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Molecular and Crystal Structure of Sodium Diatrizoate, an X-Ray Contrast Agent

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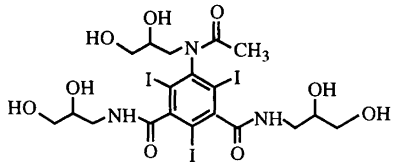
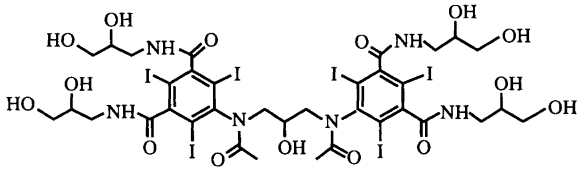
The single-crystal structure of the X-ray contrast agent sodium diatrizoate has been determined by X-ray crystallography using direct methods. Sodium-3,5-diacetamido-2,4,6-triiodobenzoate, sodium diatrizoate, $C_{11}H_8I_3NaN_2O_4 \cdot 4H_2O$, $M_w = 707.96$ g mol^{-1}, crystallizes in the triclinic space group $P\bar{1}$, $Z = 4$ with unit-cell dimensions $a = 11.754(2)$, $b = 13.091(3)$, $c = 15.129(4)$ Å, $\alpha = 76.32(2)$, $\beta = 84.56(2)$, $\gamma = 63.50(1)°$ and $V = 2024(1)$ Å^3. $R = 0.027$ for 7678 unique reflections. There are two crystallographically independent diatrizoate ions in the crystal which have essentially the same conformation. Both ions have an *endo,endo* conformation (the carbonyl moiety of the acetanilido group pointing towards the ring, *endo*, or away from it, *exo*). The carbonyl moieties of the acetanilido groups are located on the same side of the aromatic ring, *cis*, for both ions. This gives one side that is more hydrophilic, where also the sodium ions are joined to diatrizoate through a carboxylate oxygen atom. As a consequence of disordered water oxygen atoms in the coordination sphere, one of the sodium ions (Na1) is either five- or six- coordinated, while the latter sodium ion (Na2) is four- or five-coordinated. The mean sodium–oxygen bond length is 2.37(2) Å. There is an extensive intermolecular hydrogen-bonding network in the crystal.

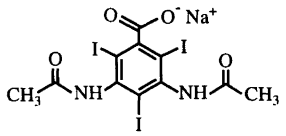
Modern contrast agents for medical X-ray imaging are hydrophilic, non-ionic compounds based on triiodinated benzene cores such as iohexol (**1**).[1] Recently, iodixanol, which is a non-ionic substance consisting of two triiodinated benzene rings, was approved for intravascular use (**2**).[2,3] However, one of the first X-ray contrast agents in clinical use based on triiodinated benzene was diatrizoic acid in the form of its sodium and/or meglumine salt (**3**).[4] (Scheme 1) Because of the relative good safety, diatrizoate remained the world's most widely used contrast medium for three decades.[5] Diatrizoate is today still widely used, although extensive clinical experience with non-ionic X-ray contrast agents confirms an important improvement in patient safety and comfort compared to the ionic agents.[6,7] Of further interest is the ability of diatrizoic acid and similar iodinated benzoic acid derivatives to be easily derivatized to organ-specific agents.[8,9] The crystal structures of the non-ionic monomer iopamidol,[10] iodixanol[11] and the particulate non-ionic monomer IEEC[12] have previously been reported. In this work we have performed a structure determination of sodium diatrizoate.



(**1**) iohexol



(**2**) iodixanol



(**3**) sodium diatrizoate

Scheme 1

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Experimental

Crystals suitable for X-ray investigation were obtained by vapour diffusion from a water–acetone system. Data collection was performed at low temperature on a Nicolet *P*3/*F* automatic diffractometer. The settings of 15 general reflections were used in a least-squares fit to determine the unit-cell parameters, $28 < 2\theta < 39°$. The intensity data have been corrected for Lorentz and polarization effects, and absorption correction has been applied by use of the program DIFABS.[13] Further details concerning crystallographic data and experimental conditions are summarized in Table 1.

Structure determination and refinement. The asymmetric unit contains two diatrizoate ions (**I** and **II**; the atoms of **II** are marked with a star), two sodium ions and eight water molecules. The structure was solved by direct methods (SIR92),[14] which gave the atomic coordinates of all non-hydrogen atoms except one of the methyl carbon atoms (C8*) of **II** and the water oxygen atoms. The positional and isotropic displacement parameters of all atoms were refined with a full-matrix least-squares refinement program.[13] All least-squares refinements have been carried out by minimization of $\sum w(\Delta F)^2$, where $w = 1$. The intensity data were at this stage corrected for absorption, and anisotropic displacement parameters were included for the iodine atoms. The missing carbon atom and six water oxygen atoms were then located by a difference Fourier synthesis.

Further least-squares refinement resulted in four relatively high peaks, $\rho = 6.3$–4.2 e Å^{-3}, in the difference Fourier map. The distance between peak 1 (Ow7) and peak 3 (Ow9) is 1.3 Å and the distance between peak 1 (Ow7) and peak 4 (Ow10) is 1.7 Å; all four peaks are within hydrogen-bonding distance to other atoms in the structure. These four peaks are considered to originate from disordered water oxygen atoms, with an occupancy factor after refinement of 0.5 each. The occupancy factors were kept fixed during further least-squares refinement, which resulted in sensible displacement parameters.

During the following least-squares refinements all non-hydrogen atoms, except the disordered water oxygen atoms, were refined with anisotropic displacement parameters. All hydrogen atoms, except those attached to the disordered water oxygen atoms, were located by difference Fourier syntheses, and included in the final structure factor calculation. The hydrogen atoms were given a *U*-value 2.5×10^{-3} Å^2 larger than that of the atoms to which they are attached.

The final difference map gave maximum and minimum residual electron densities of ± 1.18 e Å^{-3}. Atomic scattering factors were taken from Ref. 15. Final fractional coordinates and equivalent displacement parameters are given in Table 2.

Table 1. Crystal data and intensity collection.

Formula	$C_{11}H_8I_3NaN_2O_4 \cdot 4H_2O$
Formula weight/g mol^{-1}	707.96
Crystal dimensions/mm^3	$0.35 \times 0.25 \times 0.20$
Density calculated/Mg m^{-3}	2.32
Linear absorption coefficient, μ/cm^{-1}	46.40
F(000)	1320
Space group	$P\bar{1}$ (No. 2)
Z	4
a/Å	11.754(2)
b/Å	13.091(3)
c/Å	15.129(4)
α/°	76.32(2)
β/°	84.56(2)
γ/°	63.50(1)
V/Å^3	2024(1)
Diffractometer	Nicolet *P*3/*F*
Radiation	Mo*K*α
Wavelength/Å	0.710 69
Monochromator	Graphite
Temperature/K	138
Scan mode	$\theta - 2\theta$
Scan range/°	$2\theta\alpha_1 - 0.9$ to $2\theta\alpha_2 + 1.0$
Scan speed/° min^{-1}	4
2θ range/°	4.0–55.0
Background/scan ratio	0.7
No. of reflections measured	9353
No. of unique reflections [$I > 3\sigma(I)$]	7678
Stability monitoring	3 test refl./66 observ.
$R = \sum\|\|F_o\| - \|F_c\|\| / \sum\|F_o\|$	0.027
$R_w = [\sum[w(\|F_o\| - \|F_c\|)^2] / \sum[w\|F_o\|^2]]^{1/2}$	0.028
$S = [\sum[w(\|F_o\| - \|F_c\|)^2]/(n-p)]^{1/2}$	2.25

Table 2. Final fractional atomic coordinates with e.s.d.s in parentheses and equivalent isotropic displacement parameters (in Å^2).

Atom	*x*	*y*	*z*	*U*/Å^2 [a]
I1	0.661 68(3)	0.802 54(3)	1.103 19(2)	0.0229(1)
I2	0.703 26(3)	1.153 40(3)	0.774 57(2)	0.0252(2)
I3	0.504 66(3)	0.812 39(3)	0.734 27(2)	0.0237(1)
Na1	0.737 5(2)	0.436 3(2)	0.945 8(2)	0.025(1)
O1	0.758 4(3)	0.897 1(4)	0.635 2(3)	0.044(2)
O2	0.909 9(3)	0.866 2(3)	1.009 2(2)	0.031(2)
O3	0.447 2(3)	0.756 8(3)	0.976 4(2)	0.032(2)
O4	0.645 7(4)	0.630 6(3)	0.953 7(3)	0.040(2)
N1	0.579 1(3)	1.030 3(3)	0.683 6(3)	0.021(2)
N2	0.714 8(3)	1.017 3(3)	0.983 2(3)	0.024(2)
C1	0.592 9(4)	0.831 3(4)	0.909 3(3)	0.020(2)
C2	0.639 3(4)	0.876 7(4)	0.963 6(3)	0.020(2)
C3	0.671 3(4)	0.968 5(4)	0.926 4(3)	0.021(2)
C4	0.655 3(4)	1.015 9(4)	0.833 6(3)	0.020(2)
C5	0.604 9(4)	0.975 1(4)	0.777 1(3)	0.018(2)
C6	0.573 5(4)	0.882 9(4)	0.815 8(3)	0.020(2)
C7	0.659 9(4)	0.988 7(5)	0.617 8(3)	0.028(2)
C8	0.621 0(5)	1.060 2(5)	0.523 1(3)	0.040(3)
C9	0.832 4(4)	0.962 6(4)	1.021 1(3)	0.025(2)
C10	0.860 9(5)	1.028 1(5)	1.078 4(3)	0.034(3)
C11	0.559 5(5)	0.730 1(4)	0.949 7(3)	0.027(2)
I1*	0.756 94(3)	0.646 12(3)	0.562 87(2)	0.0235(1)
I2*	0.981 05(3)	0.499 34(3)	0.212 16(2)	0.0243(1)
I3*	0.920 39(3)	0.148 86(3)	0.527 60(2)	0.0294(2)
Na2	0.548 5(2)	0.470 3(2)	0.736 1(1)	0.021(1)
O1*	0.801 7(3)	0.316 5(3)	0.255 8(2)	0.031(2)
O2*	0.657 4(3)	0.752 5(3)	0.331 7(3)	0.030(2)
O3*	0.898 1(3)	0.337 9(4)	0.681 2(2)	0.038(2)
O4*	0.702 5(3)	0.380 1(3)	0.639 2(2)	0.030(2)
N1*	0.985 8(3)	0.258 0(3)	0.330 0(3)	0.021(2)
N2*	0.869 7(3)	0.656 7(3)	0.360 2(3)	0.021(2)
C1*	0.846 7(4)	0.404 0(4)	0.524 4(3)	0.020(2)
C2*	0.834 3(4)	0.516 8(4)	0.486 0(3)	0.018(2)
C3*	0.872 5(4)	0.544 9(3)	0.396 7(3)	0.018(2)
C4*	0.921 6(4)	0.459 0(4)	0.344 8(3)	0.018(2)
C5*	0.932 5(4)	0.346 3(4)	0.381 7(3)	0.019(2)
C6*	0.896 6(4)	0.320 1(4)	0.471 3(3)	0.020(2)
C7*	0.916 0(4)	0.248 5(4)	0.270 0(3)	0.024(2)
C8*	0.984 4(5)	0.150 9(5)	0.221 6(4)	0.041(3)
C9*	0.762 4(4)	0.753 2(4)	0.333 4(3)	0.024(2)
C10*	0.776 7(6)	0.865 1(4)	0.305 6(4)	0.038(3)
C11*	0.812 4(4)	0.371 4(4)	0.623 2(3)	0.025(2)
Ow1	0.680 0(3)	0.354 7(3)	1.089 0(2)	0.031(2)
Ow2	0.427 8(3)	0.664 1(3)	0.652 6(2)	0.033(2)
Ow3	0.868 1(3)	0.281 1(3)	0.878 7(3)	0.041(2)
Ow4	0.546 4(4)	0.440 8(3)	0.892 5(2)	0.036(2)
Ow5	0.383 2(4)	0.438 0(4)	0.703 3(4)	0.060(3)
Ow6	0.542 9(5)	0.357 8(5)	0.525 4(3)	0.072(3)
Ow7	0.960 4(7)	0.384 0(6)	0.996 9(5)	0.028(1)
Ow8	0.711 0(7)	0.516 3(7)	0.782 7(5)	0.033(2)
Ow9	0.891 7(8)	0.494 7(8)	0.972 4(6)	0.045(2)
Ow10	0.911 0(10)	0.686 5(9)	0.931 3(7)	0.058(2)

[a] $Ueq = 1/3\sum_i\sum_j \cdot U_{ij} \cdot a_i^* \cdot a_j^* \cdot a_i \cdot a_j$, U_{iso}, Ow7–Ow10.

Results and discussion

One of the two diatrizoate ions in the asymmetric unit, (**I**), with atomic numbering scheme is shown in Fig. 1 (ORTEP).[13] The two crystallographically independent ions have essentially the same conformation, as illustrated in Fig. 2 (MacMimic).[16] The root mean square

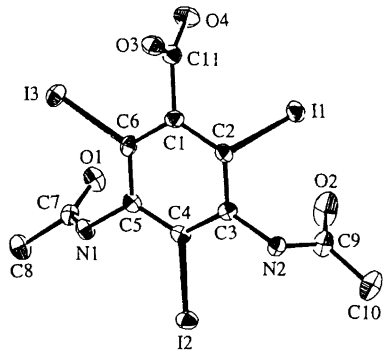

Fig. 1. Perspective drawing of one of the two diatrizoate ions in the asymmetric unit, (**I**).

(RMS) values of the distances of the fitted atoms are 0.03 Å. The lack of higher symmetry in the crystal is presumably caused by the presence of the sodium ions and the water molecules. Mean values of the bond lengths and bond angles for the two diatrizoate ions are given in Table 3. Within estimated standard deviations their values are equal, this is also the case compared to typical values.[17]

Stereoisomerism

Exo/endo *isomerism.* The *exo* conformer is characterized by the carbonyl moiety of the acetanilido group pointing away from the aromatic ring, whereas the group is pointing towards the ring in the *endo* conformation. In both **I** and **II** the orientation is *endo-endo.* The torsional angles indicating this are for **I** 3.2(5)° (C5–N1–C7–O1) and −0.4(5)° (C3–N2–C9–O2), respectively. The corresponding values for **II** are −5.3(5) and 0.4(4)°. The *endo* orientation of the carbonyl moieties leaves better space for the bulky methyl groups. The non-ionic monomer IEEC adopts an *exo-endo* conformation.[12] The IEEC molecule has an *N*-methylacetanilido group, and because this group is *exo*, a *gauche* interaction between the methyl groups is therefore prevented.

Cis/trans *isomerism.* The orientation of the carbonyl moieties of the acetanilido groups is described as *cis* when they are on the same side of the aromatic ring and as *trans* when they are on opposite sides. The carbonyl moieties are located on the same side of the ring, *cis*, for both **I** and **II**. This gives one side that is more hydrophilic, where also the sodium ions are joined to diatrizoate through the carboxylate oxygen atom. For the non-ionic dimer iodixanol all mono-*N*-alkyl substituted amide side chains are *trans*-related.[11] IEEC shows a 50–50 distribution between *cis* and *trans* for the acetanilido groups.

Coordination around sodium. The two sodium ions in the asymmetric unit are differently coordinated (Fig. 3, PLUTO).[18] Both sodium ions are coordinated by a carboxylate oxygen atom (O4 and O4*); these are from crystallographically independent diatrizoate ions. The

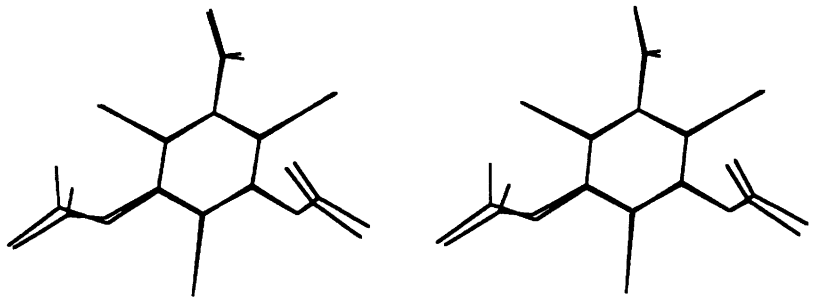

Fig. 2. Stereoscopic view of the superimposition of the two crystallographically independent diatrizoate ions.

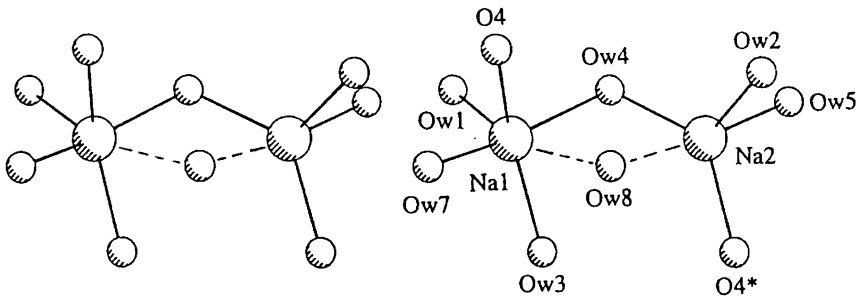

Fig. 3. Stereoscopic view of the coordination sphere around sodium. Bonds to the disordered water oxygen atom, Ow8, are marked with dotted lines. Ow7 are for clarity drawn in the position filled by one of the two disordered water oxygen atoms, Ow7 or Ow9.

Table 3. Interatomic distances (in Å) and angles (in °), with e.s.d.s in parentheses.

C_{arom}–I	2.10(1)[a]	6[b]	C–$O_{carboxylate}$	1.25(1)	4
C=O_{amide}	1.24(1)	4	N_{amide}–C_{amide}	1.34(1)	4
N_{amide}–C_{arom}	1.42(1)	4	C_{amide}–C_{sp^3}	1.50(2)	4
C_{arom}–C_{arom}	1.40(2)	12	C_{arom}–$C_{carboxylate}$	1.52(1)	2
I–C_{arom}–C_{arom}	120(1)	12	$O_{carboxylate}$–$C_{carboxylate}$–$O_{carboxylate}$	126.5(7)	2
$O_{carboxylate}$–$C_{carboxylate}$–C_{arom}	116.8(9)	4	O=C_{amide}–N_{amide}	122(1)	4
O=C_{amide}–C_{sp^3}	122(1)	4	N_{amide}–C_{amide}–C_{sp^3}	116(1)	4
C_{amide}–N_{amide}–C_{arom}	122.6(8)	4	N_{amide}–C_{arom}–C_{arom}	120(1)	8
$C_{carboxylate}$–C_{arom}–C_{arom}	120.7(8)	4	C_{arom}–C_{arom}–C_{arom}	120(1)	12

[a] Mean value, mean value of e.s.d. calculated from $(e.s.d._1{}^2+e.s.d._2{}^2+e.s.d._3{}^2+\cdots)^{1/2}$. [b] Number of observations.

Table 4. Coordination around sodium, distances (in Å) and angles (in °) with e.s.d.s in parentheses.

Na1–O4	2.307(4)	Na1–Ow1	2.359(5)
Na1–Ow3	2.326(5)	Na1–Ow4	2.429(5)
Na1–Ow7	2.543(7)	Na1–Ow8	2.431(8)
Na1–Ow9	2.357(9)	Na2–O4*	2.286(4)
Na2–Ow2	2.378(5)	Na2–Ow4	2.306(4)
Na2–Ow5	2.283(5)	Na2–Ow8	2.449(8)
O4–Na1–Ow1	99.9(2)	O4–Na1–Ow3	152.8(2)
O4–Na1–Ow4	95.4(2)	O4–Na1–Ow7	97.6(2)
O4–Na1–Ow8	83.4(3)	O4–Na1–Ow9	68.7(3)
Ow1–Na1–Ow3	106.8(2)	Ow1–Na1–Ow4	84.2(2)
Ow1–Na1–Ow7	94.4(2)	Ow1–Na1–Ow8	154.3(3)
Ow1–Na1–Ow9	107.0(3)	Ow3–Na1–Ow4	92.0(2)
Ow3–Na1–Ow7	76.0(2)	Ow3–Na1–Ow8	74.6(3)
Ow3–Na1–Ow9	98.3(3)	Ow4–Na1–Ow7	167.0(2)
Ow4–Na1–Ow8	70.2(2)	Ow4–Na1–Ow9	161.7(3)
Ow7–Na1–Ow8	110.5(3)	Ow8–Na1–Ow9	98.0(3)
O4*–Na2–Ow2	105.6(2)	O4*–Na2–Ow4	131.2(2)
O4*–Na2–Ow5	102.6(2)	O4*–Na2–Ow8	83.4(2)
Ow2–Na2–Ow4	117.1(2)	Ow2–Na2–Ow5	84.7(2)
Ow2–Na2–Ow8	93.7(3)	Ow4–Na2–Ow5	103.7(2)
Ow4–Na2–Ow8	71.9(3)	Ow5–Na2–Ow8	174.0(3)

coordination body is in both cases in addition built from water oxygen atoms. The two sodium ions have one binding site in common, Ow4. There is also another site which is shared; it is filled by a water oxygen atom with an occupancy factor of 0.5 (Ow8), meaning that Ow8 is present only in 50% of the possible sites. One of the ligands of Na1 is either one of two disordered water oxygen atoms (Ow7 or Ow9), the population being equally distributed among them. As a consequence of disordered water oxygen atoms in the coordination sphere, one of the sodium ions (Na1) is either five- or six-coordinated, while the latter sodium ion (Na2) is four- or five-coordinated. The coordination bodies can best be described as a distorted octahedron and a deformed tethrahedron, respectively.

The mean sodium–oxygen bond length is 2.37(2) Å, the distances varying from 2.283(5) to 2.543(7) Å. Bond lengths and bond angles involving the sodium ions are given in Table 4.

Packing pattern, intermolecular hydrogen bonds. The arrangement of diatrizoate and sodium ions and water molecules in the unit cell is shown in Fig. 4 (MacMimic). Hydrogen atoms were added to the disordered water oxygen atoms in the SYBYL program.[19] The water molecules are located in channels through the crystal. The close proximity of all the water molecules to each other may be an explanation of the disorder, since this allows several orientations in the crystal lattice and hence different hydrogen-bonding possibilities. There is an extensive intermolecular hydrogen-bonding network in the crystal; most of the hydrogen bonds include the water molecules. The bond lengths and angles are given in Table 5. For the disordered water oxygen atoms, where the hydrogen atom positions are unknown, hydrogen-bonding possibilities are given.

Table 5. Intermolecular hydrogen bonds, bond lengths (in Å) and angles (in °) with e.s.d.s in parentheses (including water molecules of crystallization, Ow).

	$D^a\cdots A^b$	H–A	D–H···A
N1–H71···O2*^{c}	2.936(5)	2.12	157
N2–H72···O3^d	2.891(5)	2.01	174
N1*–H71*···O1^e	2.791(5)	1.82	175
N2*–H72*···O3*^{e}	2.770(5)	1.89	161
Ow1–H811···O1*^{g}	2.849(4)	1.84	176
Ow2–H821···O1*^{h}	2.848(5)	2.01	163
Ow2–H822···Ow6^h	2.748(6)	1.90	143
Ow3–H832···O2^i	2.865(5)	2.06	163
Ow3–H831···O3*	2.931(5)	1.97	169
Ow4–H841···O3^f	2.838(5)	1.94	173
Ow4–H842···Ow1^f	2.861(5)	2.16	155
Ow5–H852···O2*^{h}	2.909(5)	1.94	175
Ow7···O2^i	2.953(8)		
Ow7···Ow3	3.001(7)		
Ow8···O3*	3.021(8)		
Ow8···Ow3	2.884(8)		
Ow8···Ow4	2.793(9)		
Ow9···O4	2.63(1)		
Ow9···Ow9^i	2.82(1)		
Ow10···O2	2.86(1)		
Ow10···Ow9	2.55(1)		

[a] Donor. [b] Acceptor. Symmetry code: [c] $1-x, 2-y, 1-z$; [d] $1-x, 2-y, 2-z$; [e] $2-x, 1-y, 1-z$; [f] $1-x, 1-y, 2-z$; [g] $x, y, z-1$; [h] $1-x, 1-y, 1-z$; [i] $2-x, 1-y, 2-z$.

Ow10 is the only disordered water oxygen atom which is not coordinated to sodium. It has possible hydrogen bonds to Ow9 and to one of the amide oxygen atoms, O2. O2 uses one of its two lone pairs in an hydrogen bond to the water molecule Ow3. Both Ow7 and Ow10 are within hydrogen-bonding distance to O2, meaning that these two disordered water oxygen atoms are not present at the same time. The other hydrogen bonds in the structure are from the four amide nitrogen atoms to

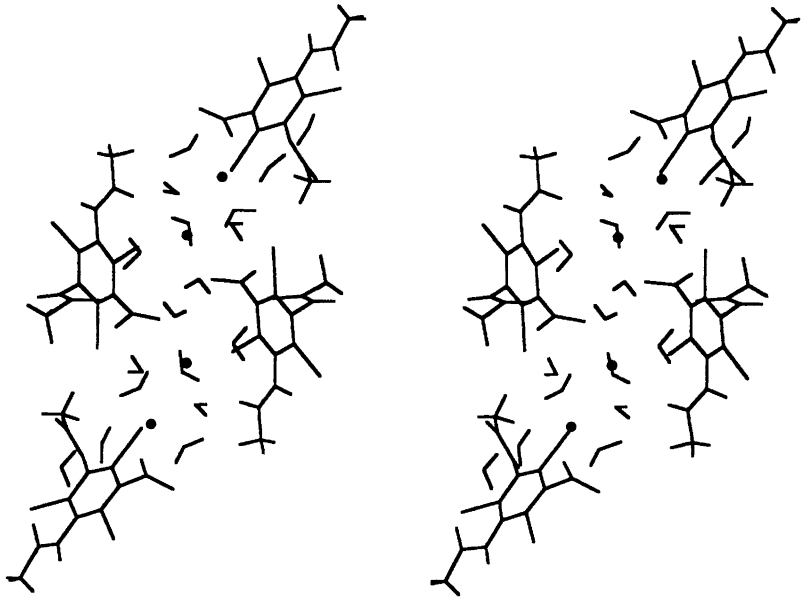

Fig. 4. Stereoscopic view showing the packing pattern in a unit cell. Sodium ions are marked as black dots.

amide and carboxylate oxygen atoms. Such an N–H···O hydrogen bond is the only hydrogen bond in the water-insoluble compound IEEC.

As found in IEEC there are short intermolecular I···I contacts, I3*···I3* = 3.758(1) Å and I3···I1* = 3.963(1) Å, respectively.

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