Yamada, T., Yanagi, T., Omote, Y., Miyazawa, T., Kuwata, S., Sugiura, M. & Matsunoto, K. (1990). *J. Chem. Soc. Chem. Commun.* pp. 1640–1641.
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Anti-Inflammatory Drugs. III. Salts of Diclofenac with *N*-(2-Hydroxyethyl)-piperidine, *N*-(2-Hydroxyethyl)morpholine and *N*-(2-Hydroxyethyl)piperazine

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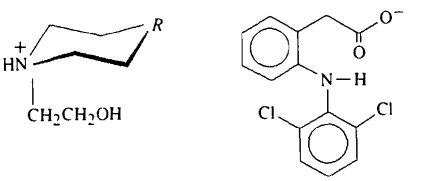
Abstract

The molecular and crystal structures of three salts of the same anion, *N*-(2-hydroxyethyl)piperidinium 2-(2,6-dichlorophenylamino)phenylacetate, $C_7H_{16}NO^+.C_{14}H_{10}Cl_2NO_2^-$, *N*-(2-hydroxyethyl)morpholinium 2-(2,6-dichlorophenylamino)phenylacetate, $C_6H_{14}NO_2^+.C_{14}H_{10}Cl_2NO_2^-$, *N*-(2-hydroxyethyl)piperazinium 2-(2,6-dichlorophenylamino)phenylacetate, $C_6H_{15}N_2O^+.C_{14}H_{10}Cl_2NO_2^-$, have been determined by X-ray diffraction. Strong anion–cation interactions *via* hydrogen bonds are the prime driving force for crystal self-assembly. Packing is determined by weak hydrogen-bonding interactions (C—H···O and C—H···Cl). The three compounds are isomorphous and are characterized by the same network of hydrogen bonds. Structural results are related to the different solubilities of the three salts.

Comment

We are currently investigating the crystal and molecular structures of some salts of diclofenac [2-(2,6-dichlorophenylamino)phenylacetic acid, hereafter HD]. These studies have been prompted by the need to rationalize the factors affecting the salt solubility, which is important in controlling the availability, and therefore the activity, of these non-steroidal anti-inflammatory drugs (NSAIDs). Although the rather low solubility of HD may be generally increased by using its salts, the solubility of the latter do not seem to follow a simple pattern as a function of the counterion (Fini, Fazio & Rapaport, 1993). We hoped, therefore, that a systematic study of the structures of these salts would cast light on the subject. In recent papers, we have investigated the salts of HD with both 1-(2-hydroxyethyl)pyrrolidine (D.HEP) (Castellari & Sabatino, 1994) and diethanolamine (D.HNDEA) (Castellari & Ottani, 1995). While the diclofenac derivative most widely used in therapy is its sodium salt, the diethylammonium and hydroxyethylpyrrolidinium (D.HEP) salts are also employed for topical applications (Rosenthal & Bauhous, 1993). Solubility, seen as the control step in a complex series of events taking place in the human body, can be described with the aid of empirical scales based, for example, on the ratio of the number of hydrophilic to the number of hydrophobic groups present in the solute (Hansch & Leo, 1979) or on an empirical parameter such as the polarity of the solvent (Reichard, 1988). HD is hydrophobic and poorly soluble in water. Substitution of the carboxyl by a carboxylate group increases the dissolution rate of the drug as a consequence of the better solubility of the solid salt particles in the surrounding saturated microphase auto-buffered at a slightly higher pH (Zecchi, Rodriguez, Tartarini & Fini, 1984; Fini, Zecchi & Tartarini, 1985). Therefore, since the long-distance ordering in the crystal corresponds somewhat to local ordering in the liquid, it becomes important to determine the solid-state structure of the salts of HD, especially when the counterion is an organic base capable of strong hydrogen bonding, as in the case of the title compounds *N*-(2-hydroxyethyl)piperidinium 2-(2,6-dichlorophenylamino)phenylacetate, (1), *N*-(2-hydroxyethyl)morpholinium 2-(2,6-dichlorophenylamino)-phenylacetate, (2), and *N*-(2-hydroxyethyl)piperazinium 2-(2,6-dichlorophenylamino)phenylacetate, (3).



(1) $R = CH_2$
(2) $R = O$
(3) $R = NH$

The crystals of compounds (1), (2) and (3) are isomorphous and this means that the packing forces present are almost identical. The common anion, D^-, shows the same geometry in all three salts, similar to that shown by HD (Moser, Sallmann & Wiesenberg, 1990). The twist angle between the two phenyl rings of D^- is 66.8 (1)° for compounds (1) and (3), and 68.3 (1)° for compound (2). The interplanar angles between the carboxyl groups and the dichloro-substituted aromatic rings are 30.8 (1), 27.6 (1) and 31.0 (1)° for compounds (1), (2) and (3), respectively. The cations, though differing

in chemical nature, take up 'chair' conformations. Torsion angles describing the orientation of the cation side chains are N2—C20—C21—O3 of 52.4 (4) for compound (1), N2—C19—C20—O3 of 51.2 (4) for (2) and N2—C19—C20—O3 of 53.1 (4)° for (3) (Fig. 1).

In all three compounds, the anion–cation pairs are held together by the same strong network of hydrogen bonding. Compounds (1), (2) and (3) contain, apart from the three-center intra-anion Cl1···H1—N1 and O1···H1—N1 hydrogen bonds, two very strong symmetrical anion–cation interactions between the O atoms of the anionic carboxylate group and the O—H and N—H groups of the cations [N2···O2 2.675 (3) and O3···O1 2.708 (3) Å for compound (1), 2.664 (3) and 2.681 (3) Å for (2), and 2.672 (3) and 2.703 (3) Å for (3)]. The anion–cation hydrogen-bonded pairs thus form a rather stable 'super molecule', which presumably passes as such into the melt. It must be emphasized that the additional electronegative atom present in the cationic rings in compounds (2) and (3) are not involved in any hydrogen bonding, despite being potentially good acceptors or donors. This suggests that the strong anion–cation double interaction is the main driving force in crystal growth, whereas any additional hydrogen bond could disturb the optimization of the lattice energy.

In addition, the packing pattern is made up of C—H···O and C—H···Cl interactions involving anion–anion or cation–cation pairs; the pattern differs from that observed in D.HEP. From differential scanning calorimetry (DSC) experiments [m.p. 374.2 (2), 365.0 (2), 393.6 (2) K; ΔH of fusion = 37.1 (4), 41.7 (4) and 46.4 (5) kJ mol^{-1} for compounds (1), (2) and (3), respectively], it can be shown that not only enthalpy but also entropy of fusion [ΔS = 99 (1), 114 (1) and 118 (1) J K^{-1} mol^{-1} for (1), (2) and (3), respectively] increases on passing from compound (1) to (2) to (3). This trend can be rationalized by assuming that in the liquid state, the O4 atom in compound (2) and the N3—H18 group

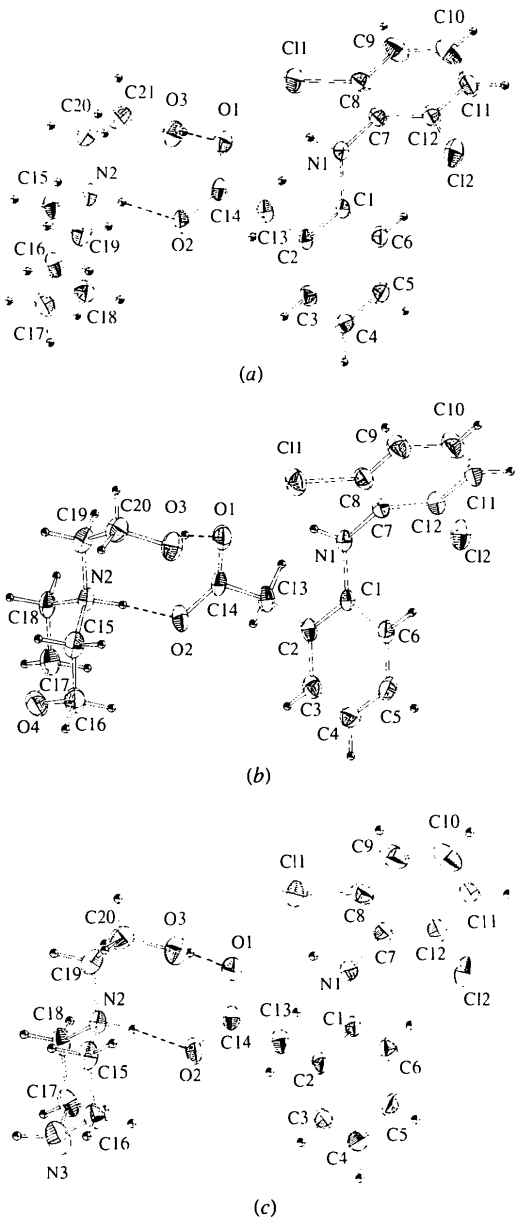


Fig. 1. The molecular conformations of (*a*) compound (1), (*b*) compound (2) and (*c*) compound (3), showing the atomic labelling schemes and anion–cation interactions. Displacement ellipsoids are at the 50% probability level and H atoms are shown as circles of arbitrary size.

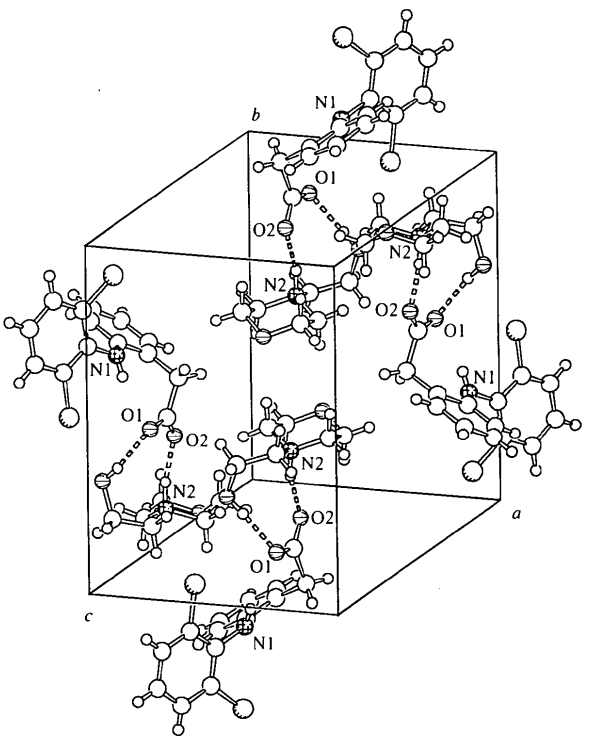


Fig. 2. The packing of compound (2) with only the anion–cation hydrogen-bond double interactions shown.

in compound (3) are involved in anion–cation hydrogen bonding not present in the crystal. In other words, while the 'super molecule' found in the crystal of (1) is also the dominant ion pair in the liquid, different ion pairs coexist in the melt of (2) and even more in that of (3), thus increasing the disorder.

Another critical parameter for drug activity is its hydrophobic character due to the presence of a positive charge. In the cations of (1), (2) and (3), positive charges are localized mainly on the protonated N2 atom and on the C atoms connected to it. In compounds (2) and (3), however, the remaining C atoms of the aliphatic ring (C16 and C17) also possess positive charges, being bound to electronegative sites [solubilities in octanol at 298 K are 2.34, 5.67 and 3.23 weight % for (1), (2) and (3), respectively; Fini, Fazio & Rapaport, 1993]. At the same time, since the substitution of the methylene group with O or NH adds an extra site of localized negative charge (strong in O and moderate in NH), the solubility in water also changes [solubilities in water at 298 K are 0.55, 1.07 and 0.64 weight % for (1), (2) and (3), respectively] as a result of a better accommodation of the molecules of (2) in the aqueous phase.

Experimental

For the preparation of compounds (1), (2) and (3), diclofenac (IBSA, Lugano, Switzerland) was dissolved in acetone. To the solution was added an equivalent amount of *N*-(hydroxyethyl)-piperidine, *N*-(hydroxyethyl)morpholine or *N*-(hydroxyethyl)-piperazine (all obtained from Fluka, Buchs, Switzerland) to give (1), (2) or (3), respectively. Crystals of (1) and (2) were grown from acetone solution, while those of (3) were grown by diffusion of *n*-hexane into a solution of (3) in acetone. The densities D_m of all three compounds were measured by flotation in 1-bromo-2-chloroethane/*p*-xylene mixtures.

Compound (1)

Crystal data

$C_7H_{16}NO^+.C_{14}H_{10}Cl_2NO_2^-$
M_r = 425.34
Monoclinic
$P2_1/a$
a = 9.680 (3) Å
b = 13.093 (3) Å
c = 16.607 (5) Å
β = 91.82 (3)°
V = 2103.7 (10) Å^3
Z = 4
D_x = 1.343 Mg m^{-3}
D_m = 1.36 (2) Mg m^{-3}

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 8–10°
μ = 0.333 mm^{-1}
T = 293 (2) K
Block
0.30 × 0.30 × 0.15 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from ω scans
Absorption correction: none
5222 measured reflections
5058 independent reflections
2188 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0193
θ_{max} = 27.97°
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 21$
3 standard reflections
frequency: 160 min
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.0399
$wR(F^2)$ = 0.1345
S = 1.003
5054 reflections
266 parameters
H atoms riding except for H1, H11 and H26, for which all parameters were refined
$w = 1/[\sigma^2(F_o^2) + (0.045P)^2 + 1.07P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.07
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

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

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

	x	y	z	U_{eq}
Cl1	0.13027 (10)	−0.00747 (6)	0.07822 (5)	0.0799 (3)
Cl2	0.00049 (9)	0.36194 (6)	0.19579 (6)	0.0746 (3)
N1	0.0043 (2)	0.1331 (2)	0.19547 (13)	0.0473 (5)
C1	0.0453 (2)	0.1362 (2)	0.27743 (14)	0.0381 (5)
C2	−0.0390 (2)	0.0895 (2)	0.33412 (15)	0.0378 (6)
C3	0.0016 (3)	0.0933 (2)	0.4147 (2)	0.0494 (7)
C4	0.1215 (3)	0.1405 (2)	0.4410 (2)	0.0596 (8)
C5	0.2043 (3)	0.1861 (2)	0.3851 (2)	0.0585 (8)
C6	0.1672 (3)	0.1839 (2)	0.3042 (2)	0.0473 (7)
C7	0.0805 (3)	0.1806 (2)	0.13567 (15)	0.0437 (6)
C8	0.1453 (3)	0.1243 (2)	0.0764 (2)	0.0560 (7)
C9	0.2210 (4)	0.1686 (3)	0.0180 (2)	0.0809 (11)
C10	0.2380 (4)	0.2711 (3)	0.0177 (2)	0.0874 (11)
C11	0.1744 (4)	0.3322 (3)	0.0732 (2)	0.0735 (10)
C12	0.0922 (3)	0.2862 (2)	0.1305 (2)	0.0541 (7)
C13	−0.1712 (3)	0.0360 (2)	0.3083 (2)	0.0448 (6)
C14	−0.1424 (2)	−0.0700 (2)	0.2740 (2)	0.0419 (6)
O1	−0.1245 (2)	−0.07596 (14)	0.20041 (12)	0.0633 (6)
O2	−0.1374 (2)	−0.14297 (13)	0.32273 (12)	0.0553 (5)
N2	−0.1142 (2)	−0.3401 (2)	0.28283 (13)	0.0419 (5)
C15	−0.2441 (3)	−0.3829 (2)	0.3166 (2)	0.0537 (7)
C16	−0.2517 (3)	−0.3629 (2)	0.4054 (2)	0.0612 (8)
C17	−0.1271 (3)	−0.4061 (3)	0.4510 (2)	0.0695 (9)
C18	0.0033 (3)	−0.3631 (2)	0.4157 (2)	0.0601 (8)
C19	0.0097 (3)	−0.3820 (2)	0.3266 (2)	0.0549 (8)
C20	−0.1168 (3)	−0.3560 (2)	0.1937 (2)	0.0557 (7)
C21	0.0118 (3)	−0.3256 (2)	0.1524 (2)	0.0624 (8)
O3	0.0580 (2)	−0.2264 (2)	0.16897 (14)	0.0662 (6)

Table 2. *Selected geometric parameters (Å, °) for (1)*

Cl1—C8	1.732 (3)	N2—C19	1.487 (3)
Cl2—C12	1.735 (3)	N2—C20	1.495 (4)
N1—C7	1.401 (3)	N2—C15	1.502 (3)
N1—C1	1.406 (3)	C20—C21	1.493 (4)
C14—O1	1.241 (3)	C21—O3	1.397 (4)
C14—O2	1.252 (3)		
C7—N1—C1	122.3 (2)	C21—C20—N2	115.4 (2)
C2—C13—C14	111.4 (2)	O3—C21—C20	115.1 (2)
O2—C14—C13	117.1 (2)		
C1—N1—C7—C12	−67.6 (3)	N2—C20—C21—O3	−52.2 (4)

Table 3. *Hydrogen-bonding geometry (Å, °) for (1)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H11···O2	0.90 (2)	1.78 (2)	2.675 (3)	172 (2)
O3—H26···O1	0.80 (4)	1.93 (4)	2.708 (3)	164 (4)
N1—H1···Cl1	0.85 (2)	2.60 (2)	2.970 (3)	107 (2)
N1—H1···O1	0.85 (2)	2.22 (3)	3.010 (3)	155 (2)
C10—H7···Cl1^{i}	0.93	2.79	3.564 (4)	141
C15—H12···O3^{ii}	0.97	2.49	3.381 (4)	156
C20—H23···O3^{ii}	0.97	2.47	3.341 (5)	149

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

Compound (2)

Crystal data

$C_6H_{14}NO_2^+.C_{14}H_{10}Cl_2NO_2^-$
M_r = 427.31
Monoclinic
$P2_1/a$
a = 9.525 (2) Å
b = 12.962 (4) Å
c = 16.579 (7) Å
β = 91.81 (3)°
V = 2045.9 (11) Å^3
Z = 4
D_x = 1.387 Mg m^{-3}
D_m = 1.37 (2) Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 6.6–9.87°
μ = 0.346 mm^{-1}
T = 293 (2) K
Prismatic
0.40 × 0.38 × 0.23 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from ω scans
Absorption correction: none
3711 measured reflections
3581 independent reflections
2316 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0177
θ_{max} = 24.96°
h = −11 → 11
k = 0 → 15
l = 0 → 19
3 standard reflections
frequency: 160 min
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.0428
$wR(F^2)$ = 0.1208
S = 1.035
3578 reflections
284 parameters
H atoms riding except for H1, H11 and H24, for which all parameters were refined
$w = 1/[\sigma^2(F_o^2) + (0.047P)^2 + 1.27P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.005
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 4. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (2)*

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

	x	*y*	*z*	U_{eq}
Cl1	0.12439 (10)	0.52531 (6)	0.07786 (5)	0.0761 (3)
Cl2	0.00741 (10)	0.14269 (6)	0.18238 (6)	0.0751 (3)
N1	0.0030 (3)	0.3744 (2)	0.19105 (14)	0.0493 (6)
C1	0.0503 (3)	0.3677 (2)	0.2713 (2)	0.0409 (6)
C2	−0.0311 (3)	0.4123 (2)	0.3313 (2)	0.0427 (6)
C3	0.0172 (4)	0.4071 (2)	0.4096 (2)	0.0568 (8)
C4	0.1418 (4)	0.3600 (2)	0.4321 (2)	0.0676 (9)
C5	0.2205 (4)	0.3156 (2)	0.3733 (2)	0.0661 (9)
C6	0.1760 (3)	0.3194 (2)	0.2942 (2)	0.0510 (7)
C7	0.0781 (3)	0.3317 (2)	0.1277 (2)	0.0459 (7)
C8	0.1396 (3)	0.3926 (2)	0.0700 (2)	0.0548 (7)
C9	0.2120 (4)	0.3527 (3)	0.0072 (2)	0.0769 (10)
C10	0.2284 (4)	0.2482 (3)	0.0016 (2)	0.0850 (11)
C11	0.1688 (4)	0.1837 (3)	0.0566 (2)	0.0736 (10)
C12	0.0913 (3)	0.2252 (2)	0.1179 (2)	0.0544 (7)
C13	−0.1669 (3)	0.4667 (2)	0.3108 (2)	0.0511 (7)
C14	−0.1382 (3)	0.5761 (2)	0.2810 (2)	0.0465 (7)
O1	−0.1178 (2)	0.5875 (2)	0.20824 (14)	0.0635 (6)
O2	−0.1343 (2)	0.64704 (14)	0.33275 (13)	0.0594 (5)
N2	−0.1165 (2)	0.8477 (2)	0.29982 (15)	0.0453 (5)
C15	0.0006 (3)	0.8958 (2)	0.3456 (2)	0.0628 (9)
C16	−0.0114 (4)	0.8764 (3)	0.4339 (2)	0.0739 (10)
C17	−0.2545 (3)	0.8615 (3)	0.4209 (2)	0.0664 (9)
O4	−0.1423 (3)	0.9124 (2)	0.46365 (14)	0.0818 (7)
C18	−0.2519 (3)	0.8830 (2)	0.3332 (2)	0.0537 (8)
C19	−0.1190 (3)	0.8677 (2)	0.2114 (2)	0.0592 (8)
C20	0.0134 (3)	0.8420 (2)	0.1700 (2)	0.0649 (9)
O3	0.0638 (2)	0.7422 (2)	0.18624 (15)	0.0692 (7)

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

Cl1—C8	1.731 (3)	N2—C19	1.489 (4)
Cl2—C12	1.726 (3)	N2—C18	1.492 (3)
N1—C1	1.394 (3)	C16—O4	1.432 (4)
N1—C7	1.403 (3)	C17—O4	1.425 (4)
C14—O1	1.237 (3)	C19—C20	1.492 (4)
C14—O2	1.257 (3)	C20—O3	1.403 (4)
N2—C15	1.468 (4)		
C1—N1—C7	122.3 (2)	O4—C16—C15	112.1 (3)
C2—C13—C14	110.3 (2)	N2—C19—C20	115.2 (2)
O2—C14—C13	117.4 (3)		
C1—N1—C7—C12	69.0 (4)	N2—C19—C20—O3	51.2 (4)

Table 6. *Hydrogen-bonding geometry (Å, °) for (2)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H11···O2	0.96 (3)	1.71 (3)	2.664 (3)	167 (2)
O3—H24···O1	0.84 (4)	1.88 (4)	2.681 (3)	158 (4)
N1—H1···Cl1	0.80 (3)	2.57 (3)	2.970 (3)	112 (2)
N1—H1···O1	0.80 (3)	2.27 (3)	3.009 (3)	153 (3)
C10—H7···Cl1^{i}	0.93	2.77	3.488 (4)	135
C18—H19···O3^{ii}	0.97	2.49	3.374 (4)	152
C19—H21···O3^{ii}	0.97	2.47	3.355 (4)	151

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

Compound (3)

Crystal data

$C_6H_{15}N_2O^+.C_{14}H_{10}Cl_2NO_2^-$
M_r = 426.33
Monoclinic
$P2_1/a$
a = 9.681 (5) Å
b = 13.083 (4) Å
c = 16.582 (5) Å
β = 91.66 (4)°
V = 2099.3 (14) Å^3
Z = 4
D_x = 1.349 Mg m^{-3}
D_m = 1.35 (2) Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 8–11.63°
μ = 0.335 mm^{-1}
T = 293 (2) K
Block
0.30 × 0.25 × 0.15 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from ω scans
Absorption correction: none
R_{int} = 0.0342
θ_{max} = 27.97°
h = −12 → 12
k = 0 → 17
l = 0 → 21

5206 measured reflections
5042 independent reflections
1942 observed reflections
$[I > 2\sigma(I)]$
3 standard reflections
frequency: 160 min
intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.0422$
$wR(F^2) = 0.1590$
$S = 1.011$
5037 reflections
288 parameters
H atoms riding except for H1, H11 and H25, for which all parameters were refined
$w = 1/[\sigma^2(F_o^2) + (0.066P)^2 + 0.62P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.090$
$\Delta\rho_{max} = 0.43$ e Å^{-3}
$\Delta\rho_{min} = -0.31$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 7. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (3)*

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

	x	y	z	U_{eq}
Cl1	0.13028 (12)	0.50755 (7)	0.07822 (6)	0.0787 (3)
Cl2	0.00066 (11)	0.13807 (7)	0.19562 (6)	0.0733 (3)
N1	0.0038 (3)	0.3676 (2)	0.19533 (14)	0.0450 (6)
C1	0.0457 (3)	0.3634 (2)	0.2773 (2)	0.0365 (6)
C2	−0.0392 (3)	0.4105 (2)	0.3337 (2)	0.0365 (7)
C3	0.0015 (4)	0.4069 (2)	0.4142 (2)	0.0490 (8)
C4	0.1213 (4)	0.3595 (3)	0.4411 (2)	0.0582 (9)
C5	0.2041 (4)	0.3138 (2)	0.3852 (2)	0.0559 (9)
C6	0.1678 (3)	0.3165 (2)	0.3044 (2)	0.0460 (8)
C7	0.0803 (3)	0.3190 (2)	0.1356 (2)	0.0441 (7)
C8	0.1449 (4)	0.3765 (3)	0.0763 (2)	0.0561 (9)
C9	0.2215 (5)	0.3316 (4)	0.0180 (2)	0.0790 (12)
C10	0.2381 (5)	0.2290 (4)	0.0173 (3)	0.0862 (13)
C11	0.1744 (4)	0.1683 (3)	0.0730 (2)	0.0725 (11)
C12	0.0919 (3)	0.2139 (2)	0.1307 (2)	0.0529 (8)
C13	−0.1712 (3)	0.4640 (2)	0.3082 (2)	0.0439 (7)
C14	−0.1427 (3)	0.5697 (2)	0.2739 (2)	0.0425 (7)
O1	−0.1246 (3)	0.5760 (2)	0.20047 (14)	0.0623 (6)
O2	−0.1374 (2)	0.64299 (15)	0.32269 (13)	0.0548 (6)
N2	−0.1143 (2)	0.8400 (2)	0.28284 (15)	0.0402 (6)
C15	0.0098 (3)	0.8824 (2)	0.3266 (2)	0.0524 (9)
C16	0.0037 (3)	0.8630 (3)	0.4156 (2)	0.0576 (9)
C17	−0.2516 (3)	0.8635 (3)	0.4054 (2)	0.0598 (9)
N3	−0.1273 (4)	0.9061 (3)	0.4528 (2)	0.0976 (12)
C18	−0.2443 (3)	0.8832 (2)	0.3166 (2)	0.0526 (9)
C19	−0.1173 (3)	0.8556 (3)	0.1936 (2)	0.0544 (8)
C20	0.0122 (4)	0.8256 (3)	0.1526 (2)	0.0614 (10)
O3	0.0576 (3)	0.7263 (2)	0.1690 (2)	0.0651 (7)

Table 8. *Selected geometric parameters (Å, °) for (3)*

N1—C7	1.405 (4)	N2—C19	1.493 (4)
N1—C1	1.409 (4)	N2—C18	1.503 (4)
C14—O1	1.238 (4)	C19—C20	1.496 (5)
C14—O2	1.255 (4)	C20—O3	1.395 (4)
N2—C15	1.492 (4)		
C7—N1—C1	121.3 (2)	N2—C19—C20	114.9 (3)
C2—C13—C14	111.4 (2)	O3—C20—C19	114.8 (3)
O2—C14—C13	117.2 (3)		
C1—N1—C7—C12	67.0 (4)	N2—C19—C20—O3	53.1 (4)

Table 9. *Hydrogen-bonding geometry (Å, °) for (3)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H11···O2	0.93 (3)	1.75 (3)	2.672 (3)	169 (3)
O3—H25···O1	0.81 (4)	1.91 (4)	2.703 (3)	167 (4)
N1—H1···Cl1	0.98 (3)	2.54 (3)	2.960 (3)	106 (2)
N1—H1···O1	0.98 (3)	2.11 (3)	2.999 (3)	151 (3)
C10—H7···Cl1^{i}	0.93	2.78	3.555 (5)	141
C18—H20···O3^{ii}	0.97	2.49	3.384 (4)	152
C19—H22···O3^{ii}	0.97	2.47	3.339 (4)	149

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

Melting points and enthalpies of fusion were obtained using a Perkin–Elmer DSC-7 calorimeter (heating rate 10 K min^{-1}, N_2 flux and Al pans). The structures were solved by direct methods (*SHELXS*86; Sheldrick, 1990), which yielded the positions of all non-H atoms, and refined by least-squares methods (on F^2) (*SHELXL*93; Sheldrick, 1993). Absorption corrections were not applied. All non-H atoms were allowed to vibrate anisotropically. The H atoms bonded to N and O atoms were experimentally located and refined. The remaining H atoms were placed in calculated positions and refined riding on their parent atoms (aromatic C—H 0.93, C_{sp^3}—H 0.97 Å).

For all compounds, data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *MolEN* (Fair, 1990); molecular graphics: *SCHAKAL*92 (Keller, 1992); software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: BM1046). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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