

## Ionisation of the Zinc–Iodine Bond of Alkylzinc Iodides in Dimethylformamide from Theory and Experiment

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The functional group compatibility of organozinc reagents ensures that they are amongst the most flexible sources of carbon nucleophiles available.<sup>[1,2]</sup> Functionalised alkylzinc iodides are compatible with acidic protons,<sup>[3]</sup> including phenolic protons<sup>[4]</sup> and trifluoroacetamides,<sup>[5]</sup> attesting to the lack of basicity of these reagents. The reasons for this behaviour, which is somewhat counterintuitive, are not at present well understood. In addition, alkylzinc halides are generally much less effective than dialkylzinc reagents as sources of nucleophilic carbon, especially in asymmetric processes. This has prompted recent efforts to shift the Schlenk equilibrium between these two species towards the generally less-favoured dialkylzinc reagents.<sup>[6,7]</sup>

A substantial amount of recent progress in the applications of functionalised alkylzinc iodides has relied on the empirical observation that dipolar aprotic solvents are beneficial both for the preparation and solution stability of the reagents.<sup>[8]</sup> For example, dimethylformamide has been employed as solvent for reactions of amino acid-derived alkylzinc reagents.<sup>[9]</sup> Evidence from <sup>13</sup>C NMR spectroscopic studies shows that dimethylformamide coordinates to zinc,<sup>[10]</sup> influencing intramolecular coordination by the carbonyl oxygen atoms of both the carbamate protecting group and the ester. This effect may also play a significant role in the stabilisation of  $\beta$ -aminoalkylzinc iodides towards elimination.<sup>[10]</sup> In order to obtain a clearer view of the relative strengths of these interactions, we have undertaken a series of quantum chemical calculations.

Initial calculations were performed on serine-derived alkylzinc reagent **1**, in which the synthetically employed Boc-

protecting group has been replaced with a methyl carbamate. In the absence of any solvent, the two energetically most important local minima were identified, featuring internal coordination of zinc by the carbonyl oxygen atoms of both the ester group and the carbamate protecting group **1a**, or simply by the carbamate group alone, **1b** (Figure 1), which was the more stable structure. While we had previously suggested **1a** to be a possible structure for the reagent,<sup>[11]</sup> it appears that hydrogen-bonding in **1b** between the carbamate NH, rendered more acidic by coordination of the carbamate to zinc, and the ester carbonyl is preferred to co-ordination of the ester carbonyl to zinc (which might be expected to induce some strain). The relative abundance of **1a** and **1b** was calculated to be 0.0196:1 at 298.15 K, assuming that interconversion is possible.

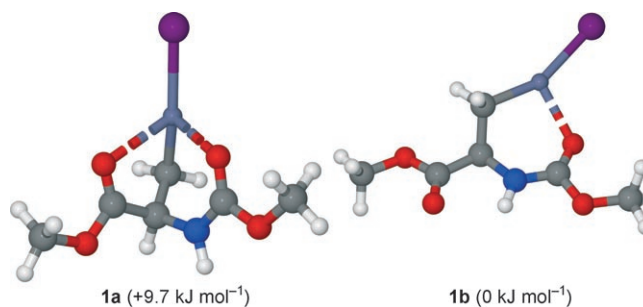
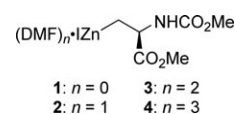


Figure 1. Calculated structures for **1** with relative energies.

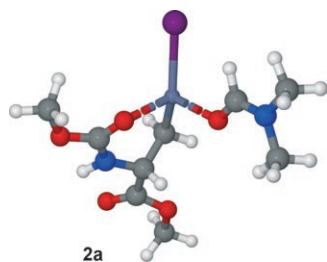
In order to understand the influence of the solvent, further calculations were carried out with the addition of one, two and three molecules of dimethylformamide, forming the adducts **2**, **3** and **4**, respectively.

In the case of **2**, one low energy conformation **2a** was identified, closely related to structure **1b**, in which the DMF molecule coordinated to zinc (Figure 2).



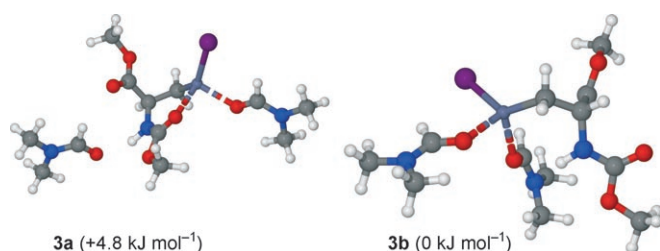
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Figure 2. Most stable calculated structure for **2**.

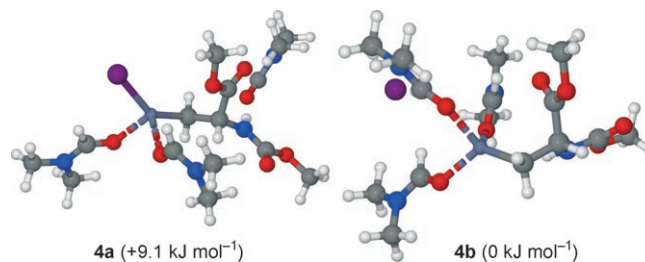
Several other stable conformations were identified, but each of them was substantially higher in energy ( $>16 \text{ kJ mol}^{-1}$ ) than **2a**.

Calculations of the structures formed by addition of a second molecule of DMF, to form **3**, revealed that the most stable arrangement had both molecules of DMF coordinated to zinc **3b**, with neither the carbamate protecting group nor the ester coordinated. This structure is reminiscent of the crystal structure of 1,1-dichloro-2,2,2-trifluoroethylzinc chloride·2DMF.<sup>[12]</sup> Structure **3a**, in which the carbamate protecting group displaced a DMF molecule (which instead formed a hydrogen bond to the carbamate proton), was slightly less stable (relative abundance **3a/3b** 0.14:1) (Figure 3).

Figure 3. Calculated structures for **3** with relative energies.

For each of the calculated structures **2a** and **3a**, a diastereomeric arrangement exists in which the DMF and iodide ligands at zinc are interchanged (**2a\***, **3a\***). Calculations carried out on each of these diastereoisomers established that, in each case, the original structures **2a**, **3a**, were more stable.

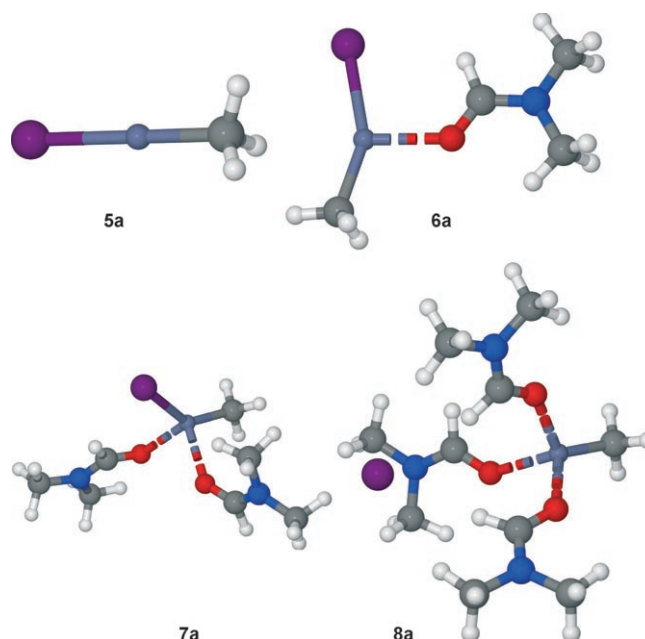
However, when calculations were carried out with three molecules of DMF, **4**, a most striking result emerged. As might be anticipated, the structure in which two DMF molecules coordinated to zinc, and the third formed a hydrogen bond to the carbamate proton, **4a** was identified as a local minimum. However, the structure in which all three DMF molecules were coordinated to zinc, inducing ionisation of the zinc–iodine bond to form the tight ion pair **4b**, was substantially more stable (Figure 4). The iodide ion sits in a pocket created by the three DMF molecules. While ionisation of the zinc–halogen bond of alkylzinc halides induced by the use of macrocyclic ligands that bind  $\text{RZn}^+$  has been

Figure 4. Calculated structures for **4** with relative energies.

proposed,<sup>[13]</sup> the suggestion that DMF might induce such ionisation is potentially significant for the properties of alkylzinc iodides in organic solvents (see below). Structure **4b** was achieved by optimising a five-coordinated zinc, and allowing the structure to relax. Pentacoordination is not preferred to ionisation.

To explore whether the presence of the amino acid functionality had any influence on this ionisation, a parallel set of calculations was performed for adducts of methylzinc iodide **5** with one, two and three molecules of DMF, compounds **6** ( $\text{MeZnI}\cdot\text{DMF}$ ), **7** ( $\text{MeZnI}\cdot 2\text{DMF}$ ) and **8** ( $\text{MeZnI}\cdot 3\text{DMF}$ ), respectively. In the first two cases, the expected adducts **6a** and **7a** were identified as local minima, with one and two molecules of DMF coordinated to zinc, respectively. The total interaction energies of the ligands with methylzinc iodide were calculated as 44.3 and 61.3  $\text{kJ mol}^{-1}$ , for **6a** and **7a**, respectively. In the case of the adduct with three molecules of DMF, **8**, the lowest energy structure **8a** once more showed complete ionisation of the zinc–iodine bond (Figure 5).

The total interaction energy of the ligands with methylzinc iodide in **8a** was calculated to be 85.7  $\text{kJ mol}^{-1}$ . Thus,

Figure 5. Calculated structures for **5**, **6**, **7** and **8**.

adding one molecule of DMF to **6** increases the interaction energy by 17 kJ mol<sup>-1</sup>, whereas adding a further DMF increases the interaction energy by an additional 24.4 kJ mol<sup>-1</sup>, clearly demonstrating the energetic advantage of ionisation. Moreover, the calculations indicate that coordination of each additional DMF molecule results in a lengthening of the zinc–iodine bond (2.47, 2.56, 2.64 and 5.36 Å, for the series **5**, **6**, **7**, and **8**, respectively). It should be remarked that DMF is a high dielectric solvent ( $\epsilon=36.7$ ), and that the effects of bulk solvent would be expected to be large. Such effects can be included in ab initio calculations using a continuum solvation approach, such as the sophisticated PCM method of Tomasi et al.,<sup>[14–16]</sup> which is included in Gaussian 2003. While we have only considered the explicit structure of the primary solvation sheath in the present work, the absence of the influence of the outer solvation sheath does not affect our primary conclusion, since bulk solvation will act so as to enhance the stability of more ionic conformations, compared to covalent ones.

While these calculations provide a self-consistent picture, it is possible that they over-emphasize the likelihood of ionisation. Experimental evidence was therefore sought in support of the ease of ionisation of the zinc–iodine bond. In addition, it was desirable to explore the balance between coordination of zinc in alkylzinc halides either internally by functional groups within the organic fragment, or externally by solvent. The most direct method both to probe the ease of ionisation of the zinc–iodine bond, and to determine the number of solvent molecules coordinated to zinc, appeared to be electrospray ionisation mass spectrometry. While it is appreciated that the results of such analyses must be interpreted with care due to potential artefacts produced by the electrospray process,<sup>[17]</sup> ESI-MS has been used to study metal ligand solution equilibria,<sup>[17]</sup> and in particular the gas-phase solvation behaviour of Ni<sup>II</sup> in water/DMF mixtures.<sup>[18]</sup> It is known that loss of a halide ligand is a reasonably general mechanism for the ionisation of neutral coordination and organometallic complexes under positive ion ESI-MS conditions,<sup>[19]</sup> but the technique does not appear to have been used to characterise alkylzinc halides. ESI-MS has been used in negative ion mode to identify the zincate [*t*Bu<sub>2</sub>ZnLi<sub>2</sub>]<sup>-</sup>, formed by addition of *t*BuLi (2 equiv) to *t*Bu<sub>2</sub>Zn.<sup>[20]</sup> Previous studies of Grignard reagents in THF have used rather specialised cold-spray ionisation techniques,<sup>[21]</sup> which are necessary to allow identification of the sensitive ions present in solution, so it was not self-evident that ESI-MS in positive ion mode could be successfully applied to the characterisation of alkylzinc halides.

The alkylzinc reagents **9** and **10** were prepared as solutions in dimethylformamide, and then analysed using ESI-MS in positive ion mode by direct injection without any special precautions. The ESI-MS spectrum of **9** (recorded at a cone voltage of 20 V) contained one principal ion at 415 [**9a**], together with a very low intensity ion at *m/z* 337 [ZnI(DMF)<sub>2</sub>]<sup>+</sup>, (Figure 6). Zinc iodide is formed during the zinc activation process (see experimental), so the mass ion at 337 was not unexpected. The ESI-MS spectrum of **10**, recorded

at the same cone voltage, had a base peak at *m/z* 503 [**10a**], with a small mass ion at 337. Interestingly, an even less intense mass ion at 430 [**10b**], in which no DMF was coordinated, was also detected. This is the only ion without coordinated DMF that we have observed in this study.

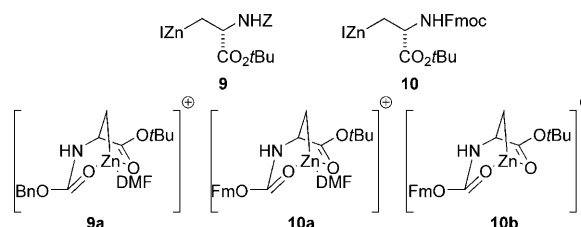


Figure 6. Observed ions derived from **9** and **10**.

While these results do not prove that ionisation of alkylzinc iodides occurs in DMF solution, they do demonstrate that ionisation of alkylzinc halides under positive ion ESI-MS conditions is an efficient process, and are consistent with weakening of the zinc–iodine bond in solution due to coordination by DMF. The results also provide further evidence that DMF does indeed coordinate to alkylzinc halides in solution, since although the ions are observed in the gas phase, they are formed in solution. While it is conceivable that DMF coordinates to the alkylzinc cations after they are formed, this seems highly unlikely since DMF is the bulk solvent.

The number of solvent molecules associated with ions that are produced during ESI-MS analysis depends on the conditions.<sup>[19]</sup> The alkylzinc reagent **11** was therefore analysed using ESI-MS in positive ion mode under increasingly energetic conditions. Two significant mass ions were observed in the ESI-MS spectrum recorded under mild conditions (cone voltage of 5 V), namely *m/z* 410 [ZnI(DMF)<sub>3</sub>]<sup>+</sup> and 339 [**11a**] (Figure 7). When the spectrum of alkylzinc re-

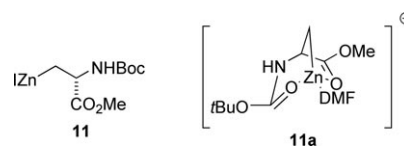


Figure 7. Observed ion derived from **11**.

agent **11** was recorded under more energetic conditions (cone voltages up to 20 V), the ion at 410 decreased in intensity, and a new ion appeared at 337 [ZnI(DMF)<sub>2</sub>]<sup>+</sup>, but the ion at 339 [**11a**] remained as the base peak. The fact that only one ion derived from the alkylzinc reagent **11** was found under a range of experimental conditions suggests that this ion is not merely a result of the precise ESI-MS conditions.

Having established the ESI-MS behaviour of the alkylzinc iodides **9–11**, ESI-MS spectra were recorded for two alkylzinc iodides, **12** and **13**, each bearing only one potentially co-

ordinating group. Under very mild conditions (cone voltage 2 V), the carbamate **12** gave rise to ions at  $m/z$  444 [**12a**] and 371 [**12b**], in addition to the previously observed ion at 410 [ $\text{ZnI}(\text{DMF})_3^+$ ] (Figure 8). Under more energetic conditions (cone voltage 10 V) the relative intensity of the ion at 444 decreased, and that at 371 increased. In a similar way, the ester **13** showed a major ion at 297 [identified as **13a**] under very mild conditions (cone voltage 2 V), together with a minor ion at 224 [**13b**] and, under more energetic conditions (cone voltage 20 V), the relative intensity of these two ions reversed. A very similar situation was observed for the intensities of the ions at 410 [ $\text{ZnI}(\text{DMF})_3^+$ ] and 337 [ $\text{ZnI}(\text{DMF})_2^+$ ]. This behaviour is entirely consistent in each case with the initial formation of four-coordinate zinc cations, from which loss of one molecule of DMF is possible. In neither case, even by using much more energetic conditions (cone voltages up to 40 V), were ions without coordinated DMF observed.

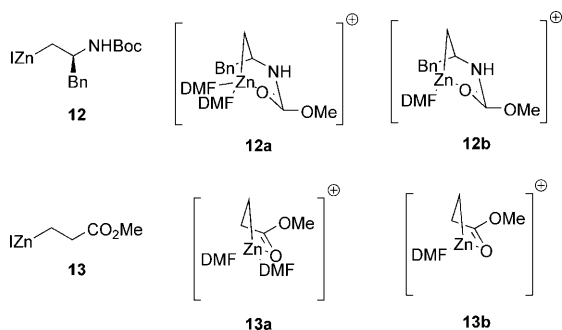
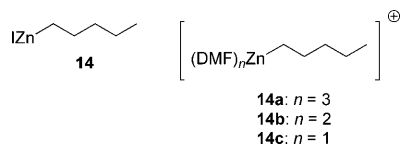


Figure 8. Observed ions derived from **12** and **13**.

Finally, the behaviour of the simple unfunctionalised pentylzinc iodide **14** was investigated. Under mild conditions (cone voltage 5 V), in addition to the zinc iodide-derived ion at  $m/z$  410, ions at 354 [**14a**] and 281 [**14b**] were observed. Structure **14a** is precisely what the calculations on methylzinc iodide in DMF had suggested. Under increasingly energetic conditions, the ion at 354 [**14a**] disappeared, and the signal for the ion at 281 [**14b**] first increased, then decreased, in intensity, and finally (at a cone voltage of 20 V) an ion at 208 [**14c**] became the predominant species derived from the solution of **14** in DMF.



Each of the samples (**9–14**) was also analysed using ESI-MS in negative ion mode. The main ion detected in each case was  $\text{I}_3\text{Zn}^-$  although in some experiments the higher homologues  $\text{I}_5\text{Zn}_2^-$  and  $\text{I}_7\text{Zn}_3^-$  were also observed. In no case were any ions of the type  $\text{RZnI}_2^-$  or  $\text{R}_2\text{ZnI}^-$  detected.

The positive ion ESI-MS data for the six alkylzinc iodides **9–14** fall into a neat pattern. Under mild conditions, the cationic zinc species each have four ligands, namely the alkyl group, any internal coordinating groups and DMF (the number of which depends on the number of internal coordinating groups present). Under more energetic conditions, sequential loss of coordinated DMF occurs, although it becomes progressively harder. The only alkylzinc iodide which was observed to give rise to an ion without any coordinated DMF was **10** (which contains two internal coordinating groups).

The implication that the zinc–iodine bond in alkylzinc iodides can (partially) ionise, either in coordinating solvents, or perhaps due to the presence of internal coordinating groups, suggests a possible reason for the lack of reactivity of these reagents towards electrophiles, namely that there is a partial positive charge on zinc. This influence also nicely explains the high functional group tolerance of alkylzinc iodides, especially towards protons, since the alkyl fragment would be less basic with a partial positive charge on zinc. Moreover, this influence explains why carboxylic acids are effective reagents for the protonation of alkylzinc iodides in organic solvents, in close analogy to the use of carboxylic acids for protonation of alkylboranes.<sup>[22,23]</sup> Thus, the carboxylic acid behaves as a Lewis base towards the alkylzinc iodide, increasingly the electron density at zinc, whilst simultaneously increasing the acidity of the carboxylic acid proton. The observation that the presence of excess halide ions has a significant effect on the rate of elimination of  $\beta$ -aminoalkyl zinc iodides<sup>[5]</sup> can also now be understood on the basis that the ionisation process would be modified in the presence of excess halide ions.

## Experimental Section

**Computational methods:** All the reported calculations were carried out with the Gaussian 2003 program,<sup>[24]</sup> and use the B3LYP<sup>[25]</sup> density functional. The implementation of the SDD basis set in Gaussian 2003 was used on zinc and iodine, which gives a double- $\zeta$  representation of the valence electrons, and contains an effective core potential which partially accounts for relativistic effects. The 6311-G(d,p) basis set was used on all other centres. The relative energies quoted for conformers involving complexed DMF have all had Boys and Bernardi basis set corrections<sup>[26]</sup> applied with respect to the complexed DMF moieties.

**Preparation and ESI-MS analysis of alkylzinc iodides:** All flasks were dried by heating under reduced pressure prior to the reaction. DMF was distilled before use. Approx. 0.07–0.09 mmol of  $\text{I}_2$  was added to a rapidly stirred suspension of zinc dust (6 equiv, 1.8 mmol) and alkyl iodide (0.3 mmol) in DMF (0.3 mL) at room temperature, under a nitrogen atmosphere. An exotherm was observed upon successful zinc insertion, which can occur up to 5 min after the addition. If no exotherm was observed, additional iodine (0.07–0.09 mmol) can be added at this stage. For mass spectral analysis, the reaction mixture was allowed to settle and a sample (0.1 mL) of the solution was removed, avoiding transfer of the zinc particulates, and diluted with dry THF (0.1 mL) to give a 0.5 M solution of the organozinc iodide. A sample of this solution was infused into a Waters LCT spectrometer at a rate of  $10 \mu\text{L min}^{-1}$ , using  $\text{N}_2$  (flow rate  $550 \text{ L h}^{-1}$ ) as the nebulising gas. A desolvation temperature of  $150^\circ\text{C}$  was employed, with a source temperature of  $100^\circ\text{C}$ .

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