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Three Stereoisomers of a Novel and Selective μ-Opioid Analgesic

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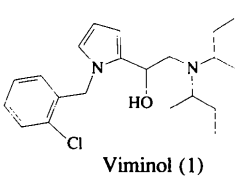
Abstract

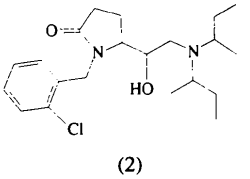
The crystal structures of the following three stereoisomers have been determined: (1*S*)-2-[(1*R*,1′*R*)-, (1*S*)-2-[(1*S*,1′*S*)- and (1*S*)-2-[(1*R*,1′*S*)-bis(1-methylpropyl)-amino]-1-[(5*S*)-1-[(2-chlorophenyl)methyl]-2-oxo-5-pyrrolidinyl]ethanol, $C_{21}H_{33}ClN_2O_2$. The configurations at the stereocentres strongly influence both the hydrogen-bonding behaviour of the OH group and the packing. The conformations of the central N—C—C(OH)—C—N chains are particularly relevant to this behaviour and to the pharmacological activity.

Comment

In the past few years research on new μ-opioid analgesics has been developed by modifying the structure of viminol, (1) (Chiarino, Della Bella, Jommi & Veneziani, 1978), a central analgesic compound developed in our laboratories in the 1970's. This has led to the synthesis and the pharmacological evaluation of all stereoisomers of 5-[2-bis(1-methylpropyl)amino]-1-hydroxyethyl]-1-[(2-chlorophenyl)methyl]-2-pyrrolidinone, (2) (Napoletano *et al.*, 1995).



Viminol (1)



(2)

The biological data clearly showed how the stereochemistry of compounds (2) deeply influenced their affinity towards the opioid receptors and the related analgesic activity.

Elucidation of the influence of the stereogenic centres of the di-*sec*-butyl chains on the conformation of the whole molecule may provide an explanation of the stereochemical requirements for binding to the receptor. Accordingly, X-ray crystal structure analyses of isomers (1*S*)-2-[(1*R*,1′*R*)-, (2*a*), (1*S*)-2-[(1*S*,1′*S*)-, (2*b*), and (1*S*)-2-[(1*R*,1′*S*)-bis(1-methylpropyl)amino]-1-[(5*S*)-1-[(2-chlorophenyl)methyl]-2-oxo-5-pyrrolidinyl]-ethanol, (2*c*), have been carried out and the results are illustrated here. These compounds were prepared starting from (3) (Napoletano, Grancini, Veneziani & Chiarino, 1992) and sterically pure di-*sec*-butylamines according to the scheme shown below.

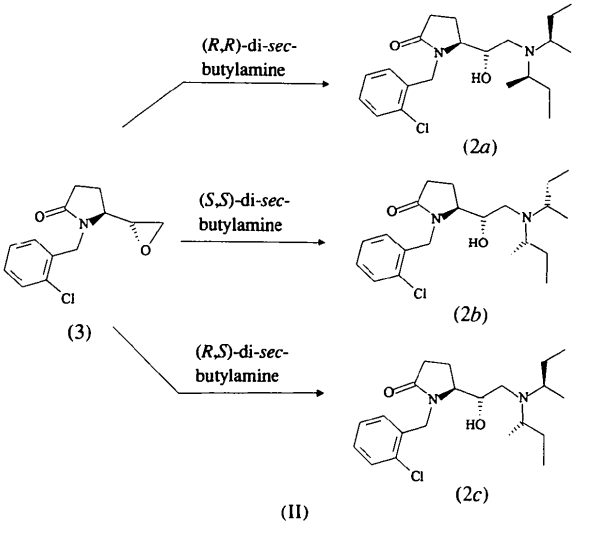


Fig. 1 contains drawings of the three molecules and Tables 4, 5 and 6 present some selected bond distances and angles. As can be seen from Fig. 1, the most relevant differences involve the conformation about the central C11—C12(O2)—C13—N2 chain. The orientation of the C—OH group with respect to the plane through the pyrrolidinone ring is defined by the torsion angle τ_1 = N1—C11—C12—O2: with respect

to C11—N1, the C12—O2 bond is (+)-antiperiplanar in (2*a*) [τ_1 = 178.9 (7)°], (−)-synperiplanar in (2*b*) [τ_1 = −29.7 (6)°] and (+)-synclinal in (2*c*) [τ_1 = 54.2 (4)°]. The orientation of the same C—OH group with respect to the di-*sec*-butylamino group is defined by the torsion angle τ_2 = O2—C12—C13—N2: with respect to C13—N2, the C12—O2 bond is (−)-synclinal in (2*a*) [τ_2 = −71.7 (9)°], (−)-antiperiplanar in (2*b*) [τ_2 = −164.1 (4)°] and (−)-synclinal in (2*c*) [τ_2 = −45.6 (4)°]. The differences between these values are relevant and related to the behaviour of the OH group in hydrogen bonding.

As shown by the three projections of Fig. 2 that illustrate packing in the crystals of the three isomers, an intermolecular hydrogen bond is the most relevant packing interaction for (2*a*) and (2*b*), while for (2*c*) the OH group is involved in an intramolecular hydrogen bond and packing involves only normal van der Waals interactions. Table 7 contains the relevant geometry of these hydrogen bonds.

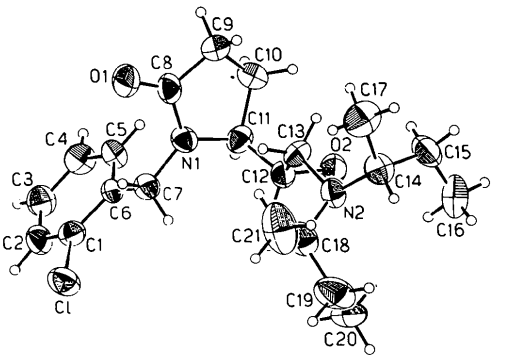
These different hydrogen-bonding arrangements rationalize the differences observed in the melting points, which are 345–346 K for (2*a*), 337–338 K for (2*b*) and 321–322 K for (2*c*); *i.e.* the difference is only of 8 K between the values for (2*a*) and (2*b*) that form intermolecular hydrogen bonds, whereas the melting point is much lower (by 16–24 K) for (2*c*) whose packing involves only van der Waals interactions.

The orientation of the lone pair (LP) at N2, the direction of which was calculated as that of the straight line equidistant from the C atoms attached to N2, is defined by the τ_3 = LP—N2—C13—C12 torsion angle: with respect to the C12—C13 bond the LP direction is (+)-synperiplanar in (2*a*) [τ_3 = 27 (2)°], (−)-synclinal in (2*b*) [τ_3 = −33 (2)°], (+)-synperiplanar (or synclinal) in (2*c*) [τ_3 = 30 (1)°], *i.e.* (2*b*) has opposite chirality to (2*a*) and (2*c*).

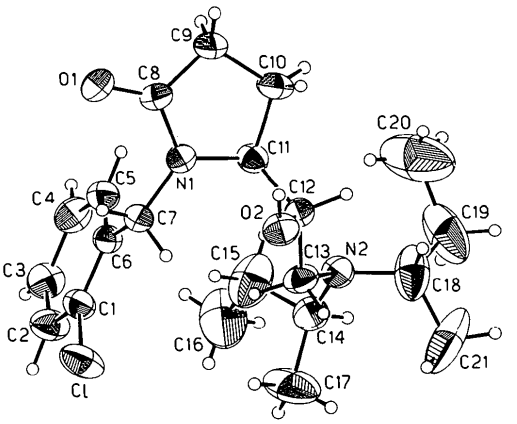
The torsion angle τ_4 = N1—C7—C6—C5 defines the orientation of the phenyl group with respect to the pyrrolidinone ring: the N1—C7 bond is synperiplanar to C5—C6 in all the three isomers, but with some twisting in (2*b*), the values of τ_4 being 0.3 (12), −17.7 (8) and −1.6 (5)° for (2*a*), (2*b*) and (2*c*), respectively. The planes through the phenyl and pyrrolidine rings tend to be orthogonal, the dihedral angles they form being 82.6 (3), 91.7(2) and 76.8 (1)° for (2*a*), (2*b*) and (2*c*), respectively.

It is interesting to consider the calculated energy profiles (deposited) for the non-bonded interations in the isolated molecule obtained by rotating the chlorobenzyl (*A*) and the di-*sec*-butylamino hydroxyethyl (*B*) substituents (positive rotations are counterclockwise). The profiles obtained by rotating the *A* substituent are similar for all three isomers: a broad miminum occurs around the experimentally found position for the molecules packed in the crystals and there is a second narrower minimum shifted from the first by *ca* −170°. These two minima are separated by high energy barriers due to the steric hindrance encountered mainly between the benzyl H atoms and the O1 keto-atom, the H atom bound to C11, the central chain methylene groups and the ethyl of the *sec*-butyl group. The height of these barriers is such as to prevent any change of conformation by simple rotation about the N1—C7 bond.

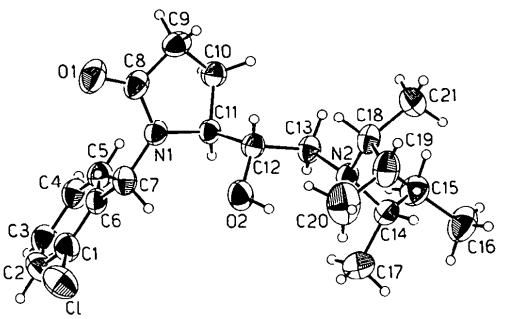
Much greater differences are found between the profiles obtained by rotating the *B* substituent: those of (2*a*) and (2*c*) are similar and unlike that of (2*b*).



(2*a*)

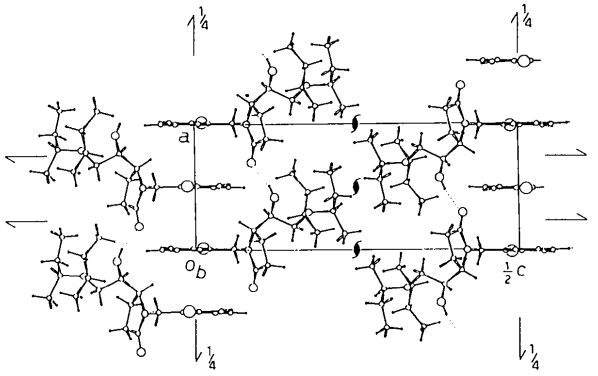


(2*b*)

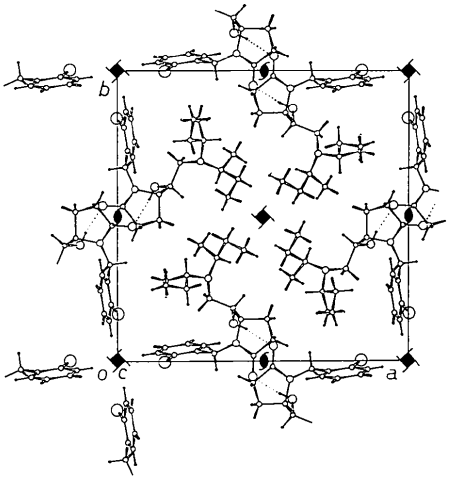


(2*c*)

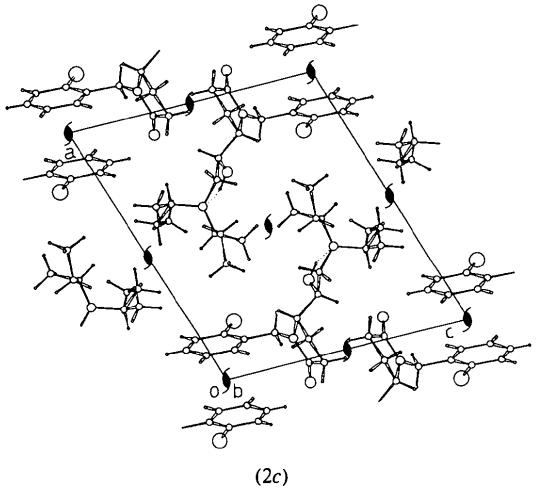
Fig. 1. *ORTEP* (Johnson, 1965) drawings of the (2*a*), (2*b*) and (2*c*) stereoisomers. Ellipsoids are plotted at the 30% probability level.



(2*a*)



(2*b*)



(2*c*)

Fig. 2. *PLUTO* (Motherwell & Clegg, 1983) projections showing packing and hydrogen bonding (dotted lines) in the crystals of the (2*a*), (2*b*) and (2*c*) stereoisomers.

The profiles of (2*a*) and (2*c*) show three minima, two being shifted by *ca* −100 and +150° with respect to the third, which corresponds to the conformation found in the crystal. These minima are separated by low energy barriers, not exceeding 40 kJ mol^{-1}, due to steric hindrance exerted during rotation by the H atoms of methylene groups of the pyrrolidinone ring and of benzyl on those of the central chain methylene. Much higher barriers are found in the profile for (2*b*) where, in addition to the aforementioned hindrance, interactions between Cl and the benzyl-methylene H atoms are also present.

The energy surfaces (deposited) for the complete range of rotations about the N1—C7 (φ_1) and C11—C12 (φ_2) bonds are similar for (2*a*) and (2*c*) and indicate some freedom of rotation about φ_2 when φ_1 is *ca* 0 and −170°, with high energy barriers for rotation about φ_1. In contrast, for (2*b*) the minima are limited to regions near $\varphi_1 = 0$ and −170° which extend only towards the positive values of φ_2.

It is important to note that only (2*a*) has marked pharmacological activity (Napoletano *et al.*, 1995). Hence, the energy profiles and surfaces, and the hydrogen-bonding arrangements observed in the three compounds suggest that the biological activity requires that rotation of the substituent carrying the hydroxyl group should not be greatly hindered and that this group should be free to form intermolecular hydrogen bonds; only when both requirements are met can the desired interaction between a molecule with the proper chirality and the receptor site take place.

Experimental

Preparation of (2*a*): A solution of epoxide (3) (15.4 g, 61 mmol) and (*R*,*R*)-di-*sec*-butylamine (8.1 g, 63 mmol) in *n*-butanol (50 ml) was refluxed for 140 h. The solvent was evaporated at reduced pressure and the residue was taken up with ethyl ether (200 ml) and extracted with hydrochloric acid 5% (200 ml). The aqueous phase was decolorized with charcoal, basified at pH 10 with potassium carbonate and extracted with diethyl ether (200 ml). The ether phase was dried on sodium sulfate and evaporated at reduced pressure; the residue was crystallized from hexane (50 ml). Compound (2*a*) (17.1 g) was obtained as a white solid. m.p. 345–346 K, $[\alpha]_D^{20} = -64.6°$ (*c* = 1%, methanol). ^{1}H NMR [200 MHz, $CDCl_3$, δ (p.p.m.)]: 7.36–7.12 (*m*, 4H); $\nu_a = 4.92$, $\nu_b = 4.63$ (*AB* system, $J_{ab} = 15.6$ Hz); 4.00 (broad signal, 1H); 3.66–3.54 (*m*, 2H); 2.60–1.80 (*m*, 8H); 1.45–1.12 (*m*, 4H); 1.80 (*d*, 6H); 0.84 (*t*, 6H).

(2*b*) was prepared as described for compound (2*a*) using (*S*,*S*)-di-*sec*-butylamine as starting material. M.p. 337–338 K (*n*-hexane, 84% yield, white solid), $[\alpha]_D^{20} = +24.8°$ (*c* = 1%, methanol). ^{1}H NMR [200 MHz, $CDCl_3$, δ (p.p.m.)]: 7.32–7.10 (*m*, 4H); $\nu_a = 4.95$, $\nu_b = 4.39$ (*AB* system, $J_{ab} = 15.8$ Hz); 3.86 (*ddd*, 1H); 3.68 (broad signal, 1H); 3.37 (*ddd*, 1H); 2.66–2.14 (*m*, 6H); 2.10–1.78 (*m*, 2H); 1.57–1.00 (*m*, 4H); 0.96 (*d*, 3H); 0.88 (*d*, 3H); 0.82 (*t*, 3H); 0.79 (*t*, 3H).

(2*c*) was prepared as described for compound (2*a*) using (*S*,*R*)-di-*sec*-butylamine as starting material. M.p. 321–322 K (*n*-hexane, 80% yield, white solid), $[\alpha]_D^{20} = -27.1°$ (*c* = 1%, methanol). ^{1}H NMR [200 MHz, $CDCl_3$, δ (p.p.m.)]: 7.34–7.09 (*m*, 4H); ν_a = 4.93, ν_b = 4.59 (*AB* system, J_{ab} = 15.7 Hz); 3.99 (broad signal, 1H); 3.61–3.47 (*m*, 2H); 2.60–2.28 (*m*, 5H); 2.16–1.74 (*m*, 3H); 1.59–0.91 (*m*, 4H); 0.95 (*d*, 3H); 0.88 (*d*, 3H); 0.81 (*t*, 3H); 0.80 (*t*, 3H).

Compound (2*a*)

Crystal data

$C_{21}H_{33}ClN_2O_2$
M_r = 380.96
Orthorhombic
$P2_12_12_1$
a = 7.494 (1) Å
b = 7.538 (3) Å
c = 38.30 (9) Å
V = 2164 (5) Å^3
Z = 4
D_x = 1.169 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 30 reflections
θ = 18.28–35.46°
μ = 1.683 mm^{-1}
T = 293 (2) K
Elongated prism
0.32 × 0.27 × 0.18 mm
Colourless

Data collection

Siemens AED diffractometer
$\theta/2\theta$ scans
Absorption correction: none
4470 measured reflections
4068 independent reflections
1084 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0440
θ_{max} = 70.40°
$h = -9 \rightarrow 9$
$k = -9 \rightarrow 1$
$l = -46 \rightarrow 46$
1 standard reflection monitored every 50 reflections
intensity variation: within statistical variation

Refinement

Refinement on F^2
$R(F)$ = 0.0784
$wR(F^2)$ = 0.2139
S = 1.236
4066 reflections
237 parameters
$w = 1/[\sigma^2(F_o^2) + (0.1692P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.003 (1)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8, 6.1.1.4)
Absolute configuration: Flack (1983)

Compound (2*b*)

Crystal data

$C_{21}H_{33}ClN_2O_2$
M_r = 380.96
Tetragonal
$P4_3$
a = 17.224 (3) Å
c = 7.416 (2) Å
V = 2200.1 (8) Å^3
Z = 4
D_x = 1.150 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 30 reflections
θ = 18.52–35.26°
μ = 1.655 mm^{-1}
T = 293 (2) K
Tabular
0.56 × 0.36 × 0.21 mm
Colourless

Data collection

Siemens AED diffractometer
$\theta/2\theta$ scans
Absorption correction: none
4626 measured reflections
2299 independent reflections
1194 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0860
θ_{max} = 70.10°
$h = -20 \rightarrow 21$
$k = -12 \rightarrow 20$
$l = -2 \rightarrow 9$
1 standard reflection monitored every 50 reflections
intensity variation: within statistical variation

Refinement

Refinement on F^2
$R(F)$ = 0.0616
$wR(F^2)$ = 0.1527
S = 1.139
2299 reflections
245 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.1228P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.009 (1)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8, 6.1.1.4)
Absolute configuration: Flack (1983)

Compound (2*c*)

Crystal data

$C_{21}H_{33}ClN_2O_2$
M_r = 380.96
Monoclinic
$P2_1$
a = 13.627 (2) Å
b = 7.298 (2) Å
c = 11.527 (2) Å
β = 108.16 (1)°
V = 1089.3 (4) Å^3
Z = 2
D_x = 1.162 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 30 reflections
θ = 20.05–36.64°
μ = 1.677 mm^{-1}
T = 293 (2) K
Tabular
0.51 × 0.38 × 0.23 mm
Colourless

Data collection

Siemens AED diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2336 measured reflections
2239 independent reflections
1267 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0205
θ_{max} = 70.08°
$h = -16 \rightarrow 16$
$k = -8 \rightarrow 0$
$l = -14 \rightarrow 3$
1 standard reflection monitored every 50 reflections
intensity variation: within statistical variation

Refinement

Refinement on F^2
$R(F)$ = 0.0369
$wR(F^2)$ = 0.0831
S = 0.997
2239 reflections
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0059 (6)

244 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.0495P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.006$
$\Delta\rho_{max} = 0.11$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8, 6.1.1.4)
Absolute configuration: Flack (1983)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (2*a*)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl	−0.4818 (4)	−0.5672 (3)	−0.01160 (6)	0.097 (1)
O1	−0.7993 (10)	−1.0426 (11)	−0.0870 (2)	0.102 (3)
O2	−0.0785 (9)	−1.1839 (10)	−0.1224 (2)	0.086 (3)
N1	−0.4962 (12)	−1.0438 (9)	−0.0806 (2)	0.067 (3)
N2	−0.1947 (11)	−0.9195 (10)	−0.1745 (2)	0.075 (3)
C1	−0.4845 (13)	−0.7845 (10)	0.0034 (3)	0.069 (3)
C2	−0.4812 (14)	−0.8116 (14)	0.0383 (3)	0.081 (4)
C3	−0.4920 (17)	−0.9832 (14)	0.0517 (2)	0.088 (4)
C4	−0.4941 (17)	−1.1223 (12)	0.0291 (3)	0.086 (4)
C5	−0.4923 (15)	−1.0932 (11)	−0.0066 (2)	0.071 (4)
C6	−0.4872 (12)	−0.9227 (11)	−0.0213 (2)	0.055 (3)
C7	−0.4884 (15)	−0.8856 (10)	−0.0591 (2)	0.071 (4)
C8	−0.6535 (17)	−1.1164 (14)	−0.0914 (3)	0.077 (4)
C9	−0.6162 (14)	−1.2830 (15)	−0.1106 (3)	0.094 (5)
C10	−0.4267 (15)	−1.3273 (14)	−0.1020 (3)	0.081 (4)
C11	−0.3380 (12)	−1.1539 (14)	−0.0893 (3)	0.071 (4)
C12	−0.2206 (12)	−1.0613 (13)	−0.1163 (2)	0.071 (3)
C13	−0.3078 (12)	−1.0263 (12)	−0.1519 (2)	0.069 (4)
C14	−0.1859 (15)	−0.9726 (15)	−0.2114 (2)	0.085 (4)
C15	−0.064 (2)	−1.1336 (15)	−0.2150 (3)	0.107 (6)
C16	0.119 (2)	−1.099 (2)	−0.2076 (3)	0.134 (6)
C17	−0.3693 (17)	−1.0116 (19)	−0.2289 (3)	0.127 (6)
C18	−0.210 (2)	−0.7277 (14)	−0.1678 (3)	0.104 (5)
C19	−0.037 (3)	−0.6294 (15)	−0.1735 (4)	0.135 (8)
C20	0.113 (2)	−0.692 (2)	−0.1500 (4)	0.150 (8)
C21	−0.358 (2)	−0.6303 (18)	−0.1872 (3)	0.161 (9)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (2*b*)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl	0.83569 (9)	0.0023 (1)	0.10230	0.1046 (8)
O1	0.5354 (3)	0.0513 (2)	0.3243 (9)	0.094 (2)
O2	0.6004 (2)	−0.1305 (2)	−0.1112 (7)	0.0752 (14)
N1	0.5922 (2)	−0.0609 (2)	0.2286 (7)	0.0614 (15)
N2	0.6870 (2)	−0.2860 (2)	0.1558 (9)	0.0717 (18)
C1	0.8039 (3)	−0.0222 (3)	0.3164 (9)	0.070 (2)
C2	0.8580 (4)	−0.0291 (4)	0.4516 (12)	0.087 (3)
C3	0.8346 (4)	−0.0469 (4)	0.6220 (12)	0.084 (3)
C4	0.7557 (4)	−0.0596 (4)	0.6564 (10)	0.083 (3)
C5	0.7026 (3)	−0.0532 (3)	0.5178 (10)	0.069 (2)
C6	0.7244 (3)	−0.0349 (3)	0.3448 (9)	0.058 (2)
C7	0.6671 (3)	−0.0267 (3)	0.1952 (9)	0.060 (2)
C8	0.5326 (3)	−0.0186 (3)	0.2939 (10)	0.071 (2)
C9	0.4658 (3)	−0.0727 (3)	0.3318 (14)	0.087 (3)
C10	0.4866 (3)	−0.1460 (4)	0.2363 (13)	0.088 (3)
C11	0.5757 (3)	−0.1453 (3)	0.2144 (9)	0.061 (2)
C12	0.6016 (3)	−0.1827 (3)	0.0377 (9)	0.062 (2)
C13	0.6828 (3)	−0.2159 (3)	0.0430 (10)	0.072 (2)
C14	0.7603 (3)	−0.2965 (3)	0.2560 (13)	0.088 (3)
C15	0.7605 (7)	−0.2505 (5)	0.4236 (18)	0.146 (5)
C16	0.8320 (6)	−0.2621 (7)	0.539 (2)	0.190 (7)
C17	0.8318 (4)	−0.2777 (6)	0.144 (2)	0.155 (6)
C18	0.6582 (5)	−0.3560 (4)	0.066 (2)	0.137 (5)
C19	0.6272 (6)	−0.4144 (5)	0.201 (3)	0.194 (8)
C20	0.5656 (6)	−0.3808 (4)	0.3455 (19)	0.278 (13)
C21	0.7120 (6)	−0.3994 (4)	−0.0577 (19)	0.225 (10)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (2*c*)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl	−0.1975 (1)	−0.1449 (2)	−0.1599 (1)	0.1201 (6)
O1	0.0803 (2)	0.2109 (5)	−0.2981 (3)	0.1102 (15)
O2	−0.2748 (2)	0.2656 (4)	−0.5238 (2)	0.0926 (12)
N1	−0.0850 (2)	0.3128 (4)	−0.3373 (2)	0.0668 (12)
N2	−0.3718 (2)	0.5203 (4)	−0.6896 (2)	0.0657 (11)
C1	−0.1607 (3)	0.0614 (6)	−0.0945 (4)	0.0809 (17)
C2	−0.1657 (3)	0.0898 (7)	0.0230 (4)	0.096 (2)
C3	−0.1369 (3)	0.2554 (8)	0.0777 (4)	0.094 (2)
C4	−0.1024 (3)	0.3948 (6)	0.0185 (3)	0.083 (2)
C5	−0.0964 (2)	0.3590 (7)	−0.0972 (3)	0.0724 (16)
C6	−0.1258 (2)	0.1938 (6)	−0.1557 (3)	0.0653 (14)
C7	−0.1206 (3)	0.1572 (6)	−0.2837 (3)	0.0763 (16)
C8	0.0132 (3)	0.3269 (7)	−0.3376 (3)	0.0800 (18)
C9	0.0258 (3)	0.5080 (6)	−0.3921 (3)	0.0844 (18)
C10	−0.0696 (3)	0.6171 (6)	−0.3907 (3)	0.0749 (15)
C11	−0.1500 (2)	0.4673 (5)	−0.3956 (3)	0.0620 (13)
C12	−0.2173 (2)	0.4250 (5)	−0.5251 (3)	0.0638 (14)
C13	−0.2922 (2)	0.5818 (5)	−0.5796 (3)	0.0662 (13)
C14	−0.4771 (3)	0.5935 (6)	−0.7073 (3)	0.0789 (16)
C15	−0.4842 (3)	0.7974 (7)	−0.6887 (4)	0.098 (2)
C16	−0.5948 (3)	0.8723 (9)	−0.7354 (4)	0.122 (2)
C17	−0.5261 (3)	0.4889 (8)	−0.6252 (4)	0.135 (3)
C18	−0.3355 (3)	0.5197 (6)	−0.7980 (3)	0.0740 (15)
C19	−0.3947 (3)	0.3813 (7)	−0.8936 (4)	0.104 (2)
C20	−0.3936 (4)	0.1917 (8)	−0.8464 (5)	0.144 (3)
C21	−0.3323 (3)	0.7028 (7)	−0.8582 (4)	0.099 (2)

Table 4. *Selected geometric parameters* (Å, °) *for* (2*a*)

Cl—C1	1.736 (8)	N2—C18	1.473 (11)
O1—C8	1.238 (12)	N2—C14	1.473 (12)
O2—C12	1.429 (10)	C8—C9	1.482 (14)
N1—C8	1.365 (12)	C9—C10	1.495 (14)
N1—C7	1.449 (9)	C10—C11	1.545 (13)
N1—C11	1.486 (11)	C11—C12	1.526 (13)
N2—C13	1.454 (10)	C12—C13	1.535 (11)
C8—N1—C7	122.5 (9)	N1—C8—C9	109.1 (9)
C8—N1—C11	113.3 (7)	C8—C9—C10	105.1 (10)
C7—N1—C11	123.8 (9)	C9—C10—C11	106.8 (9)
C13—N2—C18	113.2 (8)	N1—C11—C12	110.9 (8)
C13—N2—C14	116.5 (8)	N1—C11—C10	101.6 (7)
C18—N2—C14	115.9 (8)	C12—C11—C10	114.9 (8)
C2—C1—Cl	118.0 (7)	O2—C12—C11	104.1 (8)
C6—C1—Cl	118.6 (7)	O2—C12—C13	106.5 (7)
N1—C7—C6	113.7 (7)	C11—C12—C13	115.8 (8)
O1—C8—N1	122.7 (9)	N2—C13—C12	112.0 (7)
O1—C8—C9	128.0 (11)		

Table 5. *Selected geometric parameters* (Å, °) *for* (2*b*)

Cl—C1	1.732 (6)	N2—C13	1.470 (7)
O1—C8	1.227 (6)	N2—C14	1.475 (8)
O2—C12	1.425 (7)	C8—C9	1.506 (8)
N1—C8	1.349 (6)	C9—C10	1.492 (9)
N1—C7	1.440 (6)	C10—C11	1.543 (7)
N1—C11	1.484 (6)	C11—C12	1.527 (8)
N2—C18	1.466 (9)	C12—C13	1.512 (7)
C8—N1—C7	121.5 (4)	N1—C8—C9	108.3 (5)
C8—N1—C11	114.1 (4)	C10—C9—C8	104.6 (5)
C7—N1—C11	124.1 (4)	C9—C10—C11	106.3 (5)
C18—N2—C13	113.6 (7)	N1—C11—C12	114.7 (5)
C18—N2—C14	114.6 (5)	N1—C11—C10	101.0 (4)
C13—N2—C14	115.5 (4)	C12—C11—C10	112.2 (5)
C2—C1—Cl	118.4 (5)	O2—C12—C13	105.8 (4)
C6—C1—Cl	119.0 (5)	O2—C12—C11	113.2 (4)
N1—C7—C6	115.2 (5)	C13—C12—C11	114.1 (5)
O1—C8—N1	124.5 (5)	N2—C13—C12	111.8 (4)
O1—C8—C9	127.1 (5)		

Table 6. *Selected geometric parameters* (Å, °) *for* (2*c*)

Cl—C1	1.689 (4)	N2—C18	1.480 (4)
O1—C8	1.224 (5)	N2—C14	1.484 (4)
O2—C12	1.405 (4)	C8—C9	1.496 (6)
N1—C8	1.343 (4)	C9—C10	1.529 (5)
N1—C7	1.447 (5)	C10—C11	1.537 (5)
N1—C11	1.462 (4)	C11—C12	1.521 (4)
N2—C13	1.459 (4)	C12—C13	1.532 (5)
C8—N1—C7	121.9 (3)	N1—C8—C9	108.2 (3)
C8—N1—C11	113.7 (3)	C8—C9—C10	104.3 (3)
C7—N1—C11	124.4 (3)	C9—C10—C11	103.2 (3)
C13—N2—C18	112.4 (3)	N1—C11—C12	112.8 (3)
C13—N2—C14	115.7 (3)	N1—C11—C10	102.1 (2)
C18—N2—C14	116.6 (3)	C12—C11—C10	112.7 (3)
C6—C1—Cl	120.2 (3)	O2—C12—C11	109.0 (3)
C2—C1—Cl	118.0 (4)	O2—C12—C13	108.7 (3)
N1—C7—C6	113.6 (3)	C11—C12—C13	111.8 (3)
O1—C8—N1	125.1 (4)	N2—C13—C12	110.3 (3)
O1—C8—C9	126.7 (4)		

Table 7. *Relevant geometry* (Å, °) *of hydrogen bonds in the crystals of the* (2*a*), (2*b*) *and* (2*c*) *stereoisomers*

	D	H	*A*	*D*—H	*D*···*A*	H···*A*	*D*—H···*A*
(2*a*)	O	H2	O1^{i}	0.82	2.71 (1)	1.90	167
(2*b*)	O2	H2	O1^{ii}	0.82	2.748 (6)	1.94	169
(2*c*)	O2	H2	N2	0.82	2.698 (4)	2.22	118
(2*c*)	C7	H7*B*	O2	0.97	3.013 (4)	2.36	124

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

The integrated intensities were obtained by a modified version (Belletti, Ugozzoli, Cantoni & Pasquinelli, 1979) of the Lehmann & Larsen (1974) peak-profile analysis procedure.

The structures were solved by direct methods and refined by anisotropic full-matrix least squares. Compounds (2*b*) and (2*c*) crystallize in polar space groups; the origin of the coordinate system for each of them was fixed automatically by the *SHELXL*93 program (Sheldrick, 1993) by using the algorithm of Flack & Schwarzenbach (1988). All the H atoms were placed in calculated positions and refined isotropically riding on the attached atoms. Their U values were: for (2*a*), $1.5 \times U_{eq}$ of the parent atom for all H atoms; for (2*b*), $1.2 \times U_{eq}$ of the parent atom for 20 H atoms, the remainder being refined singly; for (2*c*), a common U value, refined for each of three groups of H atoms.

The poor quality of the crystals of (2*a*) is the reason why its analysis is of lower accuracy than those of (2*b*) and (2*c*). Nevertheless, the results are good enough to support the discussion presented above. As shown by the atomic ellipsoids of Fig. 1, the *sec*-butyl residues are affected by high thermal motion or disorder in all three analyses.

The absolute configurations, deduced from the values of the Flack (1983) index [−0.03 (7), −0.02 (4) and 0.12 (3) for (2*a*), (2*b*) and (2*c*), respectively] are in agreement with those expected on the basis of the chirality of the reagents used in the syntheses.

The calculations were carried out on the ENCORE91 and GOULD-POWERNODE 6040 computers of the Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma), and on a COMPAQ-486c portable computer.

For all compounds, data collection: local programs; cell refinement: *LQPARM* (Nardelli & Mangia,1984); data reduction: local programs; program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ORTEP* (Johnson, 1965), *PLUTO* (Motherwell & Clegg, 1978); software used to prepare material for publication: *PARST* (Nardelli, 1983), *PARSTCIF* (Nardelli, 1991); software used to perform non-bonded energy calculations: *ROTENER* (Nardelli, 1988).

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: MU1165). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The Influence of Hydrogen Bonding on the Structure of 1-Methylimidazolium D-Tartrate

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Abstract

The title compound, 1-methylimidazolium D-tartrate, $C_4H_7N_2^+.C_4H_5O_6^-$, consists of a tightly interwoven tartrate network that is hydrogen bonded to the imidazolium