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The synthesis and evaluation of trimeric X-ray contrast agents

Ian M. Newington [a,*], Gareth Humphries [a], Nicolas Lasbistes [a], Véronique Morisson-Iveson [a], James Nairne [a], Joanna Passmore [a], Mikkel Thanning [b], Lars-Göran Wistrand [b], Duncan Wynn [a]

[a] GE Healthcare, The Grove Centre, White Lion Road, Amersham, Bucks HP9 7LL, UK
[b] GE Healthcare AS, Nycoveien 1-2 Postboks 4220 Nydalen, Oslo 0401, Norway

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ABSTRACT

Novel trimeric iodinated contrast agents with low osmolality have been prepared and evaluated with the aim of improving the already good safety profile of such agents. While the aim of low osmolality was achieved, the viscosity of the trimeric agents was found to be generally higher than current dimeric agents in clinical use.

Of the approximately 600 million X-ray scans given annually, some 80 million involve the use of iodinated contrast media (ICM). The use of ICM to enhance the differences between normal body structures and lesions in soft tissue has radically changed the practice of radiology.[1] ICM are highly concentrated aqueous formulations of iodinated contrast agent and they have a very good safety profile.[2] However, for patients with pre-existing reduced renal function, contrast induced nephrotoxicity (CIN) can occur in a small number of cases, which is a leading cause of acute renal failure.[3,4] Improvements in the safety of ICM have reduced the incidence of CIN and, to a large extent, this has been associated with reduced osmolality of the agent.[5,6] This reduction in osmolality of the contrast agent, which allows beneficial addition of salts to the formulation of the ICM, is an accepted methodology for reducing CIN incidence.[7,8] The primary source of the iodine atoms used to attenuate the X-rays is a 5-amino-2,4,6-triiodoisophthalic acid unit.[9] Reduction in osmolality has been achieved over time by moving from ionic to nonionic monomers to nonionic dimeric species containing this moiety. In order to reduce the incidence of CIN even further, a reasonable approach would, therefore, be to prepare agents based on trimers of the triiodoisophthalic acid moiety.

Figure 1 shows the general structure of trimeric X-ray contrast agents **1** illustrating the range of options for linking three triiodoisophthalic acid groups, where L is a linker attached via linking groups X, Y and Z, and the groups R^1–R^6 are polyhydroxylated nonionic solubilising groups.

A virtual library of several million compounds was constructed based on a variety of linking chemistries, such as amide, sulfonamide and urea, with a wide variety of side-chain and linker variation, which are all described by general structure **1**.

A subset of this library based on more readily available building blocks with symmetrical linking chemistry, some typical examples of which are shown in Figure 2, was enumerated and prioritised for synthesis based on an in-house quantitative structure–activity relationship (QSAR) model.

Scheme 1 shows an illustrative synthesis. 5-Amino-2,4,6-triiodoisophthalic acid (**2**) was converted into the diacid chloride,

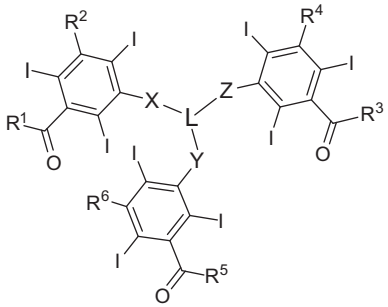

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Figure 1. General structure of trimeric X-ray contrast agents where R^1–R^6 are polyhydroxylated nonionic solubilising groups attached via linking groups X, Y and Z, where X, Y and Z may be the same or different and selected from C=O, SO_2, and NHC=O, and L is a triamine linker.

* Corresponding author. Tel.: +44 1494 544082; fax: +44 1494 543284.
E-mail address: ian.newington@ge.com (I.M. Newington).

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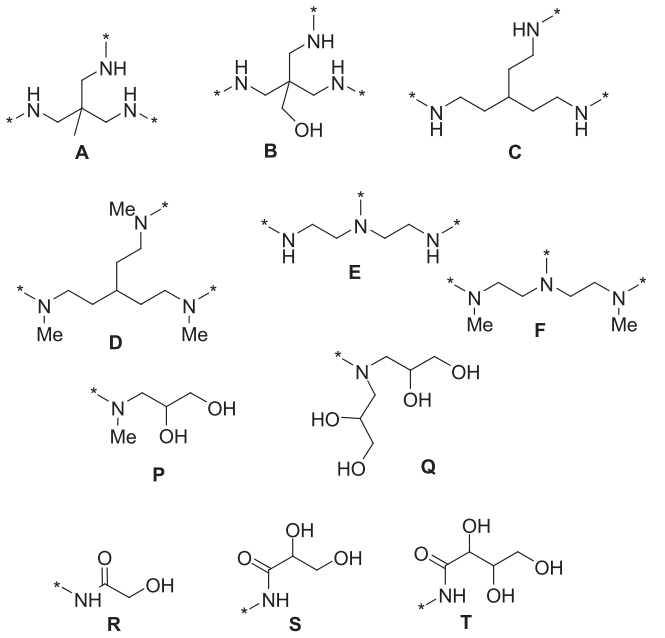


Figure 2. Some examples of readily available linkers (**A**–**F**) and side-chains (**P** and **Q** for R^1, R^3, R^5; **R**–**T** for R^2, R^4, R^6).

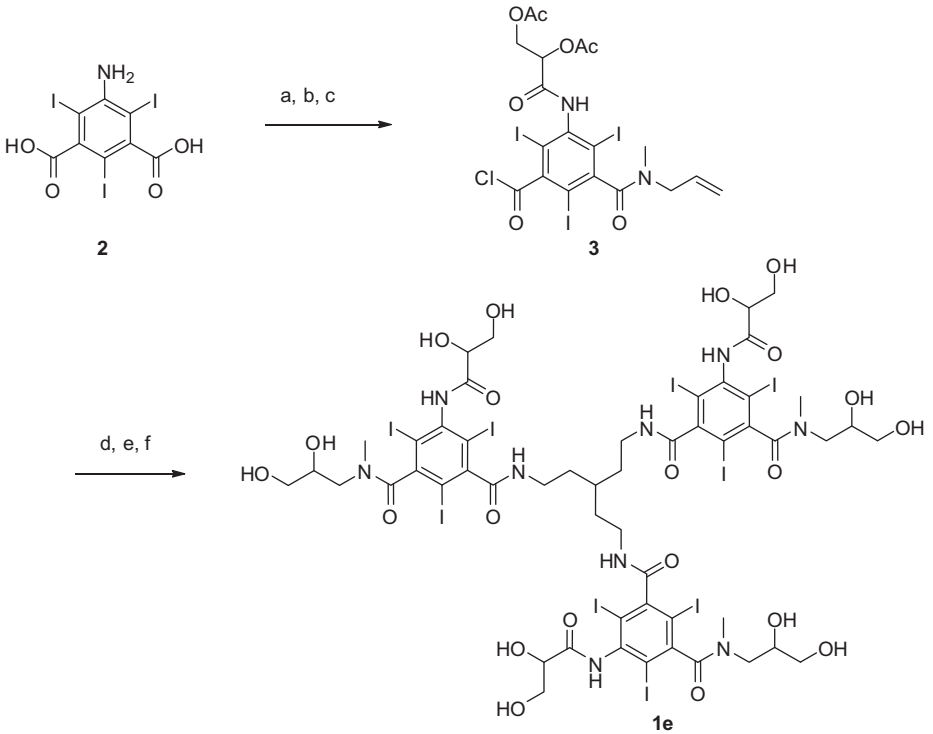
which was treated with *N*-methylprop-2-en-1-amine to generate selectively the monoamide. Treatment with a protected polyhydroxylated acyl chloride resulted in the acyl chloride **3**. This was attached to a triamine linker by heating in a 1:3 molar ratio in *N*,*N*-dimethyl acetamide to give a trimeric compound that was tris-'dihydroxylated' with osmium tetroxide and then deprotected to give the final compound **1e**.

All the compounds were purified by preparative reverse phase HPLC to ensure high purity and removal of salts, which could adversely affect the physicochemical characterisation. An alternative synthesis was employed for later examples using polyhydroxyamines, such as 3-aminopropan-1,2-diol, in the first step to avoid the dihydroxylation chemistry. This avoided repetitive treatments with metal capture resins to remove residual osmium from the final products **1**, resulting in loss of material.

A library of some 50 trimeric contrast agents was synthesised in this way.[10] The physicochemical properties of some of these are shown in Table 1. All the compounds listed have at least four hydroxy groups per triiodoaromatic unit and were highly water-soluble. The compounds were evaluated as mixtures of diastereoisomers, which could clearly be seen in the HPLC chromatograms but were too close in retention time to separate. Compounds with lower hydroxy count were generally less soluble and, in some cases, not soluble enough to achieve the required iodine concentration of 320 $mgImL^{-1}$. What can be seen from the results is that the concept of obtaining very low osmolality by using trimeric agents has, indeed, been achieved.

The current low osmolar contrast agent iodixanol (Fig. 3) has an osmolality of approximately 210 $mOsmkg^{-1}$ and is formulated to iso-osmolality at 290 $mOsmkg^{-1}$ with added electrolyte in the ICM Visipaque™. This has the benefit of improving the cardiological safety profile of the agent. A reduction in osmolality of the agent itself to below 100 $mOsmkg^{-1}$ can thus be expected to enhance the safety profile of the contrast medium by reducing both renal and cardiological impact.

As can also be seen in Table 1, the viscosity of the agents **1** varies significantly and is higher than that of iodixanol at the same concentration of iodine.[11] This is undesirable, since the rapid intravenous administration of the large volumes of ICM required for a computed tomography (CT) scan is made both slower and more painful for the patient. This result is, perhaps, not surprising in



Scheme 1. Synthesis of **1e**. Reagents and conditions: (a) $SOCl_2$, 1,2-DCE, 85 °C, 6 h, 97%; (b) *N*-methylprop-2-en-1-amine, dry THF, 50 °C, 18 h, 59%; (c) 3-chloro-3-oxopropan-1,2-diyl diacetate, DMAc, 18 h, 20 °C, 56%; (d) 3-(2-aminoethyl)pentane-1,5-diamine (0.33 equiv), DMAc, Et_3N, 60 °C, 24 h, 67%; (e) OsO_4, NMO, *t*-BuOOH, acetone, H_2O; (f) MeOH, NH_3, 20 °C, 18 h (25% over 2 steps).

Table 1
Physicochemical properties of some representative trimeric X-ray contrast agents measured at 320 mglmL^{-1}.

Product	L	$R^{1,3,5}$	$R^{2,4,6}$	Osmolality (mOsmkg^{-1})	Viscosity (mPas)	Log *P*
Iodixanol				210	25	−4.0
1a	**A**	**P**	**S**	82	48	−5.0
1b	**A**	**P**	**T**	189	41	−5.0
1c	**A**	**Q**	**R**	121	256	−4.4
1d	**B**	**P**	**S**	93	82	−5.0
1e	**C**	**P**	**S**	120	94	−2.9
1f	**C**	**P**	**T**	172	31	−6.0
1g	**C**	**Q**	**R**	87	68	−4.5
1h	**C**	**Q**	**S**	280	86	−3.4
1i	**C**	**Q**	**R**	959	64	−4.0
1j	**D**	**P**	**S**	521	51.8	−3.4
1k	**D**	**P**	**T**	575	422	−3.0
1l	**E**	**P**	**S**	76	36	−3.9
1m	**E**	**P**	**T**	297	79	−3.2
1n	**F**	**P**	**T**	249	47	−3.4

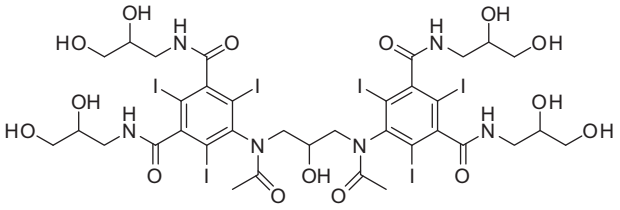


Figure 3. Structure of iodixanol.

view of the size of these trimeric compounds with molecular weight in the 2100–2500 range and with 12 hydroxy groups or more per molecule. In comparison, dimeric contrast agents will generally give solutions having a lower viscosity but, until recently,[12] have typically been found to possess higher osmolality.

The QSAR developed for these compounds did not allow a ready correlation of structure with physicochemical properties, although some general trends were indicated. The best compounds in this trimeric series, considering viscosity as well as osmolality, were, therefore, **1f** and **1l**.

In conclusion, we have shown that it is possible to achieve extremely low osmolality with trimeric X-ray contrast agents, but it has proved more difficult to simultaneously achieve low enough viscosity for clinical application. As a result, the search for very low osmolar X-ray contrast agents has continued with dimeric structures.[12]

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