Syntheses and X-ray crystal structures of derivatives of 2,2′,4,4′,6,6′-hexaiodobiphenyl

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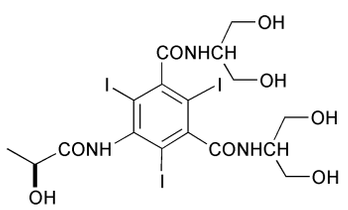
Iodination of 1,1′-biphenyl-3,3′,5,5′-tetrol and 1,1′-biphenyl-3,3′-diol with ICl afforded the corresponding 2,2′,4,4′,6,6′-hexaiodo derivatives. Hydrophilic residues aimed at masking the lipophilicity of the iodine atoms were introduced by alkylation of the OH groups. The solid state structures, which were obtained by X-ray crystallography, of three hexaiodinated derivatives (namely **5**, **7** and **13**) show that, as expected, the two aromatic rings are forced to lie in nearly perpendicular planes by the hindrance of the four iodine atoms adjacent to the inter-annular C–C bond. The hexaiodinated biphenyl skeleton was investigated as the core backbone of a new class of X-ray contrast media.

Introduction

Our interest in the chemistry of polyiodinated compounds stems from their use as X-ray contrast media. To qualify for such an application an iodinated derivative must display *i*) high iodine content, *ii*) thorough solubility in water, *iii*) chemical stability and *iv*) biological inertia.[1] To date, the best performing contrast media (*e.g.* Iopamidol, **1**, Chart 1) share a triiodinated



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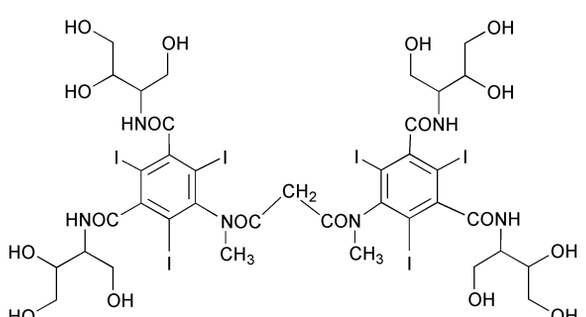

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Chart 1

benzene ring as the common structural building block.[1] Hydroxy- and polyhydroxy-alkyl substituents, which mask the lipophilicity of the iodine atoms, are also required to assure water solubility.[2] Since the opacifying power of the contrast agent is related to the iodine content (*e.g.* 49% for **1**), a product containing a higher iodine percentage could be administered at a lower dose level. As a matter of fact, said contrast agents are formulated as very concentrated (up to 750 mg ml^{-1}) water solutions. After intravenous administration they can cause, although rarely, undesirable side effects (pain, nausea, low blood pressure and vasal damages) which are related to hypertonicity and high viscosity of the solution. To circumvent these drawbacks molecules containing two triiodinated benzene rings, the so-called "dimers" (*e.g.* Iotrolan, **2**, Chart 1),[3] have been developed and brought into clinical practice although without great success. As the result of our studies[4] on biphenyl derivatives in which the iodine content can be as high as 70–75%,† we report in this paper *i*) molecular mechanics and dynamic calculations on 2,2′,6,6′-tetrahalogen-substituted biphenyl systems, *ii*) the synthesis of a series of 2,2′,4,4′,6,6′-hexaiodinated biphenyl derivatives and *iii*) the solid state structures of some of these derivatives obtained by X-ray crystallography.

Results and discussion

Preliminary inspections of molecular models suggested that in a 2,2′,6,6′-tetraiodinated biphenyl the four iodine atoms adjacent to the inter-annular bond (later called C6–C7) mask each other to a certain extent. Therefore, the "exposed" lipophilic surface of the molecule decreases and a limited number of hydrophilic residues could be required to assure water solubility. On this basis we undertook a study to evaluate the conformational behaviour of biphenyl systems bearing halogen substituents in positions 2,2′,6,6′. Despite only being interested for practical reasons in iodo derivatives, for more speculative reasons, we also investigated substitutions by fluorine, chlorine and bromine atoms in these positions.

It is well known that when there are no substituents in the *ortho* positions, the biphenyl vapour-phase energy minima are characterised by a *gauche* conformation,[6] in contrast with the planar geometry of the crystalline state.[7] Two types of interactions mainly affect the torsional potential of the biphenyl systems: *i*) the π-conjugation, which stabilises the coplanar conformer and *ii*) the non-bonding interaction, which is the dominant repulsion term and favours the non-planar arrangement of the two rings. Despite a great deal of work having been carried out on the torsional potential of the basic skeleton of biphenyl,[8,9] we could find no results involving

† Whilst we were working on this project, another research group was developing hexaiodinated biphenyl derivatives bearing different substituents.[5]

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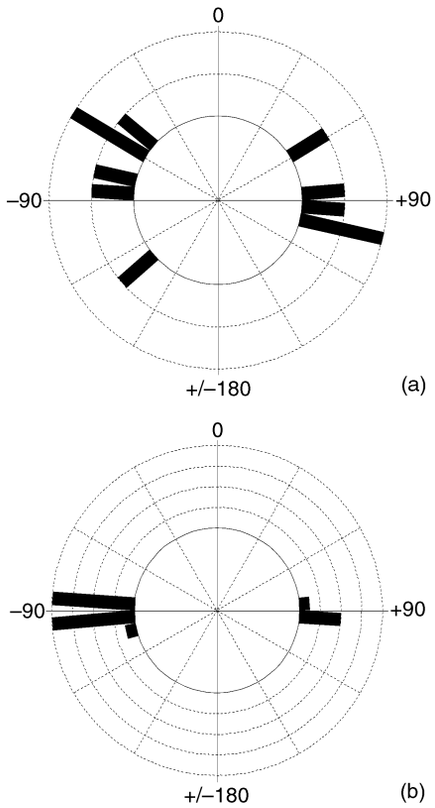


Fig. 1 Plot in polar coordinates of the number of samples retrieved from the CSD within each range (10°) of θ (torsion angle about the C6–C7 bond): a) 2,2′,6,6′-tetrahalogen-substituted biphenyl derivatives (11 molecular fragments); b) 2,2′,6,6′-tetra(C-bulky)-substituted biphenyl derivatives (22 molecular fragments).

2,2′,6,6′-tetrahalogen-substituted biphenyl systems. Therefore, we focused our attention on the evaluation of the rotational potential energy profile about the inter-annular bond of such molecules.

The solid state structures deposited in the Cambridge Structural Database (CSD)[10] which contain the biphenyl fragment and feature the presence of either four halogen atoms or four bulky C groupings at the 2,2′,6,6′ positions have been retrieved. Attention has been paid to the torsion about the C6–C7 bond and to the inter-atomic distances between the *ortho* atoms. The polar histograms (Fig. 1) concerning the above retrieved fragments are evidence that the chance of a reorientation about the C6–C7 linkage, *i.e.* the range of angular values allowed for the above torsion, is rather small. In addition, as expected, the larger the *ortho*-substituents the more perpendicular the dihedral angle defining the relative orientation of the two phenyl rings, thus allowing the *ortho* atoms to lie as far apart as possible. Nevertheless, the observed inter-atomic distances for the tetra-halogen derivatives (no iodo derivatives were found in the CSD) progressively approach the sum of the van der Waals radii going down the 7A group: the minimum X · · · X distances are 2.680, 3.746 and 3.973 Å for X = F, Cl and Br, respectively.

We decided to monitor the energy profile for the C6–C7 torsion by means of a systematic search procedure performed on 2,2′,6,6′-tetrahalogen biphenyl derivatives (X = F, Cl, Br, I).‡ Quantitative results are summarised in Fig. 2. As has

‡ The analogous conformational search performed on the biphenyl has determined the absolute minimum energy to be at a dihedral angle about the C6–C7 bond of 0 or 180°, thus reproducing the planar geometry usually observed in the solid state (the *gauche* conformation is 1.1 kcal mol^{-1} higher). Conversely, a maximum was observed when the two phenyl rings are at 90° to each other (the energy barrier is *ca.* 14 kcal mol^{-1}). Thus the used force field appears to overestimate the π-resonance term with respect to the non-bonding repulsion interactions. As a consequence, it seems appropriate to compare our computational results with solid state structures rather than with vapour phase data.

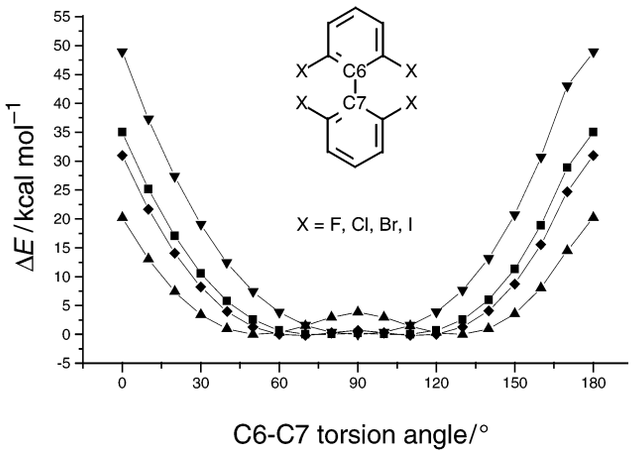


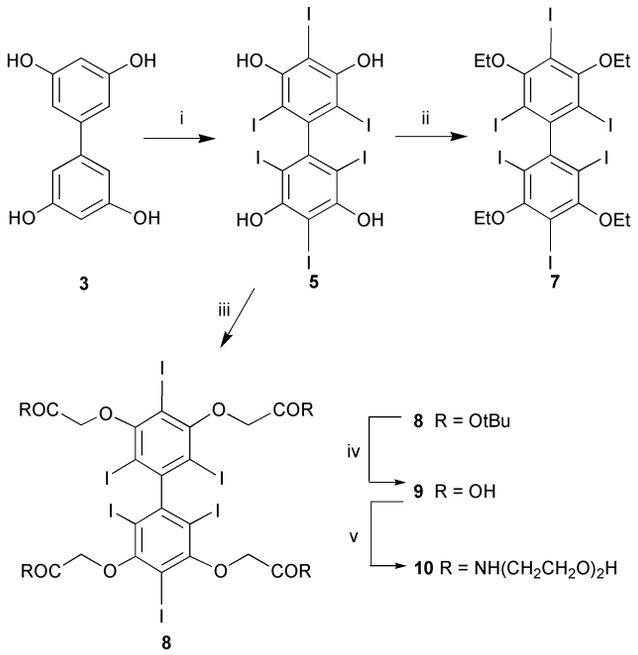
Fig. 2 Energy profiles for the torsion about the C6–C7 bond in 2,2′,6,6′-tetrahalogen-substituted biphenyl derivatives as provided by the conformational search: ▲ = F; ◆ = Cl; ■ = Br; ▼ = I.

already emerged from the analysis of the structural data in the CSD, the angular value of the torsion about C6–C7 progressively increases with the size of the halogen atoms occupying the *ortho* positions: from 50° (130°) for X = F to 90° for X = I [70° (110°) when X = Cl and Br]. It is noteworthy that at 90° the tetrafluoro-substituted biphenyl shows an energy barrier (ΔE = 3.8 kcal mol^{-1}); in this case the π-resonance term prevails over the steric hindrance of the fluorine atoms, the opposite holds for the hexaiodo-substituted molecule. Concerning the energy required for a 360° rotation about C6–C7, the energy barriers span from *ca.* 20 kcal mol^{-1} (X = F) to *ca.* 50 kcal mol^{-1} (X = I). This also indicates that for the lighter derivative we can reasonably exclude complete rotation at room temperature. Results from molecular dynamics simulations performed on the model compounds at 300 and 600 K are in keeping with the latter observation: in all cases no 360° rotation about the inter-annular bond was detected, thus confirming the intrinsic stiffness of all these molecules.

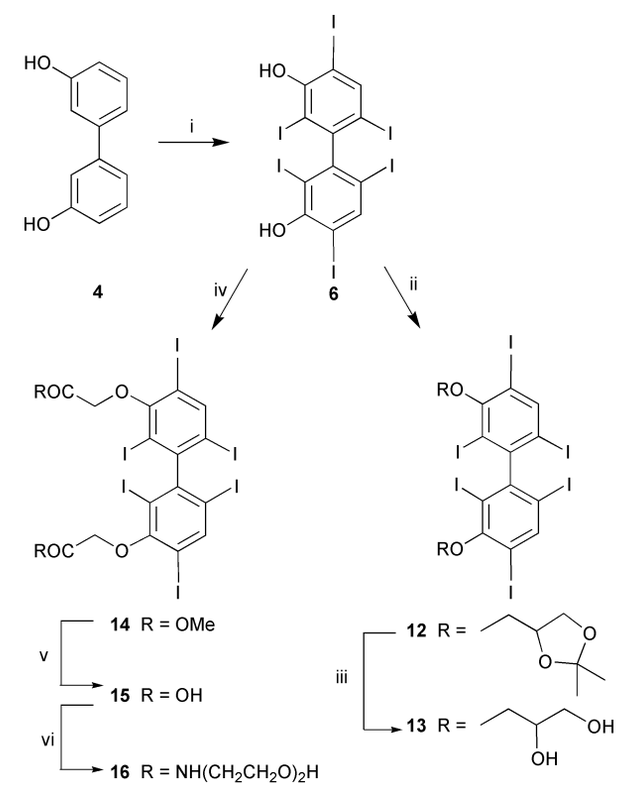
Assuming the four iodine atoms are adjacent to the C6–C7 bond, we selected biphenyl systems containing two further iodine atoms in the 4,4′ positions as target molecules. This gives molecules with an iodine content as high as 70 to 75%. The relative arrangement of the iodine atoms on each ring was chosen since *o*,*o*′,*p*-triiodination of the aromatic ring with ICl is smoothly achieved provided that a suitable activating group is present.[11] Accordingly, hydroxy groups, in a position *meta* to the inter-annular bond, were chosen. In addition, such groups could act as either ionizable functions or pivots to attach hydrophilic substituents. Starting materials for our biphenyl systems were 1,1′-biphenyl-3,3′,5,5′-tetrol[12] **3** (Scheme 1) and 1,1′-biphenyl-3,3′-diol[13] **4** (Scheme 2), which are compounds well known in the literature.

The iodination of **3** with ICl at neutral pH did not allow the isolation of any iodinated tetrol **5**. This negative result is likely to be related to the instability of **5** under the reaction conditions. However, under acidic conditions the iodination proceeded to completion, albeit slowly. For this reason **3** was iodinated at 36 °C for 4 days in H_2O–CH_3CN–MeOH (Scheme 1). The reaction medium was selected to circumvent the poor solubility in water of **3** and of the corresponding iodinated species. As expected, the iodination of the less activated diol **4** to afford **6** required even higher temperatures and longer reaction times (Scheme 2).

As mentioned before, tetrol **5** proved unstable toward bases in the presence of oxygen. Such instability is evidenced by massive loss of I_2 and I^-. Indeed, degradation of 2,4,6-triiodoresorcinol under aqueous basic conditions with loss of iodine is known.[14] Furthermore, it has been reported that, besides the well known oxidation of 1,2- and 1,4-dihydroxybenzenes to the corresponding quinones, oxygen can promote



Scheme 1 *Reagents and conditions*: i ICl, H_2O–CH_3CN–MeOH, 36 °C, 4 d; ii ethyl nitrobenzene-*p*-sulfonate (EtONs), NaOH, dioxane–H_2O, rt, 43 h; iii $BrCH_2CO_2tBu$, Et*i*Pr_2N, DMF, 40 °C, 7 h; iv TMSI, CH_2Cl_2, 0–5 °C, 1 h; v a) $SOCl_2$, reflux, 5 h, b) $NH_2(CH_2CH_2O)_2H$, dioxane–DMF, rt, 4 h.



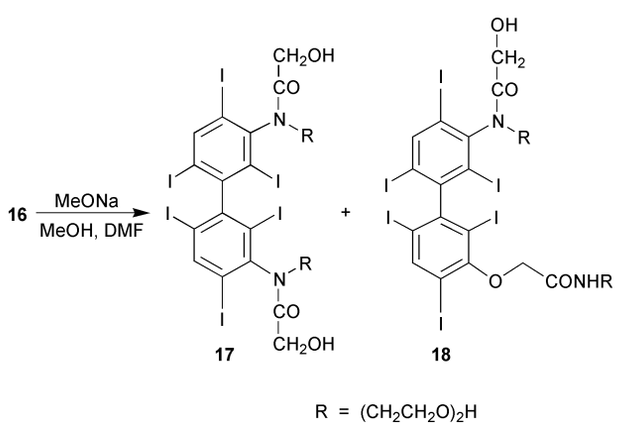
Scheme 2 *Reagents and conditions*: i ICl, H_2O–CH_3CN–MeOH, 60 °C, 20 d; ii **11**, MeONa, DMF, 50 °C, 76 h; iii PTSA, MeOH, 25 °C (72 h) then 40 °C (15 h); iv $BrCH_2CO_2Me$, MeONa, DMF, 45 °C, 4.5 h; v NaOH, dioxane–H_2O, 50 °C, 9 h; vi a) $SOCl_2$, 70 °C, 2.5 h, b) $NH_2(CH_2CH_2O)_2H$, DMF, rt, 3 h.

an oxidative degradation of 1,3-dihydroxylated aromatic systems to give 2-hydroxy-1,4-quinonic species.[15] Degradation of tetrol **5** by this mechanism justifies the presence of free iodine in the degradation mixtures. However, when deprotonated in previously degassed solvents and in inert atmosphere, **5** is perfectly stable and can be successfully alkylated (*vide infra*).

Since handling of the tetrasalt of **5** did not appear to be easy, we converted **5** into **7** in order to study various conditions for the alkylation of phenol groups. A screening procedure involving different solvents (aqueous mixtures *vs*. dipolar aprotic solvents), bases (NaOH, K_2CO_3, MeONa and tertiary amines) and sources of the ethyl residue (EtBr, Et_2SO_4 and EtONs) was performed. Several experimental conditions led to very complicated mixtures of partially alkylated compounds. However, two sets were identified as the best alkylation conditions: *i*) H_2O–dioxane, NaOH, room temperature and *ii*) DMF, *N,N*-diisopropylethylamine, 50 °C. The former conditions were used to react **5** and EtONs to give **7** in 71% yield on a preparative scale, whereas the latter allowed the conversion of **5** into **8** in 66% yield using *tert*-butyl bromoacetate as the alkylating agent (Scheme 1). Tetraester **8** was deprotected with trimethylsilyl iodide to the corresponding tetraacid **9**, which, after conversion into the tetrachloride, led to the tetraamide **10** by reaction with the appropriate amine.

The alkylation of the biphenyldiol **6** (Scheme 2) proved much easier than that of **5** since the disalt of the former is *not* sensitive to oxygen. Reaction of **6** with the nosyl derivative of 2,2-dimethyl-1,3-dioxolane-4-methanol **11** (MeONa, DMF, 50 °C) gave **12**, which was deprotected to give **13** with toluene-*p*-sulfonic acid in MeOH. Both compounds **12** and **13** were obtained as diastereomeric mixtures. Analogously, reaction of **6** with methyl bromoacetate gave the diester **14**. Saponification with aq. NaOH to the diacid **15**, conversion into the dichloride and then reaction with the amine yielded the diamide **16**.

It is noteworthy that monomeric triiodinated analogues of diamide **16** afforded, under Smiles' rearrangement conditions, products displaying very high solubility in water.[16] Accordingly, diamide **16** was treated with MeONa in DMF–MeOH (*i.e.* typical Smiles' rearrangement conditions for iodinated substrates)[17] (Scheme 3). Both products, derived from rearrangement at two or one amide moieties (*i.e.* **17** and **18**, respectively), were isolated by chromatography.



Scheme 3

Single crystals of some of the hexaiodinated derivatives were grown (see Experimental section) and submitted to X-ray diffractometry.

The solid state structures of compounds **5**, **7** and **13** (Fig. 3) confirmed the expected almost perpendicular relative disposition of the phenyl rings about the C6–C7 bond. Indeed, the dihedral angle between the aromatic mean planes is 85.9(4), 85.7(8) and 88.0(9)° in **5**, **7** and **13**, respectively. In addition, in each compound there is a couple of halogen atoms whose deviation from the mean plane of the linked aromatic ring is approximately an order of magnitude greater than that of the remaining iodine atoms (the largest deviation being −0.179(3) Å for I1 in **7**). In all cases this shift from the C_6 mean plane also helps to move the four *ortho* halogen atoms away from each other. Nevertheless, the inter-atomic distances between these halogen atoms, which range between 4.238(3) and 4.478(5) Å, are close to twice the van der Waals radius of the iodine atom

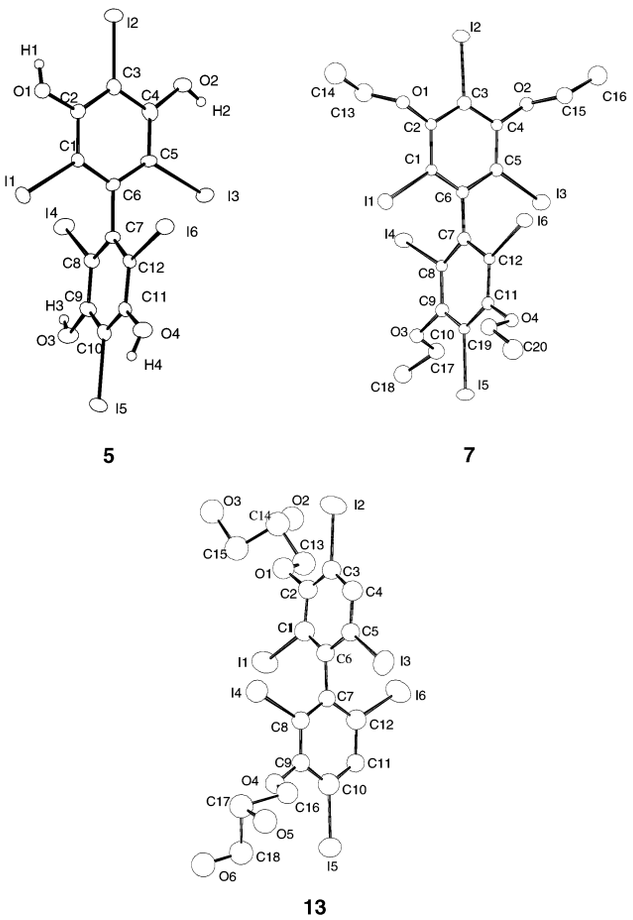


Fig. 3 ORTEP views of the crystal structures of **5**, **7** and **13**.

(2.15 Å). Therefore, the torsional degree of freedom about the C6–C7 bond appears very limited making the overall structures rather stiff (*vide supra*).

The phenyl-bound oxygen atoms lie in the mean planes of the phenyl rings, with the exception of O1 in compound **13**, which shows a deviation comparable to those of the iodine atoms (0.12(2) Å). The geometrical constraints of the sp^2 aromatic carbon atoms result in very short inter-atomic mean I–O distances (3.2(1), 3.15(2) and 3,16(3) Å in **5**, **7** and **13**, respectively) if compared with the sum of the oxygen (1.35 Å) and iodine (2.15 Å) van der Waals radii.

The ethyl ether side chains of compound **7** all display a *trans* conformation, while the two identical side arms of **13** are characterised by a *trans–gauche–trans* sequence of dihedral angles.

Concerning the crystal packing, with the exception of compound **5**, where all the hydrogens of the OH groupings interact *via* H-bonds with the carbonyl oxygen atoms of the co-crystallised acetone molecules, there are no significant intermolecular interactions.

As mentioned above, effective contrast media must give rise to highly concentrated solutions in H_2O. The solubilisation can be reached by either formation of salts of ionizable functions (*i.e.* leading to "ionic" contrast media) or, more preferably, by introducing suitable hydrophilic residues into the molecular skeleton (*i.e.* leading to "non-ionic" contrast media).[1]

In this respect, the possibility of obtaining stable solutions of **5** by conversion into the corresponding salt of the phenolic functions is prevented by the instability of **5** (*vide supra*). As expected, the behaviour of **6** towards bases is completely different so that it can be easily solubilised in H_2O by treatment with bases, but the pH required (> 10) is not compatible with *in vivo* administration. In order to achieve soluble compounds at physiological pH (*i.e.* 7.4), **5** and **6** were converted into the acetic derivatives **9** and **15**, respectively. Indeed, the sodium salts of the latter allowed highly concentrated solutions in water (up to 600 mg ml^{-1} for **9**) to be obtained. However, since "non-ionic" contrast agents are usually safer, **9** and **15** were converted into the amides **10** and **16**, which bear hydrophilic fragments. Since functionalization of the phenolic groups ineluctably leads to a decreased iodine content of the molecule, we also planned the synthesis of compound **13**, which contains rather small and compact hydrophilic fragments. Unfortunately, all the compounds potentially useful as "non-ionic" contrast media, which we prepared from the hexaiodinated biphenyl backbones (*i.e.* **10**, **13**, **16–18**), showed exceedingly low solubilities in H_2O (*i.e.* < 5 mg ml^{-1}).

In conclusion, we have shown that the hexaiodinated biphenyl skeleton can be used as the building block for the preparation of molecules displaying a very high iodine content. X-Ray crystal structures of some of these derivatives show that the four iodine atoms in 2,2′,6,6′ positions mask each other to a great extent and force the two aromatic rings to lie in nearly perpendicular planes. These results are in accord with predictions obtained by means of molecular mechanics studies. We have obtained compounds of this series which, after conversion into the corresponding salts at neutral pH give rise to highly concentrated aqueous solutions. However, to date the right combination of hydrophilic residues which has to be introduced in the hexaiodinated biphenyl moiety in order to achieve highly water soluble compounds without taking advantage of ionizable functions (*i.e.* "non-ionic" compounds) has still to be found.

Experimental

Mps (°C, uncorrected) were measured with a Büchi 510 instrument. Mass spectra were recorded on a TSQ700 Finnigan Thermoquest instrument. ^{13}C-NMR spectra were recorded at 50.3 MHz on a Bruker AC-200 spectrometer. 1,1′-Biphenyl-3,3′,5,5′-tetrol **3** and 1,1′-biphenyl-3,3′-diol **4** were prepared by the Ullman reaction from 3,5-dimethoxy(iodo)benzene[18] and 3-iodoanisole,[19] respectively, followed by deprotection with BBr_3 according to McOmie *et al.*[13]

2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl-3,3′,5,5′-tetrol (5)

To a solution of 1,1′-biphenyl-3,3′,5,5′-tetrol **3** (21.8 g; 0.10 mol) in 1 : 1 H_2O–CH_3CN (1.26 l) stirred at rt, a solution of ICl (155.9 g; 0.96 mol) in 37% HCl (130 ml) was added over 50 min. The reaction mixture was stirred at 36 °C for 4 days while MeOH (2.28 l total) was added in portions from time to time in order to maintain a clear solution. The solution was concentrated to 1.5 kg and diluted with H_2O (0.5 l). The precipitate was filtered, washed with H_2O, dried, then slurried at first with MeOH (240 ml) at rt, then three times with acetone (270 ml) at −20 °C and finally suspended in H_2O (220 ml). After filtration and drying, **5** (77.6 g; 80%) was obtained as white crystals. Mp 210 °C (dec.) (Found: C, 15.0; H, 0.5; I, 77.8; O, 6.7. $C_{12}H_4I_6O_4$ requires C, 14.8; H, 0.4; I, 78.2; O, 6.6%); δ_C (CD_3OD) 158.0 (C-3, s), 155.9 (C-1, s), 78.8 (C-2, s), 75.0 (C-4, s); MS (ESI^-, MeOH) *m*/*z* 972 $(M - H)^-$. Single crystals suitable for X-ray diffractometry were obtained by slow cooling to rt of a solution of **5** in acetone prepared at 50 °C.

3,3′,5,5′-Tetraethoxy-2,2′,4,4′,6,6′-hexaiodo-1,1′-biphenyl (7)

A 1 M aq. solution of NaOH (120 ml) was quickly added to a solution of **5** (29.2 g; 0.03 mol) in previously degassed 2.5 : 1 dioxane–H_2O (840 ml), stirred at rt while nitrogen was bubbled into the solution. A solution of 4-nitrobenzenesulfonic acid ethyl ester (30.5 g; 0.132 mol) in degassed dioxane (300 ml) was then added dropwise over 20 min. The reaction mixture was stirred at rt for 43 h while 1 M NaOH (20 + 10 ml) was added as the pH became neutral. The precipitate was filtered, washed with H_2O and dried. The crude product was dissolved in

dioxane (455 ml) and the solution was diluted with 1 M NaOH (5.1 ml) and H_2O (360 ml) (since the main impurity is the trialkylated compound, NaOH was added in order to form a salt of the residual phenolic function and allow its dissolution in the mother liquor). The precipitate was filtered, washed with H_2O and the treatment was repeated. After drying, **7** (24.0 g; 71%) was obtained as a white powder. Mp 174–175 °C (from dioxane–H_2O) (Found: C, 23.7; H, 2.15; I, 67.5. $C_{20}H_{20}I_6O_4 \cdot 0.5\ C_4H_8O_2$ requires C, 23.4; H, 2.1; I, 67.4%); δ_C (DMSO-d_6) 159.9 (C-3, s), 155.5 (C-1, s), 92.1 (C-2, s), 89.3 (C-4, s), 68.9 (CH_2, t), 15.3 (CH_3, q); MS (ESI^+, MeOH) *m*/*z* 1109 $(M + H + Na)^+$. Single crystals suitable for X-ray diffractometry were obtained by slow evaporation of a solution of **7** in $CHCl_3$.

2,2′,2″,2‴-([2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl]-3,3′,5,5′-tetrayltetraoxy)tetraacetic acid tetrakis(1,1-dimethylethyl ester) (8)

N,N-Diisopropylethylamine (72.4 g; 0.56 mol) and bromoacetic acid 1,1-dimethylethyl ester (81.9 g; 0.42 mol) were added in sequence to a solution of **5** (68.15 g; 0.07 mol) in degassed DMF (1.4 l) stirred at rt under a nitrogen atmosphere. After 7 h at 40 °C the solvent was evaporated. The residue was suspended in dioxane (1 l) and stirred at rt for 2 h. After filtration, the brown solution was diluted with H_2O (500 ml) and seeded. The precipitate was filtered, washed with 2.5 : 1 dioxane–H_2O, then with H_2O and dried to afford **8** (49.2 g; 49%) as a white solid. The mother liquor and the washings, combined and diluted with H_2O (700 ml), afforded a crude product that was analogously purified to give a second crop of **8** (17.2 g; 17%) as a white solid. Mp 168–170 °C (from dioxane–H_2O) (Found: C, 30.4; H, 3.0; I, 53.3; O, 13.3. $C_{36}H_{44}I_6O_{12}$ requires C, 30.2; H, 3.1; I, 53.2; O, 13.4%); δ_C ($CDCl_3$) 166.0 (CO, s), 159.4 (C-3, s), 155.7 (C-1, s), 90.7 (C-2, s), 87.7 (C-4, s), 82.4 ($C(CH_3)_3$, s), 69.1 (CH_2CO, t), 28.1 (CH_3, q); MS (ESI^+, MeOH–acetone) *m*/*z* 1453 $(M + Na)^+$.

2,2′,2″,2‴-([2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl]-3,3′,5,5′-tetrayltetraoxy)tetraacetic acid (9)

Trimethylsilyl iodide (36.0 g; 0.18 mol) was added dropwise over 30 min into a solution of **8** (42.9 g; 0.03 mol) in CH_2Cl_2 (400 ml) stirred at 0–5 °C. After 30 min, 4% aq. $NaHCO_3$ (410 ml) was added under vigorous stirring. After separation, the organic layer was extracted with 4% aq. $NaHCO_3$ (2 × 50 ml). The aqueous phases were combined, washed with CH_2Cl_2 (2 × 100 ml), concentrated, decolourised with charcoal and adjusted to pH 1.8 with 37% aq. HCl to precipitate a whitish solid. After filtration the crude precipitate was dissolved in H_2O (600 ml) by addition of 1 M NaOH (96 ml) and the solution was adjusted to pH 1.7 with 1 M aq. HCl (140 ml). The precipitate was filtered, washed with H_2O and dried to give **9** (33.7 g; 93%) as a white solid. Mp 284 °C (dec.) (Found: C, 19.9; H, 1.0; I, 63.1; O, 15.7. $C_{20}H_{12}I_6O_{12}$ requires C, 19.9; H, 1.0; I, 63.15; O, 15.9%); δ_C (D_2O + KOD) 178.8 (CO, s), 162.2 (C-3, s), 158.4 (C-1, s), 93.3 (C-2, s), 90.8 (C-4, s), 90.8 (CH_2, t); MS (ESI^+, MeOH–H_2O) *m*/*z* 1228 $(M - H + Na)^+$.

N,*N*′,*N*″,*N*‴-Tetrakis[2-(2-hydroxyethoxy)ethyl]-2,2′,2″,2‴-([2,2′,4,4′,6,6′-hexaiodo-1,1′-biphenyl]-3,3′,5,5′-tetrayltetraoxy)tetraacetamide (10)

Quinoline (13 mg; 0.1 mmol) was added to a suspension of **9** (12.06 g; 10 mmol) in $SOCl_2$ (47.60 g; 400 mmol) then the mixture was refluxed for 5 h. Cooling to rt led to the precipitation of the crude tetrachloride which was filtered, washed with *n*-hexane and dried. Without further purification the crude tetrachloride was dissolved in 5 : 1 dioxane–DMF (60 ml) and the solution added dropwise over 1 h into a solution of 2-(2-aminoethoxy)ethanol (12.60 g; 120 mmol) in 5 : 1 dioxane–DMF (70 ml) stirred at rt. After 4 h the solvent was evaporated and the oily residue was added to H_2O (700 ml). The precipitate was filtered and purified by flash-chromatography [silica gel; CH_2Cl_2–EtOH gradient (7 : 1 to 1 : 1)] to afford **10** (7.71 g; 50%) as a white solid. Mp 181–183 °C (Found: C, 27.7; H, 3.1; I, 48.9; N, 3.6. $C_{36}H_{48}I_6N_4O_{16}$ requires C, 27.8; H, 3.1; I, 49.0; N, 3.6%); δ_C (DMSO-d_6) 166.2 (CO, s), 158.5 (C-3, s), 155.6 (C-1, s), 92.6 (C-2, s), 89.1 (C-4, s), 72.2 (CH_2CH_2OH, t), 70.2 ($NHCH_2CH_2$, t), 68.7 (CH_2CO, t), 60.3 (CH_2OH, t), 38.3 ($NHCH_2$); MS (ESI^+, MeOH) *m*/*z* 1577 $(M + Na)^+$.

2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl-3,3′-diol (6)

To a solution of 1,1′-biphenyl-3,3′-diol **4** (13.4 g, 0.072 mol) in 1 : 1 H_2O–CH_3CN (900 ml) stirred at rt, a solution of ICl (111 g; 0.684 mol) in 37% HCl (93 ml) was added. The reaction mixture was stirred at 60 °C for 20 days while MeOH (2.7 l total) was added from time to time in order to maintain a clear solution. The solution was concentrated causing precipitation of the crude product. The suspension was diluted with H_2O (500 ml), stored overnight at 5 °C and filtered. After drying, the crude was dissolved in EtOAc (400 ml), the solution was washed with 5% aq. $Na_2S_2O_3$ (400 ml) and H_2O (400 ml) then dried. After evaporation, **6** (51.7 g; 76%) was obtained as a whitish solid. Mp 270 °C (dec.) (Found: C, 15.8; H, 0.5; I, 79.4; O, 4.0. $C_{12}H_4I_6O_2$ requires C, 15.3; H, 0.4; I, 80.9; O, 3.4%); δ_C (acetone–d_6) 157.1 (C-3, s), 156.1 (C-1, s), 148.8 (C-5, d), 91.1, 88.4, 85.5 (C-2, C-4, C-6, 3 × s); MS (ESI^-, MeOH) *m*/*z* 941 $(M - H)^-$.

4-Nitrobenzenesulfonic acid (2,2-dimethyl-1,3-dioxolan-4-yl)-methyl ester (11)

A solution of triethylamine (51.1 g; 0.505 mol) in CH_2Cl_2 was added dropwise over 45 min into a solution of 4-nitrobenzenesulfonyl chloride (104.2 g; 0.470 mol) and 2,2-dimethyl-1,3-dioxolane-4-methanol (66.7 g; 0.505 mol) stirred at 0–5 °C. After 1 h triethylamine hydrochloride was filtered off and the solution was washed with H_2O (150 ml), 4% aq. $NaHCO_3$ (100 ml) and H_2O (3 × 150 ml), dried and evaporated. The crude product was purified by crystallisation from 8 : 5 *n*-hexane–THF (700 ml) to afford **11** (112.66 g; 76%) as a white solid. Mp 85–86 °C (Found: C, 45.9; H, 5.0; N, 4.4; S, 9.9. $C_{12}H_{15}NO_7S$ requires C, 45.4; H, 4.8; N, 4.4; S, 10.1%); δ_C ($CDCl_3$) 150.7 (C-4, s), 141.4 (C-1, s), 129.3 (C-2, d), 124.4 (C-3, d), 110.1 (C, s), 72.7 (CH, d), 70.7 (SO_3CH_2, t), 65.6 ($CH(O)CH_2O$, t), 26.5, 24.9 (CH_3, 2 × q); MS (ESI^+, MeOH) *m*/*z* 340 $(M + Na)^+$.

3,3′-Bis[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-2,2′,4,4′,6,6′-hexaiodo-1,1′-biphenyl (12)

A 1.05 M solution of MeONa in MeOH (62.9 ml; 66 mmol) was added to a solution of **6** (31.07 g; 33 mmol) in DMF (300 ml) stirred at rt, then MeOH was evaporated and **11** (24.10 g; 76 mmol) was added. The reaction mixture was stirred at 50 °C for 76 h. As the solution became neutral, K_2CO_3 (2 × 2.28 g; 32 mmol) and additional **11** (3.10 g; 10 mmol) were added. After 64 h at rt the reaction mixture was concentrated to about half volume, the inorganic salts were filtered off and the solvent was evaporated. The oily residue was vigorously stirred with H_2O (350 ml) at rt overnight to afford a solid that was filtered, washed with H_2O and dried. The crude product was purified by solvation in dioxane (360 ml) followed by dilution with 1 M aq. NaOH (12 ml) and H_2O (230 ml) to give a two-phase system. The lower layer was separated and stirred with H_2O (600 ml) at rt overnight. After filtration, washing with H_2O and drying, **12** (32.12 g; 83%) was obtained as a whitish solid. Mp 77–110 °C (broad softening range) (Found: C, 25.5; H, 2.2; I, 63.55. $C_{24}H_{24}I_6O_6$ requires C, 24.6; H, 2.1; I, 65.1%); δ_C (DMSO-d_6) 163.3 (C-3, s), 160.3 (C-1, s), 152.9 (C-5, d), 114.2 ($C(CH_3)_3$, s), 103.6, 100.6, 98.1 (C-2, C-4, C-6, 3 × s), 78.9 (CH, d), 78.1 ($ArOCH_2$, t), 71.4 ($CHCH_2O$, t), 32.2, 30.7 (CH_3, 2 × q); MS (ESI^+, MeOH–NaCl) *m*/*z* 1192 $(M + Na)^+$, 1208 $(M + K)^+$.

3,3′-([2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl]-3,3′-diyldioxy)-dipropane-1,2-diol (13)

PTSA·H_2O (0.42 g; 2.2 mmol) was added to a solution of **12** (25.79 g; 22 mmol) in MeOH (250 ml) stirred at rt. After 72 h, additional PTSA·H_2O (0.42 g; 2.2 mmol) was added and the solution heated at 40 °C for 15 h. The reaction mixture was concentrated to about half volume and purified by preparative HPLC [stationary phase: Lichroprep RP-18 25–40 μm (250 × 50 mm column); mobile phase: 65 : 35 to 20 : 80 H_2O–CH_3CN gradient] to afford **13** (17.77 g; 74%) as a white solid. Mp 183–186 °C (Found: C, 19.95; H, 1.45; I, 69.7. $C_{18}H_{16}I_6O_6$ requires C, 19.8; H, 1.5; I, 69.9%); δ_C (DMSO-d_6) 158.6 (C-3, s), 155.0 (C-1, s), 147.5 (C-5, d), 98.4, 94.9, 92.7 (C-2, C-4, C-6, 3 × s), 74.5 ($ArOCH_2$, t), 70.5 (CH, d), 63.5 (CH_2OH, t); MS (ESI^+, MeOH) *m*/*z* 1112 $(M + Na)^+$. Several attempts to obtain single crystals suitable for X-ray diffraction were made. Finally, by slow evaporation of a solution of **13** in H_2O–CH_3CN single crystals were obtained, however their diffraction quality was rather poor (*vide infra*).

2,2′-([2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl]-3,3′-diyldioxy)-diacetic acid dimethyl ester (14)

A 1.1 M solution of MeONa in MeOH (63 ml; 69.3 mmol) was added to a solution of **6** (28.2 g; 29.9 mmol) in DMF (240 ml) stirred at rt, then MeOH was evaporated and bromoacetic acid methyl ester (11.2 g; 73.2 mmol) was added. After 4.5 h at 45 °C, the solvent was evaporated and the oily residue was stirred with H_2O (300 ml). The resulting solid was filtered, washed with H_2O then stirred with MeOH (300 ml) at 50 °C for 30 min and at rt for 15 h. The solid was filtered, washed with MeOH and dried to afford **14** (30 g; 92%) as a white solid. Mp 174–177 °C (Found: C, 19.95; H, 1.15; I, 70.1. $C_{18}H_{12}I_6O_6$ requires C, 19.9; H, 1.1; I, 70.1%); δ_C (DMSO-d_6) 167.3 (CO, s), 157.5 (C-3, s), 154.9 (C-1, s), 147.7 (C-5, d), 98.0, 95.9, 92.7 (C-2, C-4, C-6, 3 × s), 68.7 (CH_2, t), 52.1 (CH_3, q); MS (ESI^+, acetone–MeOH–NaCl) *m*/*z* 1108 $(M + Na)^+$.

2,2′-([2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl]-3,3′-diyldioxy)-diacetic acid (15)

A 1 M aq. solution of NaOH (46 ml; 46 mmol) was added over 9 h to a solution of **14** (24.9 g; 22.9 mmol) in 4 : 1 dioxane–H_2O (375 ml) stirred at 50 °C and maintaining pH at 10.5–11.5. After adjusting to pH 8.5 with 2 M HCl, the solvent was evaporated and the residue was dissolved in H_2O (300 ml). The solution was decolourised with charcoal and poured into 0.28 M aq. HCl (210 ml; 58.8 mmol) under vigorous stirring. The precipitate was filtered, washed with H_2O and dried to give **15** (23.1 g; 95%) as a white solid. Mp 162–166 °C (Found: C, 18.2; H, 0.8; I, 72.2. $C_{16}H_8I_6O_6$ requires C, 18.2; H, 0.8; I, 72.0%); δ_C (DMSO-d_6) 168.2 (CO, s), 157.6 (C-3, s), 154.9 (C-1, s), 147.6 (C-5, d), 98.0, 95.7, 92.7 (C-2, C-4, C-6, 3 × s), 68.5 (CH_2, t); MS (ESI^+, acetone–MeOH) *m*/*z* 1056 $(M + Na)^+$.

N,*N*′-Bis[2-(2-hydroxyethoxy)ethyl]-2,2′-([2,2′,4,4′,6,6′-hexaiodo-1,1′-biphenyl]-3,3′-diyldioxy)diacetamide (16)

Quinoline (13 mg; 0.1 mmol) was added to a suspension of **15** (32.34 g; 30.6 mmol) in $SOCl_2$ (147.5 g; 1.24 mol), then the mixture was heated at 70 °C for 2.5 h. The pale yellow solution was concentrated to about 90 g and allowed to cool to rt. After 1 h the crystalline precipitate was filtered, washed with *n*-hexane and dried. The chloride thus obtained was dissolved in DMF (100 ml) and the solution was quickly added to a solution of 2-(2-aminoethoxy)ethanol (12.60 g; 120 mmol) in DMF (1 l) stirred at rt. After 3 h the solvent was evaporated and the oily residue was stirred with H_2O (400 ml) to afford a crude solid that was purified by flash-chromatography [$CHCl_3$–96% EtOH (95 : 5)]. Compound **16** (23.5 g; 62%) was obtained as a white solid. Mp 197–200 °C (Found: C, 23.4; H, 2.1; I, 61.9; N, 2.3. $C_{24}H_{26}I_6N_2O_8$ requires C, 23.4; H, 2.1; I, 61.8; N, 2.3%); δ_C (DMSO-d_6) 166.2 (CO, s), 157.3 (C-3, s), 154.9 (C-1, s), 147.7 (C-5, d), 98.1, 95.9, 92.8 (C-2, C-4, C-6, 3 × s), 72.2 (CH_2CH_2OH, t), 70.3 ($NHCH_2CH_2$, t), 68.7 (CH_2CO, t), 60.3 (CH_2OH, t), 38.4 ($NHCH_2$); MS (ESI^+, MeOH–H_2O) *m*/*z* 1254 $(M + Na)^+$.

N,*N*′-[2,2′,4,4′,6,6′-Hexaiodo-1,1′-biphenyl]-3,3′-diyl-*N*,*N*′-bis[2-(2-hydroxyethoxy)ethyl]diacetamide (17) and *N*-[2-(2-hydroxyethoxy)ethyl]-2-[3-(3-{(2-hydroxyacetyl)[2-(2-hydroxyethoxy)ethyl]amino}-2,4,6-triiodophenyl)-2,4,6-triiodophenyloxy]acetamide (18)

A 1.12 M solution of MeONa in MeOH (38 ml; 42.6 mmol) was added to a solution of **16** (21 g; 17 mmol) in DMF (730 ml)–MeOH (50 ml) stirred at rt. After 10 min the solution was acidified by addition of 1 M HCl in MeOH (80 ml; 80 mmol) and evaporated. The oily residue was suspended in H_2O (500 ml) and stirred overnight, then the solid was filtered and dried. The crude product was purified by column chromatography [silica gel; $CHCl_3$–EtOH gradient (92 : 8 to 85 : 15)] to give **17** (8.78 g; 42%) and **18** (2.30 g; 11%) as white solids. Compound **17**: mp 198–205 °C (Found: C, 23.4; H, 2.1; I, 61.6; N, 2.3. $C_{24}H_{26}I_6N_2O_8$ requires C, 23.4; H, 2.1; I, 61.8; N, 2.3%); δ_C (DMSO-d_6) 170.9 (CO, s), 155.8, (C-1, s), 148.6, (C-5, d), 145.4 (C-3, s), 108.3, 102.7, 101.0 (C-2, C-4, C-6, 3 × s), 72.3, (CH_2CH_2OH, t), 67.5 ($COCH_2$, t), 61.5 (NCH_2CH_2, t), 60.1 (CH_2CH_2OH, t), 48.3 (NCH_2, t); MS *m*/*z* (ESI^+, MeOH–$CHCl_3$) 1254 $(M + Na)^+$. Compound **18**: mp 75–120 °C (broad softening range) (Found: C, 23.5; H, 2.0; I, 61.7; N, 2.3. $C_{24}H_{26}I_6N_2O_8$ requires C, 23.4; H, 2.1; I, 61.8; N, 2.3%); δ_C (DMSO-d_6) 170.9 (NCO, s), 166.2 (CONH, s), 157.5 (C-3, d), 155.4, 155.3 (C-1, C-1′, 2 × s), 148.5, 147.8 (C-5, C-5′, 2 × d), 145.3 (C-3′, d), 108.4, 102.6, 101.0 (C-2′, C-4′, C-6′, 3 × s), 98.0, 95.9, 92.9 (C-2, C-4, C-6, 3 × s), 72.3, 72.2 (CH_2CH_2OH, 2 × t), 70.3 ($NHCH_2CH_2$, t), 68.7 (CH_2CONH, t), 67.5 ($COCH_2OH$, t), 61.5 (NCH_2CH_2, t), 60.3, 60.1 (CH_2CH_2OH, 2 × t), 48.3 (NCH_2, t), 39.4 ($NHCH_2CH_2O$); MS (ESI^+, MeOH–$CHCl_3$) *m*/*z* 1254 $(M + Na)^+$.

Computational details

Conformational searches and molecular dynamics (MD) simulations were performed on the 2,2′,6,6′-tetrahalogen substituted biphenyl derivatives by using the InsightII (98.0) package supplied by MSI[20] and implemented on an IBM 3AT computer. Model built molecules were used as starting structures for all the derivatives; before performing the conformational search and the MD protocols the geometry of each compound was fully optimised by using the CFF91 force field provided by the Discover® module. The conformational search was carried out about the inter-annular C6–C7 bond by rotating it in constant steps of 10° (range 0–180°) and the energetics of each conformation was evaluated by means of the CFF91 force field. MD simulations were performed in a vacuum at 300 and 600 K. In each case the equilibration procedure lasted 15 ps and the trajectories were monitored for 1500 ps, snapshot conformations were saved every ps.

Crystal structure determination of compounds 5, 7 and 13—crystal data

Unit cell parameters and intensity data for compounds **5**, **7** and **13** were obtained with a Nonius CAD4 diffractometer by using a graphite monochromated Mo-Kα radiation. Cell parameters were determined by least-squares fitting of 25 centered reflections for all the structures. Intensity data were corrected for Lorentz and polarization effects. Structures were solved using the SIR97 program[21] and subsequently refined by the full-matrix least squares method of SHELXL97.[22] Absorption corrections were applied once the structures were solved using

the Walker and Stuart method.[23] The hydrogen atoms of **5**, **7** and **13** were introduced at calculated positions and their coordinates refined in agreement with those of the linked atoms with overall isotropic temperature factors refined to 0.09(4), 0.08(3) and 0.07(2) Å^2, respectively. In all cases the iodine atoms were refined anisotropically. The same refinement was applied to the oxygen atoms of **5** and **13** and the carbon atoms of **5**. For the remaining atoms individual isotropic temperature factors were used. Concerning compound **13**, the rather high R indices could be ascribed to the poor quality of the crystal sample. Only the racemic mixture of the two enantiomers, having opposite stereochemical configuration at the two stereogenic carbon atoms, crystallizes. Geometrical calculations were performed by PARST97.[24] The molecular plots were produced by ORTEP.[25]

Compound **5**. $C_{12}H_4I_6O_4 \cdot 3C_3H_6O$, $M = 1147.8$, monoclinic, $a = 13.818(3)$, $b = 16.400(6)$, $c = 14.252(3)$ Å, $\beta = 106.10(2)°$, $V = 3103(2)$ Å^3, $T = 298$ K, space group $P2_1/c$, $Z = 4$, $\mu = 6.04$ mm^{-1}, 4259 reflections collected, 4063 unique, final R indices $R1 = 0.0497$ ($I > 2\sigma I$), $R1 = 0.0691$ and $wR2 = 0.1215$ (all data), 312 refined parameters.

Compound **7**. $C_{18}H_{16}I_6O_6$, $M = 1089.71$, orthorhombic, $a = 21.361(6)$, $b = 29.226(6)$, $c = 8.776(3)$ Å, $V = 5479(3)$ Å^3, $T = 298$ K, space group $Ccc2$, $Z = 8$, $\mu = 6.83$ mm^{-1}, 2161 reflections collected, 2161 unique, final R indices $R1 = 0.0680$ ($I > 2\sigma$I), $R1 = 0.0869$ and $wR2 = 0.2101$ (all data), 182 refined parameters.

Compound **13**. $C_{20}H_{20}I_6O_4$, $M = 1085.76$, monoclinic, $a = 33.10(3)$, $b = 9.30(2)$, $c = 24.23(1)$ Å, $\beta = 124.92(7)°$, $V = 6116(15)$ Å^3, $T = 298$ K, space group $C2/c$, $Z = 8$, $\mu = 6.12$ mm^{-1}, 3382 reflections collected, 3285 unique, final R indices $R1 = 0.0974$ ($I > 2\sigma$I), $R1 = 0.1311$ and $wR2 = 0.2391$ (all data), 172 refined parameters.

CCDC reference numbers 155439–155441. See http://www.rsc.org/suppdata/p1/b0/b009666k/ for crystallographic data in CIF or other electronic format.

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References

1 M. Sovak, *Radiocontrast Agents, Handbook of Experimental Pharmacology, Vol. 73*, Springer-Verlag, Berlin, 1993.
2 M. Sovak, in *Contrast Media: Biologic Effects and Clinical Application*, ed. Z. Parvez, CRC Press, Boca Raton, 1987, vol. 1, p. 27.
3 U. Speck, *Eur. Radiol.*, 1995, **5**, S8.
4 (*a*) Bracco S.p.A., Italy, EP 0 731 786 B1/1995 (*Chem. Abstr.*, 1995, **123**, 169364); (*b*) Bracco S.p.A.–Dibra S.p.A., Italy, EP 0 714 879 A1/1996 (*Chem. Abstr.*, 1996, **125**, 114277).
5 (*a*) Guerbet S.A., France, EP 0 501 875 A1/1993 (*Chem. Abstr.*, 1993, **118**, 38602); (*b*) Guerbet S.A., France, WO 94/04488 (*Chem. Abstr.*, 1994, **120**, 322950).
6 A. Almenningen, O. Bastiansen, L. Fernholt, B. N. Cyvin and S. J. Cyvin, *J. Mol. Struct.*, 1985, **128**, 59.
7 C. P. Brock and R. P. Minton, *J. Am. Chem. Soc.*, 1989, **128**, 59.
8 A. Karpfen, C. H. Choi and M. Kertesz, *J. Phys. Chem. A*, 1997, **101**, 7426 and references therein.
9 S. Tsuzuki, T. Uchimaru, K. Matsamura, M. Mikami and K. Tanabe, *J. Chem. Phys.*, 1999, **110**, 2858 and references therein.
10 F. H. Allen and O. Kennard, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1131.
11 *Houben-Weyl Methoden der Organischen Chemie Band V/4*, ed. E. Müller, Georg Thieme Verlag, Stuttgart, 1960, pp. 582–588.
12 (*a*) *Beilstein Handbuch der Organischen Chemie*, Vol. 6, eds. B. Prager, P. Jacobsen, P. Schmidt and D. Stern, Springer Verlag, Berlin, 1923, p. 1164; (*b*) *Beilstein Handbuch der Organischen Chemie*, Vol. 6 (I supplement), ed. F. Richter, Springer Verlag, Berlin, 1931, p. 573; (*c*) *Beilstein Handbuch der Organischen Chemie*, Vol. 6 (II supplement), ed. F. Richter, Springer Verlag, Berlin, 1944, p. 1129.
13 J. F. W. McOmie and D. E. West, *Org. Synth.*, 1969, **49**, 50.
14 F. L. Weitl, M. Sovak, T. M. Williams and J. H. Lang, *J. Med. Chem.*, 1976, **19**, 1359.
15 M. Tateishi,, T. Kusumi and H. Kakisawa, *Tetrahedron*, 1971, **27**, 237.
16 E. Felder, A. Gallotti and A. Favilla, *Invest. Radiol.*, 1988, **3**, S101.
17 P. L. Anelli, M. Brocchetta, L. Calabi, C. Secchi, F. Uggeri and S. Verona, *Tetrahedron*, 1997, **53**, 11919.
18 W. Riedl and F. Imhof, *Liebigs Ann. Chem.*, 1955, **597**, 153.
19 J. Van Alphen, *Recl. Trav. Chim. Pays-Bas*, 1931, **50**, 1111.
20 MSI, 9685 Scranton Road, San Diego, CA 92121–3752, USA.
21 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
22 G. M. Sheldrick, SHELXL-97, University of Göttingen, Germany, 1997.
23 N. Walker and D. D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **39**, 158.
24 M. Nardelli, *Comput. Chem.*, 1983, **7**, 95.
25 C. K. Johnson, ORTEP, Rep. ORNL 3794, Oak Ridge National Laboratory, TN, USA, 1971.