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Synthesis of carbon-11 radiolabelled transition metal complexes using ^{11}C-dithiocarbamates†

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A novel radiolabelling method exploiting ^{11}C-dithiocarbamate ligands has been used to generate ^{11}C-labelled Au(I), Au(III), Pd(II) and Pt(II) complexes in high radiochemical yields (71–99%). Labelled complexes were prepared in a rapid one-pot procedure *via* the substitution reaction of ^{11}C-dithiocarbamate ligands with appropriate transition metal chloride precursors.

Positron emission tomography (PET) is a functional imaging technique that enables the visualisation and quantification of radiolabelled position emitting tracer compounds *in vivo*.[1,2] PET provides a wealth of information on the biodistribution, kinetic and metabolic profiles of tracers for a range of clinical applications in oncology, cardiology and neurology, enabling more accurate diagnoses and improved interventions.[3–5] PET is also used in drug discovery programmes where knowledge of the pharmacokinetic behaviour of novel radiolabelled drug candidates can accelerate selection and improve dosing regimens.[6]

Carbon-11, along with fluorine-18, is a key positron emitting radionuclide commonly used for the synthesis of small organic molecule-based PET tracers.[7,8] Its physical characteristics: high positron yield (>99%), 20.4 min half-life, favourable positron energy (E_{max} = 0.960 MeV), high yielding cyclotron production routes and high theoretical molar activities mean that carbon-11 is at the forefront of novel PET radiotracer development.[9,10] However, the short half-life of carbon-11 presents significant time challenges and hence limits the number of chemical reactions that can be completed within a short reaction window (*ca.* <60 min). To add to this challenge, [^{11}C]CO_2 is the main precursor to almost all carbon-11 labelled compounds, and is often transformed to more reactive [^{11}C]CH_3I *via* a reduction and free-radical iodination process. [^{11}C]CH_3I is then added to a target molecule *via* a nucleophilic substitution reaction to generate the ^{11}C-methylated tracer. In recent years, much effort has been devoted to expanding the scope of ^{11}C chemistry beyond simple *N*-, *S*-, and *O*-methylation reactions and into developing new ^{11}C precursors and labelling strategies. For example, notable progress has been made in the ^{11}C-labelling of carbonyl groups with [^{11}C]CO,[11] [^{11}C]CO_2 [12] and [^{11}C]COF_2,[13] cyano groups using [^{11}C]HCN[14,15] and trifluoromethyl groups with [^{11}C]HCF_3.[16]

The novel ^{11}C precursor [^{11}C]CS_2 [17] has been developed by us and used to access ^{11}C-labelled organosulfur compounds that would be challenging to prepare with established precursors. To date, our group and others have used this method to generate ^{11}C-labelled organic molecules including: dithiocarbamates, thioureas, isothioureas, thiocyanates, thiazolones, and the progesterone agonist Tanaproget.[18–21] Dithiocarbamate compounds in particular have found wide ranging applications as precursors to nanomaterials,[22] agrochemicals[23] and therapeutics.[24] They are readily prepared *via* the reaction of carbon disulfide and primary or secondary amines in the presence of organic or inorganic bases. Dithiocarbamates are non-selective ligands known to form complexes with all the transition metals in a range of oxidation states, typically forming thermodynamically stable bidentate chelates.[25,26] The formation of dithiocarbamate complexes is normally fast and straightforward, and often simply involve mixing the dithiocarbamate with transition metal precursors in solvent at room temperature. The ease of formation of dithiocarbamates and their chelating abilities, coupled with their technically simple and fast complexation reactions have led to their investigation as ligands for the development of imaging agents with ^{99m}Tc,[27–29] ^{64}Cu,[30] and other metal ions (Fig. 1).[31] Dithiocarbamate complexes have also received recurrent interest as therapeutics for targeting cancer, in particular Au(I) and Au(III) complexes have

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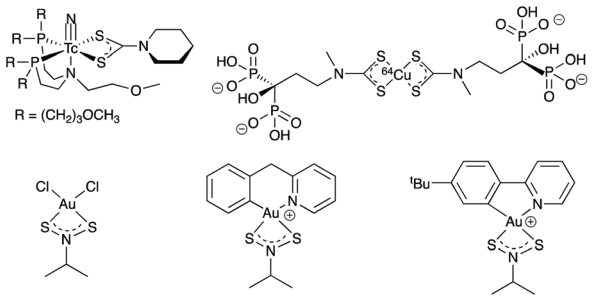


Fig. 1 ^{99m}Tc and ^{64}Cu nuclear imaging agents bearing dithiocarbamate chelators (top). A range of Au(III) dithiocarbamate complexes that have anti-cancer properties (bottom).

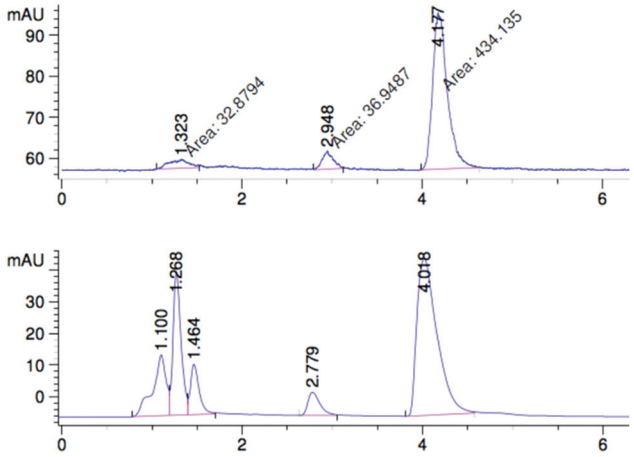
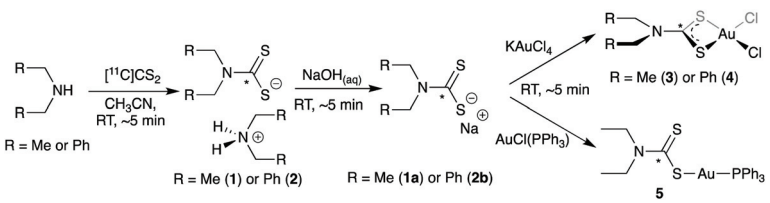


Fig. 2 A representative radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of [$AuCl_2$([^{11}C]S_2CNEt_2)] (**3**) (4.177 min) with co-injection the unlabelled reference compound [$AuCl_2(S_2CNEt_2)$] (4.018 min).

displayed anti-cancer properties for a range tumour cell lines.[32–36] Given the extensive coordination chemistry of dithiocarbamates, we hypothesised that the generation of ^{11}C-labelled dithiocarbamates would facilitate access to a diverse range of ^{11}C-labelled transition metal complexes with generic and straightforward labelling protocols. Such labelled complexes could therefore aid in the understanding of the behaviour of transition metal-based therapeutics and result in the development new PET imaging agents. Herein, we report a proof-of-principle strategy for labelling a range of late transition metal complexes *via* coordination with ^{11}C-labelled dithiocarbamates.

[^{11}C]Carbon disulfide was produced as previously reported *via* the high temperature gas phase reaction of [^{11}C]CH_3I with elemental sulfur.[18] Passing the gaseous [^{11}C]CS_2 into a acetonitrile solution of secondary amine, either diethylamine or dibenzylamine, resulted in the quantitative trapping of [^{11}C]CS_2 and formation the carbon-11 labelled ammonium dithiocarbamate salts: [^{11}C]*N*,*N*-diethyldithiocarbamate (**1**) and [^{11}C]*N*,*N*-dibenzyldithiocarbamate (**2**) (Scheme 1). Au(III) and Au(I) complexes were selected for proof-of-concept labelling studies owing to their abilities to from well-defined and stable bidentate or monodentate dithiocarbamate complexes, and also because of their potential for developing imaging agents to complement therapeutic gold–dithiocarbamate complexes. Addition of aqueous NaOH solution to [^{11}C]*N*,*N*-diethyldithiocarbamate (**1**) followed by a solution of the gold precursor K[$AuCl_4$] and stirring for 5 min at room temperature resulted in the rapid and efficient labelling of [$AuCl_2$([^{11}C]

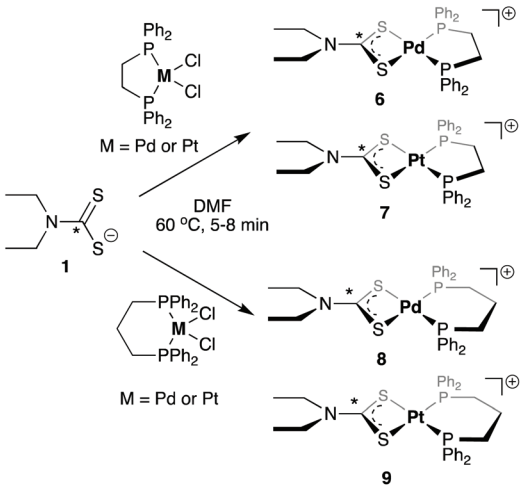


Scheme 1 Radiosynthesis of ^{11}C-labelled Au(III) and Au(I) complexes *via* the reaction of [^{11}C]diethyldithiocarbamate (**1a**) or [^{11}C]dibenzyldithiocarbamate (**2b**) with $KAuCl_4$ or $AuCl(PPh_3)$ precursors.

Table 1 Summary of results for ^{11}C-labelling of Au(III), Au(I), Pd(II) and Pt(II) complexes

Entry	Transition metal Precursor	^{11}C-labelling precursor	^{11}C-labelled transition metal complex	RCY[a]
1	K[$AuCl_4$]	[^{11}C][S_2CNEt_2]$^-$	[$AuCl_2$([^{11}C]S_2CNEt_2)] (**3**)	86% (n = 2)
2	K[$AuCl_4$]	[^{11}C][S_2CNBn_2]$^-$	[$AuCl_2$([^{11}C]S_2CNBn_2)] (**4**)	71% (n = 2)
3	[$AuCl(PPh_3)$]	[^{11}C][S_2CNEt_2]$^-$	[Au([^{11}C]S_2CNEt_2)(PPh_3)] (**5**)	86% (n = 3)
4	[$PdCl_2$(dppe)]	[^{11}C][S_2CNEt_2]$^-$	[Pd([^{11}C]S_2CNEt_2)(dppe)]$^+$ (**6**)	96% (n = 3)
5	[$PtCl_2$(dppe)]	[^{11}C][S_2CNEt_2]$^-$	[Pt([^{11}C]S_2CNEt_2)(dppe)]$^+$ (**7**)	89% (n = 3)
6	[$PdCl_2$(dppp)]	[^{11}C][S_2CNEt_2]$^-$	[Pd([^{11}C]S_2CNEt_2)(dppp)]$^+$ (**8**)	99% (n = 3)
7	[$PtCl_2$(dppp)]	[^{11}C][S_2CNEt_2]$^-$	[Pt([^{11}C]S_2CNEt_2)(dppp)]$^+$ (**9**)	94% (n = 3)

[a] Non-isolated radiochemical yield (RCY) determined by analytical radio-HPLC of the crude product.



Scheme 2 Radiosynthesis of ^{11}C-labelled Pd(II) and Pt(II) complexes *via* the reaction of [^{11}C]*N*,*N*-diethyldithiocarbamate (**1**) with [MCl_2(dppe)] or [MCl_2(dppp)], M = Pd or Pt.

S_2CNEt_2)] (**3**) (Scheme 1, Table 1 entry 1 and Fig. 2) in 86% RCY. The reaction conditions for the formation of unlabelled of Au(III)–DTC complexes typically need to be carefully controlled owing to possible DTC ligand exchange reactions and formation of undesired [$Au(DTC)_2$][$AuCl_4$] complexes. We expect, however, that the formation of such ^{11}C labelled $[Au(DTC)_2]^+$ bischelates would be limited owing to the stoichiometry of ^{11}C labelling reactions making them statistically unlikely to form in any significant amounts. The labelled [^{11}C]*N*,*N*-dibenzyldithiocarbamate (**2**) was also found to react with K[$AuCl_4$] to give the analogous complex [$AuCl_2$([^{11}C]S_2CNBn_2)] (**4**) (Scheme 1, Table 1 entry 2), however, the average RCY of 71% obtained for **4** was reduced compared to complex **3**. Based on the higher RCYs for complex **3** using [^{11}C]*N*,*N*-diethyldithiocarbamate, all remaining labelling studies were performed with this ligand. Reaction of **1** with the Au(I) precursor [AuCl(PPh_3)] to form [Au([^{11}C]S_2CNEt_2)(PPh_3)] (**5**) under the same reaction conditions was also equally efficient giving a RCY of 86%, and demonstrating the method can also be used to form simple mono-dentate Au(I) complexes.

In order to expand the scope of these ^{11}C-labelling reactions with other transition metals, a range of well-defined Pd(II) and Pt(II) diphosphine complexes were also investigated. Pd(II) and Pt(II) diphosphine complexes are known to form stable cationic chelating dithiocarbamate complexes,[37,38] and therefore present as suitable complexes for preliminary labelling reactions. We focused on labelling a small library of four Pd(II) and Pt(II) complexes containing the diphosphine ligands, 1,2-bis-diphenylphosphinoethane (dppe) and 1,3-bis-diphenylphosphinopropane (dppp), (Scheme 2). Unlabelled reference complexes were prepared *via* the reaction of sodium *N*,*N*-diethyldithiocarbamate with Pd(II) or Pt(II) diphosphine chloride salts.[37,38] Single crystal X-ray crystal structures were obtained for the reference complexes [$Pd(S_2CNEt_2)$(dppp)]Cl and [$Pt(S_2CNEt_2)$(dppp)]Cl (Fig. 3). The square planar molecular structures of the two complexes are isostructural and confirm the expected chelation of the dithiocarbamate ligand, varying only slightly in the bond lengths and angles at their respective metal centres (Table 2) and are similar to previously published DTC complexes.[38,39] Unlike the labelling reactions of the Au precursors that proceeded at room temperature, the reaction of ^{11}C-dithiocarbamate **1** with [$PdCl_2$(dppe)] or [$PtCl_2$(dppe)] required heating to 60 °C to give appreciable RCYs within 5–8 min in DMF to facilitate solubility. Under these conditions the labelled complexes [Pd([^{11}C]S_2CNEt_2)(dppe)]Cl (**6**) and [Pt([^{11}C]S_2CNEt_2)(dppe)]Cl (**7**) were obtained in high RCYs of 96% and 89% respectively (Scheme 2, Table 1 entries 4 and 5). Labelling of the

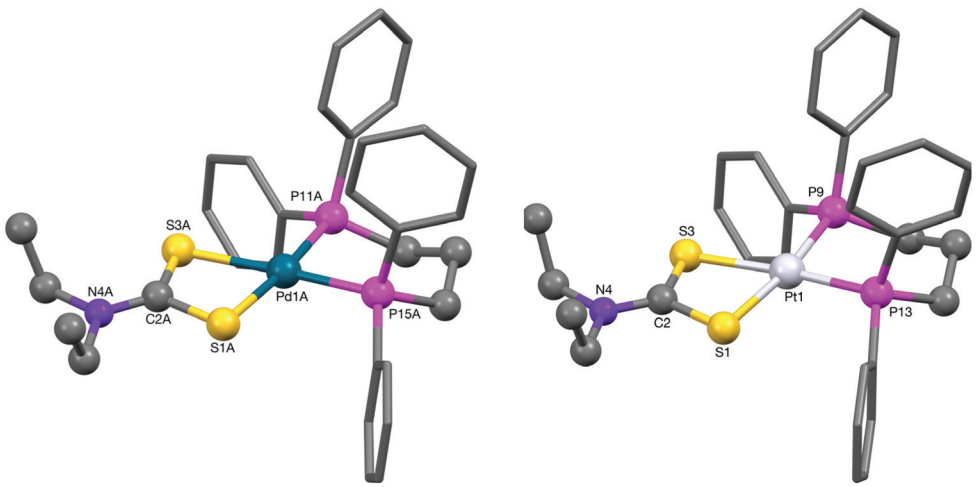


Fig. 3 Isostructural X-ray crystal structures of the square planar dithiocarbamate complexes: [$Pd(S_2CNEt_2)$(dppp)]Cl (one of the two independent complex cations present in the crystal of **8**, left) and [$Pt(S_2CNEt_2)$(dppp)]Cl (**9**, right), counter ions and solvent molecules have been removed for clarity.

Table 2 Selected bond lengths (Å) and angles (°) data for complexes in crystals of [Pd(S_2CNEt_2)(dppp)]Cl (**8**) and [Pt(S_2CNEt_2)(dppp)]Cl (**9**)

Selected bond lengths (Å) for [Pd(S_2CNEt_2)(dppp)]Cl (**8**)		Selected bond lengths (Å) [Pt(S_2CNEt_2)(dppp)]Cl (**9**)	
Pd(1A)–P(15A)	2.2701(11)	Pt(1)–P(9)	2.2501(10)
Pd(1A)–P(11A)	2.2846(11)	Pt(1)–P(13)	2.2526(10)
Pd(1A)–S(1A)	2.3487(12)	Pt(1)–S(1)	2.3541(10)
Pd(1A)–S(3A)	2.3498(11)	Pt(1)–S(3)	2.3529(10)
Selected bond angles (°)		**Selected bond angles (°)**	
P(15A)–Pd(1A)–P(11A)	92.10(4)	P(9)–Pt(1)–P(13)	92.84(4)
S(1A)–Pd(1A)–S(3A)	75.25(4)	S(3)–Pt(1)–S(1)	74.99(4)

related Pd(II) and Pt(II) dppp complexes was discovered to be slightly more efficient resulting in near quantitative RCYs for both [Pd([^{11}C]S_2CNEt_2)(dppp)]Cl (**8**) and [Pt([^{11}C]S_2CNEt_2)(dppp)]Cl (**9**) (Scheme 2, Table 1 entries 6 and 7).

Conclusions

In conclusion, a small range of novel ^{11}C-labelled late transition metal complexes has been prepared *via* the substitution reaction of ^{11}C-dialkyldithiocarbamates with metal chloride precursors. The method was discovered to be an efficient, rapid and practical one-pot process that was amenable to labelling Au(I), Au(III), Pd(II) and Pt(II) complexes in high RCYs. The versatility of such dithiocarbamates for coordination to transition metals opens the possibility for the generation of a wide range of labelled complexes that could find applications as PET imaging agents beyond the scope of conventional radiolabelled small organic molecules or could be used to complement a better understanding of the biology of transition metal-based therapeutics. We are currently investigating other DTC complexes that we anticipate could be translated to further ^{11}C radiolabelling studies and PET imaging applications.

Author contributions

C. S carried out the synthetic chemistry and ^{11}C-radiochemistry. F. E. and T. L. assisted in the isolation and crystallisation of complexes. P. W. M. and C. P. supervised ^{11}C-radiolabelling experiments. A. J. P. W. conducted the single crystal X-ray structure determinations. P. W. M. supervised the project. All authors contributed to the writing and proofreading of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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