).

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *MERCURY* (Bruno *et al.*, 2002) and *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *PLATON* (Spek, 2003).

We thank Dr Victor G. Young Jr for use of the X-Ray Crystallographic Laboratory at Kolthoff Hall, University of Minnesota. We also thank the University of Minnesota Supercomputing Institute for financially supporting our use of the Medicinal Chemistry–Supercomputing Institute Visualization Workstation Laboratory.

Table 3
Comparison of reported structures showing structural similarity between racemic and enantiomeric crystals.

Compound name	Racemic Space group	Z	Z'	Reference	Enantiomeric Space group	Z	Z'	Pseudosymmetry	Reference
4-Hydroxy-3-(1-phenylpropyl)coumarin	$P2_1/n$	4	1	*a*	$P2_1$	4	2	Center of symmetry	*b*
3-[Benzyl(phenyl)phosphinyl]-2-butenoic acid	$P2_1/c$	4	1	*c*	$P2_1$	4	2	Twofold axis	*d*
Mandelic acid	$P2_1/c$	8	2	*e*	$P2_1$	4	2	Twofold axis	*f*
{2-[4-(3-Ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl}trimethylammonium *p*-bromobenzenesulfonate	$P\overline{1}$	2	1	*g*	$P1$	2	2	Twofold axis	*g*
Ibuprofen sodium dihydrate	$P\overline{1}$	2	1	*h*	$P1$	2	2	Twofold screw axis	*h*

References: (*a*) Bravic *et al.* (1971); (*b*) Valente *et al.* (1976); (*c*) Główka (1978); (*d*) Główka (1981); (*e*) Fischer & Profir (2003); (*f*) Patil *et al.* (1987); (*g*) Takahashi *et al.* (2002); (*h*) this work.

Supplementary data for this paper, including reduced-cell data for (II), are available from the IUCr electronic archives (Reference: SQ1215). Services for accessing these data are described at the back of the journal.

References

Armitage, B. J., Coe, P. F., Lampard, J. F. & Smith, A. (1992). World Patent PCT Int. Appl. WO 9220334, A1 19921126; Chemical Abstracts accession numbers CAN 118:132148, AN 1993:132148.

Bravic, G., Gaultier, J. & Hauw, C. (1971). *C. R. Acad. Sci. Ser. C*, **272**, 1112–1114.

Bruker (2000). *SADABS* (Version 2.03) and *SHELXTL* (Version 6.12). Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (2001). *SMART*. Version 5.054. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (2003). *SAINT-Plus*. Version 6.45. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M. K., Macrae, C. F., McCabe, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst*. B**58**, 389–397.

Fischer, A. & Profir, V. M. (2003). *Acta Cryst.* E**59**, o1113–o1116.

Gaikar, V. G. & Latha, V. (1997). *Drug Dev. Ind. Pharm.* **23**, 309–312.

Główka, M. L. (1978). *Acta Cryst.* B**34**, 3089–3091.

Główka, M. L. (1981). *Acta Cryst.* B**37**, 1780–1783.

Gruber, P. (2003). Swiss Patent CH 693586 A 20031031 CH 2002-1703 20021014; Chemical Abstracts accession numbers CAN 141:415973, AN 2004:930062.

Patil, A. O., Pennington, W. T., Paul, I. C., Curtin, D. Y. & Dykstra, C. E. (1987). *J. Am. Chem. Soc.* **109**, 1529–1535.

Soergel, F., Fuhr, U., Minic, M., Siegmund, M., Maares, J., Jetter, A., Kinzig-Schippers, M., Tomalik-Scharte, D., Szymanski, J., Goeser, T., Toex, U., Scheidel, B. & Lehmacher, W. (2005). *Int. J. Clin. Pharmacol. Ther.* **43**, 140–149.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Takahashi, H., Tamura, R., Fujimoto, D., Lepp, Z., Kobayashi, K. & Ushio, T. (2002). *Chirality*, **14**, 541–547.

Valente, E. J., Trager, W. F. & Lingafelter, E. C. (1976). *Acta Cryst.* B**32**, 277–279.

Zhang, G. G. Z., Paspal, S. Y. L., Suryanarayanan, R. & Grant, D. J. W. (2003). *J. Pharm. Sci.* **92**, 1356–1366.