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Chiral carbonyl hypoiodites†

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Three chiral carbonyl hypoiodites, R–C(O)OI, have been prepared from N-protected (*S*)-valine to give the ligand-stabilised (*S*)-valinoyl hypoiodite complexes with 4-dimethylaminopyridine, 4-pyrrolidinopyridine, and 4-morpholinopyridine as the stabilising ligands. The identity of the complexes was established by NMR (^{1}H, ^{13}C, ^{1}H–^{15}N HMBC) and single crystal X-ray diffraction analysis.

Weak intermolecular interactions comprise all chemical entities, though halogen bonding (XB) has only recently been defined as the attraction between an electrophilic halogen atom and a neutral or anionic nucleophile,[1] and systematically studied as a key interaction. The supramolecular research has previously focused on the construction of non-covalent systems using hydrogen bonding or through metal coordination, but over the last two decades halogen bonding has expanded rapidly as a field of research,[2–4] and now is one of the most studied non-covalent interactions.

Halogen(I) (or *halenium*) ions are the extreme case of a fully ionised halogen atom to a formally positive ion that is stabilised by a pair of Lewis bases (L; usually nitrogen-based) in the form $[L–X–L]^+$ (X = Cl, Br, I; also termed a *halonium* complex),[5–8] and as such fall under the umbrella of complexes that exhibit strong halogen bonds, even though their reactivity differs greatly from other classical XB complexes.[4] Due to the origin of XB as a σ-hole interaction,[4] which bestows a reliable high degree of linear directionality in its behaviour, halogen(I) ions have found great utility in self-assembling supramolecular architectures.[9–11]

Prof. Jose Barluenga's eponymous reagent, [*bis*(pyridine)iodine(I)]BF_4 (*Barluenga's Reagent*, **BR**) has enjoyed widespread use as a mild iodinating species and oxidant since the 1990s, making it the quintessential iodine(I) reagent.[12–14] Notable uses of **BR** include the iodination of alkenes, alkynes, and arenes under mild conditions, the conversion of 1,2-diols to their respective dicarbonyls, and due to being mild enough, the selective iodination of tyrosine in peptides or proteins, as well as the activation of thio- and *n*-pentenyl glycosides for glycosylation or conversion to the corresponding glycosyl fluorides.[15] However, these studies were performed with an unrestrained homoleptic iodine(I) complex (**BR**), with the chiral iodine(I) complexes only being studied only as their restrained, bidentate complexes,[16] which is also hindered by their availability (or lack thereof).[17]

Whilst heteroleptic iodine(I) complexes have been confirmed in the solid state,[18] the observation of them undergoing ligand scrambling in solution has stifled potential studies into their use.[18,19] These results negate synthetic strategies toward creating heteroleptic iodine(I) complexes *via* the use of chiral ligands, given that the unwanted recovery of meso isomers is highly probable. However, strategies involving the use of bidentate ligands have successfully circumvented these issues,[7,16,20] but often entails extensive synthetic protocols, and the influence of the chelation effect of these bidentate ligands on the reactivity cannot be overlooked.

The recent revitalisation of carbonyl hypoiodites,[17,21–23] as seen from the viewpoint of halogen bonding as isolable iodine(I) complexes, offers an alternative to the traditional $[N–I–N]^+$ complexes like **BR**. The carbonyl hypoiodites are inherently heteroleptic, but can still be synthesised in an analogous fashion *via* a similar Ag^+ to I^+ cation exchange as the $[N–I–N]^+$ complexes. Until now, alkyl hypoiodites (R–OI; R = alkyl) and carbonyl hypoiodites (R–C(O)OI, R = alkyl, aryl) have almost entirely been used as *in situ* reagents.[24] These hypoiodites have been reported to perform a variety of exotic transformations,[25,26] as well as recently being confirmed to perform the same straightforward iodinations that **BR** can.[17] Discerning structure–reactivity relationships can be difficult though, as such hypoiodite reagents like $CH_3C(O)OI$ and ^{t}BuOI have only limited solution-state data available in the literature,[27,28] with the identities of the actual reactive species being unresolved.[29,30]

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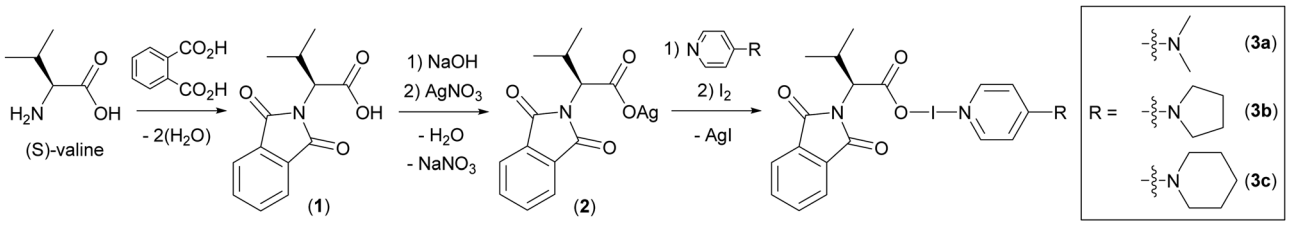

Scheme 1 The reaction protocols used to synthesis the hypoiodite compounds (**3a–3c**) in three steps starting from commercially available (*S*)-valine.

Herein, the first examples of chiral carbonyl hypoiodite complexes from N-protected (*S*)-valine are reported. The availability of α-amino acids as inexpensive, enantiopure starting materials is ubiquitous in organic synthesis, making them ideal chemical feedstocks. However, the double functionality of amino acids makes them incompatible with the Ag^+ to I^+ cation exchange necessary to produce the desired C(O)O–I–N carbonyl hypoiodites, therefore, (*S*)-valine was converted to (*S*)-*N*-phthaloylvaline (**1**; Scheme 1) *via* a double condensation reaction using phthalic anhydride under melt conditions as per a literature protocol.[31] Subsequent to the *N*-phthaloyl protection, **1** could be treated as a straightforward carboxylic acid (analogous to previous carbonyl hypoiodite studies[21–23]) and was converted to Ag[(*S*)-*N*-phthaloylvalinate] (**2**; Scheme 1) *via* deprotonation with NaOH, followed by cation exchange with $AgNO_3$ in 43% yield (Scheme 1). The reaction of **2** in dichloromethane with elemental iodine and a pyridine-based ligand, either 4-dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine (4-pyrpy), or 4-morpholinopyridine (4-morpy), gave the carbonyl hypoiodites DMAP (*S*)-*N*-phthaloylvalinoyl hypoiodite (**3a**), 4-pyrpy (*S*)-*N*-phthaloylvalinoyl hypoiodite (**3b**), 4-morpy (*S*)-*N*-phthaloylvalinoyl hypoiodite (**3c**) (Scheme 1). All the hypoiodite complexes (**3a–3c**) could be isolated as pure solids in 65% to 91% yields, ideal for prospective reagents,[17] which can be a weakness of highly reactive iodine(I) complexes.[8,32] The synthesis of the analogous derivative with pyridine, (*S*)-*N*-phthaloylvalinoyl hypoiodite(pyridine), was attempted given that it would be the directly comparable to **BR**. However, NMR studies immediately after synthesis of the compound revealed decomposition from its inception.

The complexes **1–3(a–c)** were studied in solution by ^{1}H, ^{13}C, and ^{1}H-^{15}N HMBC NMR spectroscopy. However, the poor solubility of **2** necessitated that strongly polar $(CD_3)_2SO$ be used, unlike **1** and **3a–3c** which favoured organic solvents, making direct comparisons of **2** with the hypoiodite compounds (**3a–3c**) ambiguous. Nevertheless, the comparison of the free ligand 4-morpy,[23] N-protected amino acid **1**, and **3c** (Fig. 1) did reveal the general trend of the **3c** ^{1}H NMR signals moving upfield. The pyridinic hydrogen atoms of **3c** (H_a and H_b; compared to 4-morpy) and the hydrogen atoms of the N-protected valine moiety (H_e, H_f, H_g, H_h, H_i, H_j; compared to **1**) were both shifted upfield with noticeable, but modest, differences all within the range of 0.02–0.13 ppm (for **3c** compared to 4-morpy and **1**). The same general trends were also observed for **3a** (with free DMAP and **1**) and **3b** (with free 4-pyrpy and **1**), with **3a** demonstrating the largest coordination shift of 0.23 ppm for its respective α-hydrogen atom (*cf.* H_e in Fig. 1) in comparison to **1**. Interestingly, this is contrary to the general trend

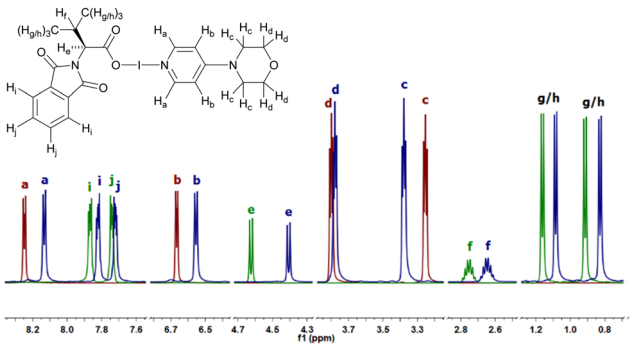

Fig. 1 The superimposed and condensed ^{1}H NMR spectra of the free ligand 4-morpy (red), the N-protected valine **1** (green), and 4-morpy hypoiodite **3c** (blue), showing the general trend of the hypoiodite shifting upfield compared to its constituent components (inset: Annotated molecule of **3c**; hydrogen labels for the subcomponents, 4-morpy and **1**, follow the same nomenclature as **3c**).

observed for $[N–I–N]^+$ complexes where the I^+ complexes experience a downfield shift of their ^{1}H NMR peaks compared to their respective free ligands and linear $[N–Ag–N]^+$ precursor complexes.[8,33]

The ^{1}H–^{15}N HMBC studies in CD_2Cl_2 were used to determine the ^{15}N NMR chemical shifts of the pyridinic nitrogen atoms, with those being aptly positioned to reflect the characteristic iodine(I) to nitrogen interaction upon complexation. The ^{15}N NMR chemical shifts of the pyridinic nitrogen atoms of −212.5 ppm (**3a**), −214.7 ppm (**3b**), and −204.2 ppm (**3c**), all demonstrated significant, and characteristically indicative, coordination shifts ($\Delta\delta_N$; defined as $\delta[^{15}N_{hypoiodite}]$-$\delta[^{15}N_L]$) from their respective free ligands (L = DMAP: −108.6 ppm;[21] 4-pyrpy: −110.0 ppm; 4-morpy: −99.1 ppm[23]) of −103.9 ppm (DMAP to **3a**), −104.7 ppm (4-pyrpy to **3b**), and −105.1 ppm (4-morpy to **3c**) upon formation of the carbonyl hypoiodite complexes. These $\Delta\delta_N$ values were in line with previous observations for other carbonyl hypoiodite complexes,[21–23] as were the values of the ^{15}N NMR chemical shifts themselves which fell within the range of −150 to −250 ppm for reported O–I–N carbonyl hypoiodite compounds (*cf.* −209.5 ppm for PhC(O)OI-(DMAP) and −202.1 ppm for PhC(O)OI-(4-morpy); both in CD_2Cl_2).[21] Whilst the phthalimido ^{15}N NMR chemical shifts were observed in high concentration samples of **1** (−219.4 ppm) and **2** (−212.9 ppm), the phthalimido ^{15}N NMR peaks were not observed for **3a–3c**, which not surprising given that the HMBC parameters were optimised for the more informative pyridine-based ligands, and with the possibility of the much weaker

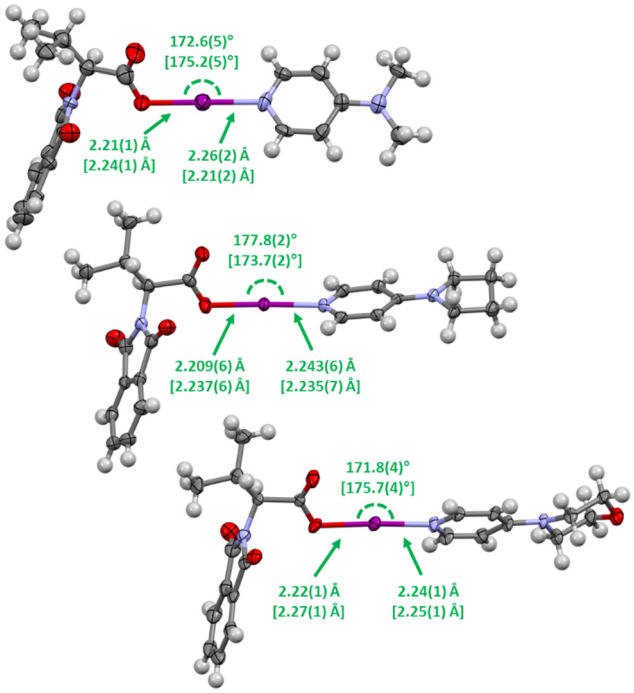

Fig. 2 The molecular structures of **3a** (top), **3b** (middle), and **3c** (bottom), annotated with their O–I–N angles (°) and I–N/I–O bond lengths (Å) (minor disordered positions of **3a** and **3b** omitted for clarity; thermal parameters at 50% probability; only one of each pair of crystallographically independent molecules shown for **3a–3c**, with parameters for the omitted second molecule in each case annotated in square brackets).

phthalimido resonances being obscured under the stronger pair of ligand resonances present in **3a–3c**.

The identity of the hypoiodite compounds **3a–3c** were also established by single crystal X-ray diffraction (SCXRD; Fig. 2), which confirmed their chirality with the non-centrosymmetric space groups $P2_1$ (**3a**), $P1$ (**3b**), and $I2$ (**3c**). Interestingly, all three compounds were found to have two independent molecules in the asymmetric unit cell (all with *S*-stereochemistry), with the slight differences observed in the bonding parameters between each pair being ultimately within the error of the measurements to a 3σ tolerance.‡ The I–N and I–O bond lengths of 2.26(2)/2.21(2) and 2.21(1)/2.24(1) Å (**3a**), 2.243(6)/2.235(7) and 2.209(6)/2.237(6) Å (**3b**), 2.24(1)/2.25(1) and 2.22(1)/2.27(1) Å (**3c**), respectively, are comparable to those of similar carbonyl hypoiodite complexes previously reported based on simple carboxylic acids (*cf.* MeC(O)OI-(DMAP): I–N = 2.24(1) Å and I–O = 2.20(1) Å and PhC(O)OI-(DMAP): I–N = 2.241(3) Å and I–O = 2.210(3) Å). The O–I–N bond angles of 172.6(5)/175.2(5)° (**3a**), 177.8(2)/173.7(2)° (**3b**), and 171.8(4)/175.7(4)° (**3c**), reflect the strong preference toward linearity enforced by the halogen bonding, though are some of the largest known deviations from 180° observed for carbonyl hypoiodites (*cf.* MeC(O)OI-(DMAP): O–I–N = 172.9(5)°; PhC(O)OI-(DMAP): O–I–N = 178.1(1)°), possibly due to **3a–3c** possessing the most sterically encumbered substituents of known carbonyl hypoiodite compounds with the presence of the phthaloyl and ^{i}Pr groups at the α-position of the N-protected amino acid backbone. The packing of **3a–3c** revealed no intermolecular or close-proximity interactions with the $I^{+}\cdots I^{+}$ distances for all compounds being greater than 4.81 Å (*cf.* combined van der Waals radii for I···I = 3.96 Å).

In conclusion, the first chiral carbonyl hypoiodite complexes have been synthesised, based on the cheap and abundantly available enantiopure amino acid (*S*)-valine. In only a three-step reaction, (*S*)-valine was N-protected to **1**, its carboxylic acid transformed into the prerequisite silver(I) carboxylate precursor **2**, and finally converted into the desired carbonyl hypoiodite complexes with a variety of pyridine-based stabilising ligands (**3a–3c**). The complexes were found to demonstrate relatively good stability for iodine(I) species, permitting full NMR and SCXRD studies, and enabling them to be isolated as pure solids. Despite their sterically more encumbered substituents, the chiral carbonyl hypoiodite complexes **3a–3c** displayed NMR and crystallographic metrics comparable to other previously reported carbonyl hypoiodites. The carbonyl hypoiodites **3a–3c** represent an elegant workaround to the potential complications of chiral $[N–I–N]^{+}$ complexes analogous to Barluenga's reagent (which suffer from ligand scrambling), and opens up a new avenue of approach toward potentially enantioselective iodination reactions, with studies currently ongoing to this end.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ With the exception of the I–O bond lengths (2.22(1)/2.27(1) Å) between the pair of independent molecules in **3c**, which are just beyond a 3σ tolerance by less than 0.01 Å.

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