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The synthesis and evaluation of unsymmetrical dimeric X-ray contrast agents

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ABSTRACT

Novel dimeric iodinated contrast agents with low osmolality have been prepared and evaluated with the aim of improving the already good safety profile of such agents. The aim of low osmolality was achieved, and the viscosity of these dimeric agents was also found to be beneficially lower than current dimeric agents in clinical use.

Iodinated contrast agents are widely used in X-ray diagnostic procedures such as angiography, urography and computed tomography. The clinical safety of iodinated X-ray contrast media has continuously been improved over recent decades through development of new agents; from ionic monomers, such as Isopaque™, to non-ionic monomers, such as Omnipaque™ (**1**), (iohexol), and non-ionic dimers, e.g. Visipaque™ (**2**) (iodixanol) (Fig. 1). This improvement in safety has, to a large extent, been associated with a decrease in osmolality of the agent, going from the highly hypertonic ionic agents to isotonic agents.[1] In the case of Visipaque™, the low osmolality of the agent even allows the addition of sodium and calcium ions, making the electrolyte composition of the agent more physiological and blood-like than all other X-ray contrast media hitherto developed. However, among patients with pre-existing renal impairment, some can develop contrast media induced nephrotoxicity (CIN).[2–5] The incidence of CIN accounts for

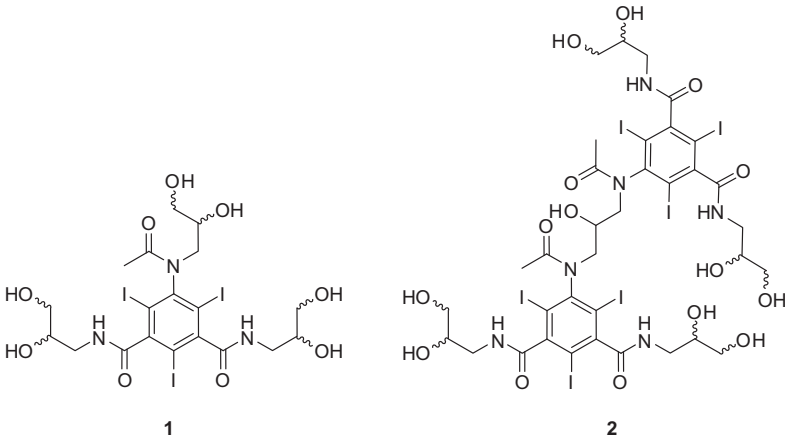

Figure 1. The structures of iohexol (**1**) and iodixanol (**2**).

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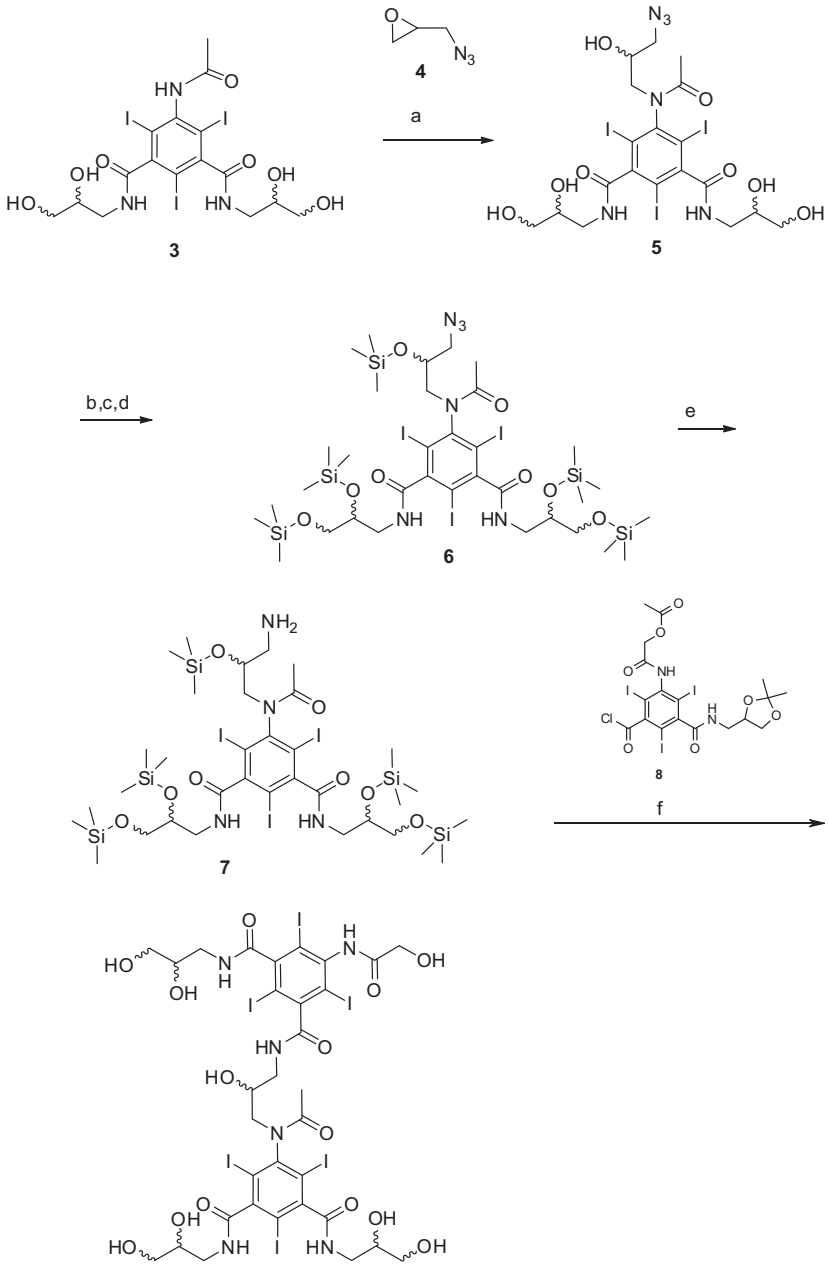
more than 12% of hospital-acquired renal failures and is a leading cause of acute renal failure.[6] Reduction in renal function increases morbidity, mortality, length of hospitalisation and acceleration towards end-stage renal disease. Consequently, there is a need for new contrast agents with improved clinical safety with regard to nephrotoxicity, especially in at risk individuals. It is thought, in high-risk patients, that there is a link between the osmolality of the contrast medium and the incidence of CIN.[7,8]

Our focus was to synthesise novel unsymmetrical dimeric iodinated agents with the aim of lowering the viscosity and achieving low osmolality. The reason for this is that, as discussed earlier, the physicochemical properties of the agents are thought to play a key role in CIN.

The asymmetry of the dimers is defined with respect to the attachment points of the linker to the two triiodoaromatic core groups and across one of the aromatic groups. It was hoped that this asymmetry would, in the first instance, reduce the ability of the compounds to readily form crystals, leading to highly water soluble compounds. For compounds with high water solubility, the viscosity, osmolality and log *P* were determined.

Scheme 1 shows an illustrative synthesis of a typical dimer **9**. Compound **4** was synthesised by reaction of sodium azide with epibromohydrin. (**Caution**: due to the relative explosive nature of azides only 73 mg of the crude material was isolated to aid characterisation). Azide **4** was exposed to the iodixanol intermediate **3** in MeOH/water with sodium hydroxide buffered with boric acid to give crude **5**. This was then peracetylated with acetic anhydride to enable purification by silica gel chromatography, hydrolysed, then persilylated to give **6** in 62% yield over three steps. The exchange of protecting groups was necessary to avoid aziridine formation



Scheme 1. Synthesis of **9**: (a) NaOH, H_3BO_3, MeOH/H_2O (2:1), 40 °C, 6 h, 70%; (b) Ac_2O, pyridine, 20 °C, 24 h, 90%; (c) NaOH, MeOH/H_2O (2.5:1), 18 h, 20 °C, 90%; (d) TMSCl, CH_2Cl_2, Et_3N, 20 °C, 20 h, 77%; (e) DPPE, CH_2Cl_2, 20 °C, 24 h, 87%; (f) **8**, DMF, Et_3N, 20 °C, 18 h, then HCl, MeOH (48% over 2 steps).

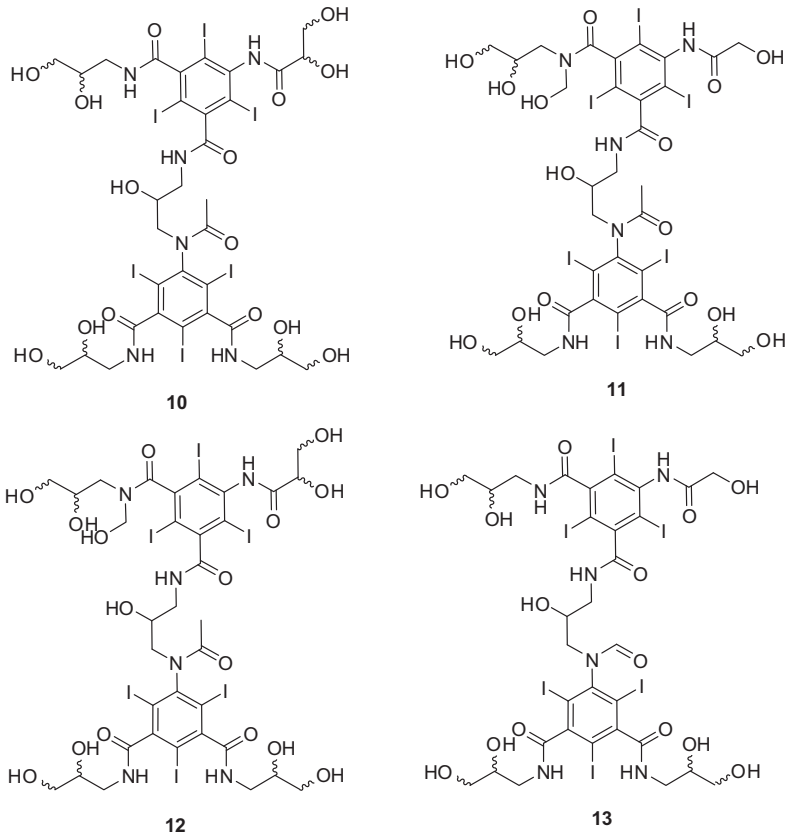


Figure 2. Structures of the products **10**–**13**.

during the treatment of **6** with 1,2-bis(diphenylphosphino)ethane (DPPE) to form the amine **7**, of which 87% was the desired material. Amine **7** was mixed with the acid chloride **8** in DMF with triethylamine present to give the corresponding product in approximately 80% purity.[9] This was deprotected with 2 M HCl at reflux in methanol, treated with ion exchange resins (Amberlite® 200C resin and Amberlite® IRA-67 resin) to remove any salts, and purified by preparative HPLC to yield the final compound **9**. The synthesis of **9** as described was unoptimised. Nevertheless, it was possible to prepare 25 g of **9** using this route.

Using analogous chemistry it was possible to synthesise four other compounds, **10**, **11**, **12**, and **13**, which are shown in Figure 2. All compounds were purified by preparative reversed phase HPLC to ensure high purity, after removal of salts by the use of an ion exchange resin, which could adversely affect the physicochemical characterisation.

The physicochemical properties of the five products are shown in Table 1. All the compounds listed have at least four hydroxy groups per triiodoaromatic unit and were highly water-soluble. It can be seen from the results that the concept of obtaining low osmolality and low viscosity by using unsymmetric dimeric agents has, indeed, been achieved.

The five compounds prepared all displayed good water solubility (Table 1). The viscosity of the agents was consistently lower than that of iodixanol (25 mPas) at the same concentration of iodide. This lower viscosity would allow the rapid intravenous administration of the large volumes of Iodinated Contrast Media (ICM) required for a Computerised Tomography (CT) scan to be less painful for the patient. There was a range of osmolalities from 216 to 422 mOsm/kg. This demonstrated that relatively small changes to the structures of the compounds led to significant differences in osmolality.

Table 1
Physicochemical properties of the unsymmetrical dimeric X-ray contrast agents measured at ~320 mgImL^{-1}

Compound	Aqueous solubility (mgI/mL)	Osmolality (mOsm/kg)	Viscosity (mPas@320 mgI/mL)	Log *P*
9	319	216	17	−3.0
10	307	255	22	−2.8
11	320	270	16	−2.9
12	296	422	20	−3.6
13	322	278	20	−3.4
Iodixanol	320	210	25	−2.6

In conclusion, we have shown that it is possible to achieve low osmolality with unsymmetric dimeric X-ray contrast agents and it has proved equally successful to simultaneously achieve low viscosities.

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