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Molecular and Crystal Structure of Iodixanol, a New X-Ray Contrast Agent

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3,3′,5,5′-Tetrakis(2,3-dihydroxypropylcarbamoyl)-2,2′,4,4′,6,6′-hexaiodo-*N*,*N*′-(2-hydroxypropane-1,3-diyl)diacetanilide monohydrate, iodixanol, $C_{35}H_{44}I_6N_6O_{15}\cdot H_2O$, $M_w = 1568.21$ g mol^{-1}, crystallizes in the triclinic space group $P\bar{1}$, $Z = 4$ with unit cell dimensions $a = 16.864(3)$, $b = 18.164(3)$, $c = 19.360(4)$ Å, $\alpha = 95.68(2)$, $\beta = 102.43(2)$, $\gamma = 114.56(1)°$ and $V = 5147(2)$ Å^3. $R = 0.068$ for 4380 unique reflections.

The X-ray single-crystal structure of the contrast agent iodixanol has been determined by direct methods and difference Fourier syntheses. The asymmetric unit contains two stereoisomers (**I** and **II**) of iodixanol. The molecule consists of two triiodinated benzene rings with two mono-*N*-alkyl substituted amide side chains on each of the rings, which are further interconnected by a bridging group: –N–C–C–C–N–. The torsional angles of the bridging group are different in stereoisomers **I** and **II**, the angles being (from left to right) in **I**: –84(3)°, 178(4)°, –80(3)°, –88(3)° and in **II**: –90(3)°, 177(3)°, –166(4)° and –93(4)°. The difference in torsional angles for the two stereoisomers reflects the folded conformation of molecule **I**, caused by the two intramolecular hydrogen bonds of 3.1(2) Å and 2.91(3)° Å between O–H···O and N–H···O groups of the mono-*N*-alkyl substituted amide side chains, in contrast with the single intramolecular hydrogen bond of 3.02(4) Å between O–H···O in the bridge in stereoisomer **II**.

All mono-*N*-alkyl substituted amide side chains are *trans*-related with respect to the ring plane. Stereoisomer **I** has an *endo, exo* configuration, stereoisomer **II** is *exo,exo* (the carbonyl oxygen atoms of the acetyl groups in the bridge pointing towards the ring; *endo* or away from it; *exo*). There is an extensive intermolecular hydrogen-bonding network.

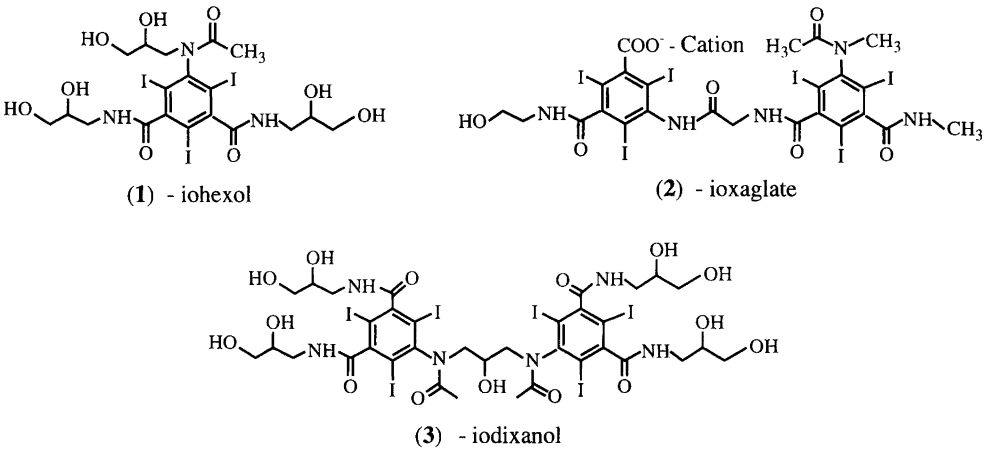
Molecular mechanics calculations have been performed to determine the difference in energy between the two stereoisomers, showing stereoisomer **I** to have an energy 41 kJ mol^{-1} lower than stereoisomer **II**.

Almost all X-ray contrast agents for medical diagnosis are triiodinated benzene derivatives with hydrophilic substituents which give compounds with high water solubility and low toxicity. The most important physicochemical properties of a contrast agent with low toxicity and few side effects include, in addition to high water solubility, low osmolality, acceptable viscosity and sufficient stability.[1,2]

Owing to the high dose and concentration of iodinated substance necessary to obtain contrast enhancement, modern contrast agents are non-ionic compounds like iohexol (**1**).[3,4] Extensive clinical experience with non-ionic X-ray contrast agents confirms the important improvement in patient safety and comfort, compared with the ionic agents, based on the reduced osmotic loading of the patient.[5,6] Another approach to reduce osmolality of the contrast agent has been to incorporate six iodine atoms into the anionic part of the salt, as is done for the ionic dimer ioxaglate (**2**).[7]

High concentrations (> 150 mg I/ml) of non-ionic monomers such as **1** or ionic dimers such as **2** result in an osmolality higher than that of blood.[8] Iodixanol (**3**), which is a new non-ionic dimeric contrast agent containing six iodine atoms per molecule, is isotonic with blood in all clinically relevant concentrations (up to 320 mg I/ml). Iodixanol has recently been approved for intravascular administration.

Several stereoisomers of iodixanol are possible,[9] and as part of our on-going program on crystallographic structure determinations of pharmaceuticals in medical imaging,[10,11] it was of interest to perform a structure determination of this new agent. The structure of a non-ionic monomer, iopamidol, has previously been reported.[12]



Scheme 1.

Experimental

Data collection was performed at low temperature on a Nicolet *P3/F* automatic diffractometer. The three test reflections showed no significant fluctuation as a function of time. The settings of 25 general reflections were used in a least-squares fit to determine the unit cell parameters, $23 < 2\theta < 31°$. The intensity data were corrected for Lorentz and polarization effects, and an absorption correction was 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. Phases were obtained using direct methods (MITHRIL),[14] which gave the atomic coordinates of the twelve iodine atoms (for the

Table 1. Crystal data and intensity collection.

Formula	$C_{35}H_{44}I_6N_6O_{15} \cdot H_2O$
Formula weight/g mol^{-1}	1568.21
Crystal dimensions/mm^3	0.35×0.25×0.15
Density calculated/Mg m^{-3}	2.02
Linear absorption coefficient, μ/cm^{-1}	36.49
F(000)	2976
Space group	$P\bar{1}$ (No. 2)
Z	4
a/Å	16.864(3)
b/Å	18.164(3)
c/Å	19.360(4)
α/°	95.68(2)
β/°	102.43(2)
γ/°	114.56(1)
V/Å^3	5147(2)
Diffractometer	Nicolet *P3/F*
Radiation	Mo *K*α
Wavelength/Å	0.71069
Monochromator	Graphite
T/K	138
Scan mode	θ–2θ
Scan range/°	$2\theta\alpha_1 - 1.0$ to $2\theta\alpha_2 + 1.2$
Scan speed/°min^{-1}	3–20
2θ range/°	3.0–40.0
Background/scan ratio	0.7
No. of reflections measured	11404
No. of unique reflections [$I > 3\sigma(I)$]	4380
Stability monitoring	3 test refl./135 observ.
No. of parameters	575
No. of restraints	476
$R(F) = \Sigma \|\|F_o\| - \|F_c\|\| / \Sigma \|F_o\|$	0.068
$R_w(F^2) = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$	0.165[a]
$S = [\Sigma w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$	1.10

[a] $w^{-1} = [\sigma^2(F_o^2) + (0.0883P)^2 + 205.61P]$, where $P = (F_o^2 + 2F_c^2)/3$.

two stereoisomers). Since the unit cell contains four molecules, there are two molecules in the asymmetric unit.

The positional and displacement parameters of the iodine atoms were refined with a full-matrix least-squares refinement program.[13,15] All least-squares refinements were carried out by minimization of $\Sigma w\,(\Delta F)^2$. While locating the outermost atoms in the mono-*N*-alkyl substituted amide side chains the least-squares refinement was performed with $w = 1$, otherwise the weighting scheme $w = 1/\sigma^2$ was used. A difference Fourier synthesis gave 80 out of the 124 non-hydrogen atoms, and after some cycles of least-squares refinement another 15 atoms were located. The intensity data were at this stage corrected for absorption, and anisotropic vibration was included for the iodine atoms.

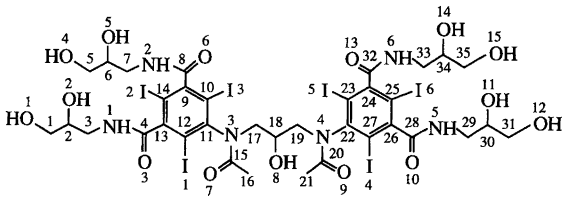
Alternating least-squares refinement and difference Fourier syntheses were carried out until all the remaining non-hydrogen atoms were localized. Least-squares refinement resulted in large displacement parameters of the outermost atoms of the four mono-*N*-alkyl substituted amide side chains and obviously wrong geometry, with for example C_{sp^3}–O_{sp^3} distances of over 2 Å. The difficulties in determining exact positions for the outermost atoms are probably caused by the high flexibility of the side chains and the presence of the heavy iodine atoms. 17 of the atoms with most uncertain parameters were included at positions found from difference Fourier syntheses, but their positions were not refined (displacement parameters obtained from initial refinement were kept fixed). Three water molecules of crystallization were also included in positions found in difference Fourier syntheses but not refined. They were given a *U*-value of 0.20, and the mean of the standard deviations for the hydroxy-oxygen atoms in the mono-*N*-alkyl substituted amide side chains were used as standard deviations in their positions.

Since the local version of the full-matrix least-squares refinement program used only allows 350 parameters to be refined simultaneously, each of the two molecules in the asymmetric unit was refined separately.

The final *R*-value ($= \Sigma||F_o| - |F_c||/\Sigma|F_o|$) is 0.071, and $R_w\{ = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}\}$ is 0.079 for 489 refined parameters, of a total of 569 parameters. $S\{ = [\Sigma w(F_o - F_c)^2]/(n-p)\}$ is 4.10 for $w = 1/\sigma^2$ and 12.47 for $w = 1$, respectively. The final difference map gave maximum and minimum residual electron densities of ± 1.36 e Å^{-3}. Atomic scattering factors were taken from Ref. 16.

The atomic coordinates and displacement parameters from this refinement can be obtained from the authors upon request.

SHELXL-93 refinement. The structure was further refined with restraint on the mono-*N*-alkyl substituted amide side chains using the SHELXL-93 program.[17] Interatomic distances and angles from the best described side chain, C9*–C8*–O6*–N2*–C7*–C6*–O5*–C5*–O4* (Scheme 2), was used in the calculations with $\sigma = 0.03$ (the atoms



Scheme 2.

of stereoisomer **II** are marked with a star). Only the unique reflections with $I > 3\sigma(I)$ were used in the refinement. This was done because the data had been corrected for absorption, which was considered more important than to use the weak reflections in the refinement. Five possible positions for water oxygen atoms were located from difference Fourier syntheses. They were given fixed displacement parameters ($U = 0.05$, which might be too low), and the positional parameters and occupancies were refined. The occupancy factors varied from 0.3 to 0.5, indicating a total of two water molecules of crystallization.

The final difference map gave maximum and minimum residual electron densities of ± 1.07 e Å^{-3}.

Final fractional coordinates and equivalent displacement parameters from the SHELXL-93 refinement are given in Table 2.

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$^{2\,a}$
Stereoisomer I				
I1	−0.0609(2)	0.3037(2)	0.2280(2)	0.074(2)
I2	−0.0365(2)	0.0085(2)	0.3288(2)	0.098(2)
I3	0.0852(2)	0.1091(1)	0.0670(1)	0.058(2)
I4	0.2141(2)	0.2440(2)	0.3176(2)	0.068(2)
I5	0.4799(2)	0.5889(2)	0.3180(1)	0.064(2)
I6	0.3396(2)	0.5171(2)	0.5779(2)	0.110(3)
O1	−0.058(8)	0.141(9)	0.600(4)	0.61(8)
O2	−0.135(6)	0.202(5)	0.536(4)	0.47(6)
O3	−0.165(1)	0.134(1)	0.213(1)	0.067(8)
O4	0.070(10)	−0.259(6)	0.263(5)	0.65(9)
O5	−0.024(4)	−0.192(4)	0.230(3)	0.34(4)
O6	0.139(1)	0.039(1)	0.238(1)	0.060(7)
O7	−0.112(2)	0.186(1)	0.045(1)	0.061(7)
O8	0.128(1)	0.443(1)	0.165(1)	0.043(6)
O9	0.351(1)	0.350(1)	0.160(1)	0.048(6)
O10	0.164(2)	0.317(2)	0.477(2)	0.11(1)
O11	0.287(4)	0.138(3)	0.497(3)	0.29(3)
O12	0.069(5)	0.082(6)	0.545(6)	0.53(7)
O13	0.539(1)	0.642(1)	0.513(1)	0.074(8)
O14	0.500(6)	0.904(3)	0.517(4)	0.47(6)
O15	0.540(7)	0.829(7)	0.408(5)	0.52(7)
N1	−0.021(1)	0.213(2)	0.386(1)	0.055(9)
N2	0.006(1)	−0.058(1)	0.160(1)	0.056(9)
N3	0.037(2)	0.256(1)	0.116(1)	0.037(7)
N4	0.318(2)	0.404(2)	0.254(1)	0.042(8)
N5	0.290(2)	0.297(2)	0.513(2)	0.07(1)
N6	0.420(2)	0.671(2)	0.474(2)	0.10(1)

Table 2 Continued

Atom	*x*	*y*	*z*	*U*/Å$^{2\,a}$
C1	−0.017(6)	0.157(6)	0.535(5)	0.40(7)
C2	−0.088(3)	0.174(3)	0.484(2)	0.15(6)
C3	−0.053(3)	0.244(2)	0.447(2)	0.10(2)
C4	−0.080(2)	0.165(2)	0.323(1)	0.06(1)
C5	0.084(5)	−0.229(4)	0.191(3)	0.21(3)
C6	0.065(3)	−0.152(3)	0.205(3)	0.25(4)
C7	0.043(3)	−0.120(2)	0.141(2)	0.10(2)
C8	0.059(2)	0.017(1)	0.200(2)	0.04(1)
C9	0.021(2)	0.078(1)	0.202(2)	0.033(9)
C10	0.034(2)	0.128(2)	0.154(2)	0.029(8)
C11	0.018(2)	0.199(2)	0.165(2)	0.038(9)
C12	−0.025(2)	0.207(2)	0.212(2)	0.038(9)
C13	−0.040(2)	0.154(2)	0.263(1)	0.04(1)
C14	−0.018(2)	0.086(2)	0.252(2)	0.05(1)
C15	−0.031(3)	0.243(2)	0.055(2)	0.06(1)
C16	−0.010(3)	0.302(2)	0.003(2)	0.07(1)
C17	0.138(2)	0.313(2)	0.132(2)	0.04(1)
C18	0.165(2)	0.386(2)	0.192(2)	0.05(1)
C19	0.271(2)	0.442(2)	0.208(2)	0.04(1)
C20	0.361(2)	0.364(2)	0.224(2)	0.04(1)
C21	0.429(2)	0.344(2)	0.276(2)	0.05(1)
C22	0.338(2)	0.426(2)	0.331(2)	0.034(9)
C23	0.398(2)	0.510(2)	0.369(2)	0.036(9)
C24	0.396(2)	0.531(2)	0.441(2)	0.06(1)
C25	0.344(3)	0.474(2)	0.477(2)	0.06(1)
C26	0.294(2)	0.396(2)	0.439(2)	0.06(1)
C27	0.285(2)	0.368(2)	0.366(2)	0.05(1)
C28	0.244(2)	0.333(2)	0.479(2)	0.09(1)
C29	0.249(3)	0.235(2)	0.560(2)	0.11(2)
C30	0.206(3)	0.151(2)	0.511(2)	0.14(2)
C31	0.160(4)	0.077(3)	0.546(3)	0.19(3)
C32	0.458(2)	0.620(2)	0.480(2)	0.07(1)
C33	0.476(3)	0.762(2)	0.519(2)	0.14(2)
C34	0.436(4)	0.810(3)	0.479(3)	0.25(4)
C35	0.438(6)	0.809(5)	0.399(3)	0.34(6)
Stereoisomer II				
I1*	0.3002(2)	−0.0203(1)	−0.1834(1)	0.055(2)
I2*	0.6910(2)	0.1532(2)	0.0070(2)	0.065(2)
I3*	0.4120(2)	0.2540(1)	0.0747(1)	0.052(2)
I4*	0.1846(2)	0.3728(2)	−0.3135(2)	0.098(2)
I5*	0.3616(2)	0.4520(2)	0.0084(2)	0.084(2)
I6*	0.0517(2)	0.5304(2)	−0.1070(2)	0.119(3)
O1*	0.665(9)	−0.050(8)	−0.317(5)	0.58(8)
O2*	0.705(7)	0.083(7)	−0.241(12)	1.4(3)
O3*	0.501(2)	−0.045(1)	−0.108(1)	0.061(7)
O4*	0.629(3)	0.213(2)	0.327(2)	0.16(2)
O5*	0.736(3)	0.382(3)	0.322(2)	0.25(3)
O6*	0.652(1)	0.326(1)	0.085(1)	0.060(7)
O7*	0.150(2)	0.071(1)	−0.062(1)	0.057(7)
O8*	0.225(2)	0.252(2)	−0.070(2)	0.084(9)
O9*	0.436(2)	0.380(2)	−0.180(2)	0.11(1)
O10*	0.101(2)	0.528(1)	−0.280(1)	0.090(9)
O11*	−0.180(3)	0.403(3)	−0.280(2)	0.21(2)
O12*	−0.235(3)	0.398(3)	−0.424(2)	0.19(2)
O13*	0.178(2)	0.482(1)	0.047(1)	0.070(8)
O14*	0.372(3)	0.762(3)	0.198(2)	0.27(3)
O15*	0.517(3)	0.742(3)	0.193(3)	0.23(2)
N1*	0.546(2)	0.051(2)	−0.176(2)	0.10(1)
N2*	0.620(2)	0.223(1)	0.147(1)	0.048(8)
N3*	0.291(2)	0.119(2)	−0.074(1)	0.039(7)
N4*	0.306(2)	0.373(2)	−0.163(1)	0.049(8)
N5*	−0.007(2)	0.399(1)	−0.284(2)	0.07(1)
N6*	0.266(2)	0.606(1)	0.025(1)	0.07(1)

Table 2 Continued

Atom	*x*	*y*	*z*	*U*/Å$^{2\,a}$
C1*	0.680(8)	−0.058(8)	−0.237(6)	0.8(2)
C2*	0.654(4)	0.009(5)	−0.206(4)	0.29(5)
C3*	0.556(3)	−0.010(3)	−0.233(2)	0.17(3)
C4*	0.511(3)	0.023(2)	−0.123(2)	0.07(1)
C5*	0.586(3)	0.264(3)	0.291(3)	0.15(2)
C6*	0.657(3)	0.318(2)	0.257(2)	0.15(2)
C7*	0.699(2)	0.277(2)	0.216(1)	0.06(1)
C8*	0.608(2)	0.252(1)	0.088(1)	0.039(9)
C9*	0.535(2)	0.191(1)	0.023(1)	0.027(8)
C10*	0.449(2)	0.183(2)	0.007(2)	0.035(9)
C11*	0.383(2)	0.127(2)	−0.052(2)	0.030(8)
C12*	0.401(2)	0.071(2)	−0.097(2)	0.034(9)
C13*	0.490(2)	0.080(2)	−0.077(2)	0.04(1)
C14*	0.557(2)	0.138(2)	−0.019(2)	0.05(1)
C15*	0.227(2)	0.074(2)	−0.045(2)	0.04(1)
C16*	0.246(2)	0.029(2)	0.012(2)	0.035(9)
C17*	0.267(2)	0.152(2)	−0.137(2)	0.035(9)
C18*	0.288(2)	0.245(2)	−0.109(2)	0.05(1)
C19*	0.266(2)	0.280(2)	−0.181(2)	0.06(1)
C20*	0.388(3)	0.418(3)	−0.171(2)	0.09(1)
C21*	0.426(3)	0.509(3)	−0.166(2)	0.08(1)
C22*	0.253(2)	0.411(2)	−0.146(2)	0.037(9)
C23*	0.264(2)	0.449(2)	−0.078(2)	0.04(1)
C24*	0.209(2)	0.484(2)	−0.068(1)	0.039(9)
C25*	0.142(2)	0.483(2)	−0.124(2)	0.04(1)
C26*	0.137(2)	0.452(2)	−0.195(2)	0.05(1)
C27*	0.187(2)	0.413(2)	−0.208(2)	0.05(1)
C28*	0.074(2)	0.463(2)	−0.257(2)	0.06(1)
C29*	−0.077(2)	0.410(3)	−0.350(2)	0.13(2)
C30*	−0.110(3)	0.458(3)	−0.319(2)	0.17(3)
C31*	−0.170(4)	0.484(3)	−0.374(3)	0.40(7)
C32*	0.218(2)	0.524(2)	0.007(1)	0.06(1)
C33*	0.265(2)	0.655(2)	0.095(2)	0.13(2)
C34*	0.354(3)	0.679(3)	0.148(2)	0.18(3)
C35*	0.438(3)	0.704(5)	0.121(3)	0.26(4)
Ow1	0.081(3)	0.440(3)	0.477(3)	0.05
Ow2	0.784(3)	0.316(3)	0.462(2)	0.05
Ow3	0.932(3)	0.437(3)	0.424(2)	0.05
Ow4	0.225(4)	0.033(4)	0.398(3)	0.05
Ow5	0.718(5)	0.017(4)	0.378(4)	0.05

^{a} $U_{eq} = 1/3\,\Sigma_i\Sigma_j \cdot U_{ij} \cdot \boldsymbol{a}_i^* \cdot \boldsymbol{a}_j^* \cdot \boldsymbol{a}_i \cdot \boldsymbol{a}_j$ (iodine atoms), U_{iso}, remaining atoms.

Molecular mechanics calculations. As it would be of interest to determine the difference in energy between the two stereoisomers, both stereoisomers have been energy-minimized with the MM2(91) force field.[18] The MM2(91) molecular mechanics program used was included in the MacMimic program package,[19] and run on a Macintosh IIsi. Hydrogen atoms were added to the structures in the SYBYL program,[20] and lone-pairs on the hydroxy oxygen atoms were included using MacMimic. It was necessary to estimate some missing force field parameters. The torsional parameters for C_{sp^3}–C_{sp^2}–N_{sp^2}–H were used in place of the parameters for C_{sp^2}–C_{sp^2}–N_{sp^2}–H, and the parameters for C_{sp^2}–C_{sp^2}–C_{sp^2}–I instead of N_{sp^2}–C_{sp^2}–C_{sp^2}–I. The C_{sp^3}–I stretching and dipole parameters were used for C_{sp^2}–I.

The energy-minimized conformations of both stereoisomers were least-squares fitted to the X-ray structures.

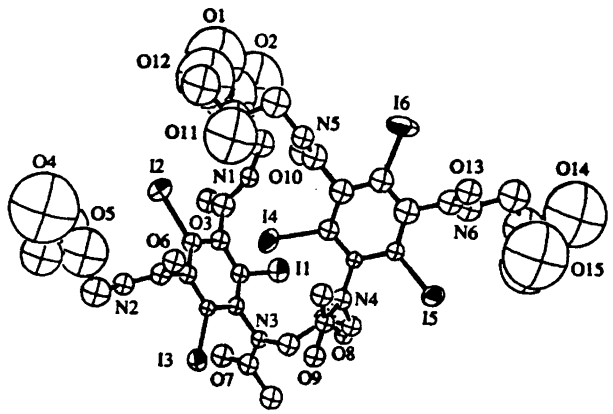


Fig. 1. Perspective drawing of stereoisomer **I**.

This was performed by fitting the aromatic rings using the MacMimic program.

Results and discussion

Estimated standard deviations in the atomic positions do not permit a detailed discussion of the interatomic distances and angles. However, no unusual features are observed in the overall geometry. The outermost atoms of the mono-*N*-alkyl substituted amide side chains have large displacement parameters, which could be an indication of either static or dynamic disorder. Refinement along these lines have been tried, but the data do not allow a definite conclusion. The molecule is large and flexible reflecting that it is very difficult to crystallize.

Conformation and intramolecular hydrogen bonding. Figs. 1 and 2 are ORTEP-drawings[13] of the two molecules of iodixanol in the asymmetric unit. They are denoted stereoisomers **I** and **II**. The conformations are rather different. In stereoisomer **I** there are two intramolecular hydrogen bonds (Table 3). One of them between two hydroxy oxygen atoms (O1 and O12), and the other from an amide nitrogen atom (N1) to an amide oxygen atom (O10). Both bonds are from atoms on a mono-*N*-alkyl substituted amide side chain of one aromatic ring to a mono-*N*-alkyl substituted amide side chain on the other aromatic ring. Stereoisomer **II** has an intramolecular hydrogen bond from a hydroxy oxygen atom (O8*) to a carbonyl oxygen atom (O7*), both located in the bridge. This gives **I** a folded conformation, compared with the more extended conformation of **II**. In stereoisomer **I** there is only one *trans* bond in the bridge between the two aromatic rings compared to the two *trans* bonds in stereoisomer **II** (Table 4). Stereoscopic views of both stereoisomers are given in Figs. 3 and 4 (PLUTO).[21]

Table 3. Intra- and inter-molecular hydrogen bonding possibilities (in Å), with e.s.d.s in parentheses (including water molecules of crystallization, Ow).

Intramolecular			
O1···O12	3.1(2)	N1···O10	2.91(3)
O8*···O7*	3.02(4)		
Intermolecular			
O1···Ow4 [a]	3.3(2)	O2···Ow2 [b]	3.2(1)
O4···N5* [c]	2.4(1)	O8···O11* [d]	3.07(5)
O8···O13*	2.65(3)	O11···O15 [e]	2.9(1)
O11···Ow4	2.27(8)	O12···O12 [a]	3.0(1)
O15···N6	3.3(1)	N2···O7* [c]	2.79(3)
N5···O13 [e]	2.82(3)	O1*···O6 [f]	3.2(1)
O1*···Ow4 [f]	2.6(1)	O4*···Ow2	3.03(6)
O5*···O10* [g]	2.89(5)	O5*···Ow2	3.14(6)
O5*···Ow3	3.14(6)	O12*···Ow2 [h]	2.70(6)
O12*···N6 [d]	2.73(5)	O14*···N1* [g]	3.20(6)
O15*···O9* [g]	2.64(6)	N2*···O3* [f]	2.92(3)
N6*···O6* [g]	2.88(3)	Ow1···O10	3.07(6)
Ow1···Ow3 [b]	2.48(7)	Ow2···Ow3	2.85(7)
Ow3···O10* [g]	2.90(5)	Ow4···O6	3.16(7)
Ow5···O3 [b]	2.87(8)		

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

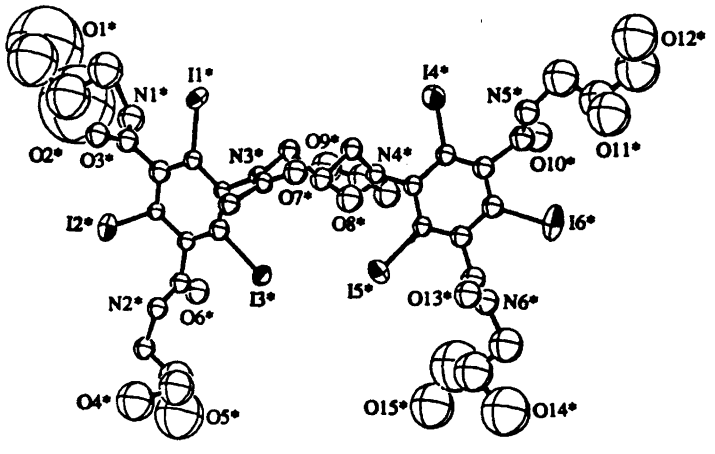
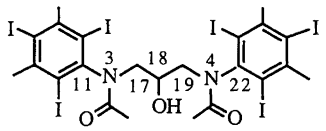


Fig. 2. Perspective drawing of stereoisomer **II**.

Table 4. Torsional angles (°) of the bridge, with e.s.d.s in parentheses, (numbering of the atoms in question).



τ_1=C11–N3–C17–C18, τ_2=N3–C17–C18–C19,
τ_3=C17–C18–C19–N4, τ_4=C18–C19–N4–C22

	τ_1	τ_2	τ_3	τ_4
Stereoisomer **I**	−84(3)	178(4)	−80(3)	−88(3)
Stereoisomer **II**	−90(3)	177(3)	−166(4)	−93(4)

Stereoisomerism

cis/trans *isomerism*. The orientation of the mono-*N*-alkyl substituted amide side chains can be either *cis*- or *trans*-related to each other. It is apparent from Figs. 5 and 6 (PLUTO) that all amide side chains are *trans*-related in the crystal.

exo/endo *isomerism*. The carbonyl oxygen atoms of the acetyl groups in the bridge are oriented either towards the aromatic ring, *endo*, or away from it, *exo*. In stereoisomer **I** the orientation is *endo*, *exo* and in stereoisomer **II** it is *exo*, *exo*, (Figs. 5 and 6). The torsional angles indicating this are for **I** 6(3)° (C11–N3–C15–O7) and −175(5)° (C22–N4–C20–O9), respectively. The corresponding values for **II** are 177(5)° and 174(6)°.

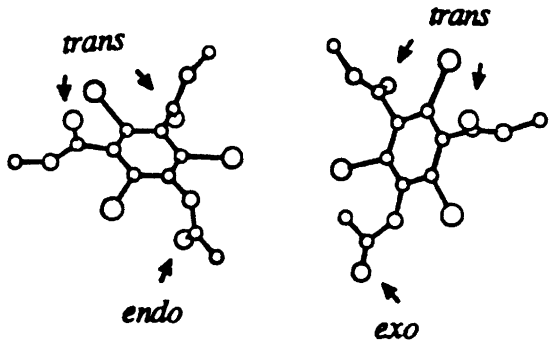


Fig. 5. The *cis/trans* and *endo/exo* isomerism of stereoisomer **I**, only two subunits of the molecule are given.

E/Z *isomerism*. The mono-*N*-alkyl substituted primary amide groups can have either an *E* or *Z* configuration. As expected all groups are *E*.

Chiral centres. There is a chiral carbon atom in each mono-*N*-alkyl substituted amide side chain. The configurations found for the chiral atoms are; (2*S*, 6*R*, 30*R*, 34*R*), stereoisomer **I** and (2**S*, 6**S*, 30**S*, 34**S*), stereoisomer **II**, respectively. This indicates that the two stereoisomers exist as diastereoisomers. The presence of a diastereoisomeric pair is strengthened by the environment around C2. An *R* configuration at C2 (**I**) would have disrupted one of the hydrogen bonds in the molecule, between O1 and O12, hence losing the extra gain in energy which an additional hydrogen bond gives. The configu-

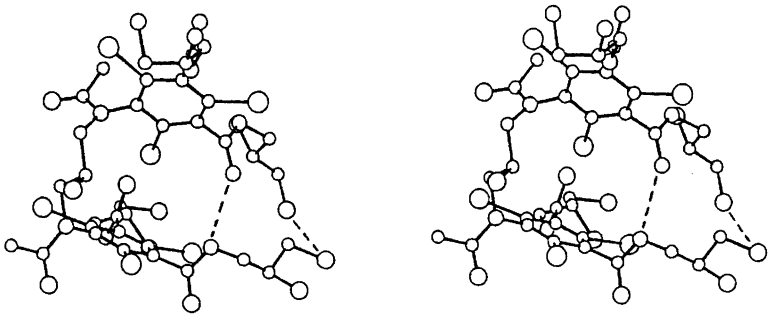


Fig. 3. Stereoscopic view of stereoisomer **I**, intramolecular hydrogen bonds are marked with dotted lines.

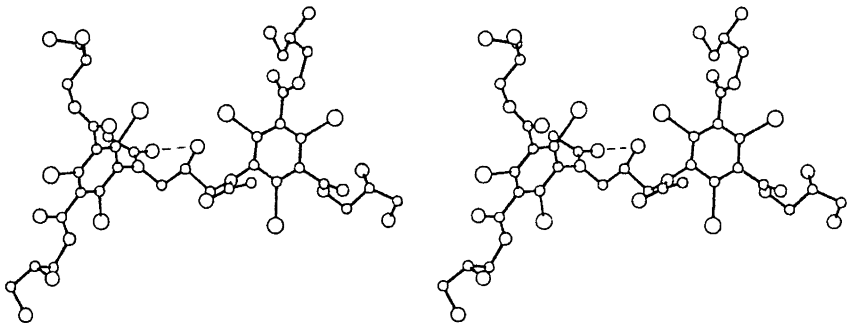


Fig. 4. Stereoscopic view of stereoisomer **II**, the intramolecular hydrogen bond is marked with dotted lines.

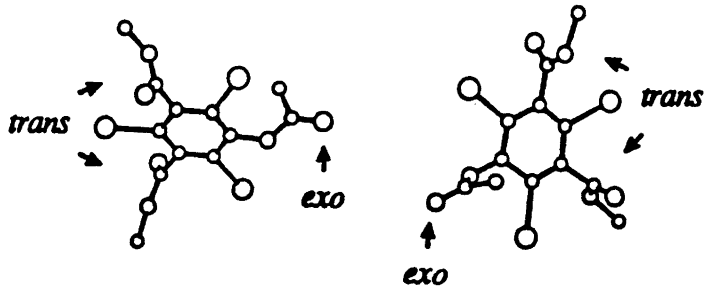


Fig. 6. The *cis/trans* and *endo/exo* isomerism of stereoisomer **II**, only two subunits of the molecule are given.

rations are the same in the energy-minimized structures. As we have a centrosymmetric space group, the molecules exist as racemates of the two diastereoisomers.

The number of stereoisomers of iodixanol have been corroborated by the symmetry species approach and the method of convergence, and rotational barriers in the molecule have been calculated. There are 16 stereoisomers (nine if one assumes free rotation around the phenyl–N bonds).[9]

Packing pattern, intermolecular hydrogen bonds. There is an extensive intermolecular hydrogen-bonding network in the crystal. Since the hydrogen atom positions are unknown, only hydrogen-bonding possibilities are given in Table 3. The distances in the intramolecular hydrogen bonds in the energy-minimized structures are 2.76 Å (O1···O12), 3.01 Å (N1···O10) and 2.79 Å (O8*···O7*), respectively.

Molecular mechanics calculations. From the energy minimizations it was found that stereoisomer **I** (folded conformation) has the lowest steric energy. The difference in steric energy between the two stereoisomers is 41 kJ mol^{-1}. This difference may be explained by the gain in energy from hydrogen bonds and hydrophobic interactions between the mono-*N*-alkyl substituted amide side chains in the folded conformation. All the calculations were performed *in vacuo* and as such are not fully representative of the energy in the solid or liquid phase.

A comparison of the energy-minimized conformation and the one found from X-ray diffraction analysis for both stereoisomers is shown in Figs. 7 and 8 (MacMimic). There are no principal differences between the energy-minimized and the X-ray structures, the main deviations are as expected found in the flexible mono-*N*-alkyl substituted amide side chains. The root mean square (RMS) values of the distances of the fitted atoms are 0.18 Å (stereoisomer **I**) and 0.12 Å (stereoisomer **II**), respectively.

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Fig. 7. Stereoscopic view of the superimposition of the energy-minimized and the X-ray conformations of stereoisomer **I**.

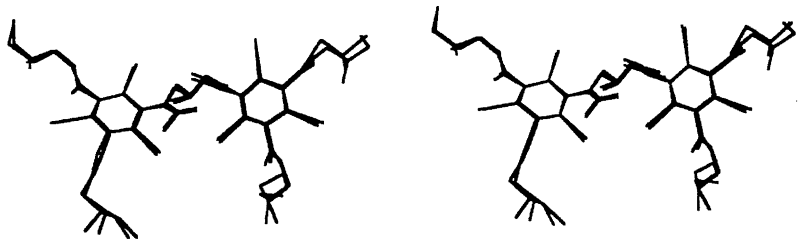

Fig. 8. Stereoscopic view of the superimposition of the energy-minimized and the X-ray conformations of stereoisomer **II**.

ing a stay at the University of Copenhagen, and refinement by SHELXL-93, possible.

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