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www.rsc.org/chemcomm ¹³C NMR analyses of a series of metalated arylacetonitriles and cyclohexanecarbonitriles with the synthetically relevant metals Li, Mg, and Cu identifies the influence of the carbon scaffold and the

nature of the metal on the preference for N- or C-metalation.

Metalated nitriles are chemical chameleons whose precise structural identity depends upon the solvent, the carbon scaffold, the temperature, and the metal.¹ In general, electropositive metals, and transition metals in high oxidation states, coordinate to metalated nitriles through the electron-rich nitrile nitrogen whereas less electropositive metals, and transition metals in low oxidation states, preferentially coordinate to the nucleophilic carbon.² Solid-state structures of metalated nitriles containing transition metals are roughly equally partitioned into N- and C-coordinated structures.² Often the ligand dictates the metal coordination site as illustrated in the ruthenium N- and C-phenylsulfonylacetonitriles **1** and **2** that can be equilibrated upon heating (Fig. 1).³

Despite the seminal position of lithiated and magnesiated nitriles in alkylations,^{1*c,d*} significantly less structural information is available than for comparable structures with transition metal cations. Pioneering crystallographic⁴ and solution NMR analyses⁵ of lithiated phenylacetonitrile identify the dimeric,⁶ N-lithiated structure **3**⁵ as the predominant structure in solution and in the solid state (Fig. 1).⁷ Only in lithiated cyclopropanecarbonitriles such as **4**⁸ or in the presence of proximal, strong donor ligands⁹ are lithiated nitriles coaxed into coordinating with the nucleophilic carbon.¹⁰

¹³C NMR provides an excellent method of determining the metal coordination in metalated nitriles because the chemical shift of the nitrile carbon is sensitive to the local environment.¹¹ The ¹³C NMR signal for the nitrile carbon of N-metalated nitriles containing a transition metal counter ion,² resonates between $\delta = 140-157$ whereas the corresponding C-metalated nitriles² resonate between $\delta = 115-138$. The chemical shift ranges of the ruthenium-complexed phenylsulfonylacetonitriles **1** and **2** are

N-Metalated C-Metalated ٩Ru NÈC δ 140-155 .SO₂Ph δ 110-125 2 TMEDA δ 140-155 THE THE 3 TMEDA ÓFt δ 155.3 MeÒ -c≡n H_{ℓ} -cΞŅ δ 148.5 5 FtÓ 6

Fig. 1 Comparison of N- and C-metalated nitrile structures.

Metalated nitriles: N- and C-coordination preferences

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of Li, Mg, and Cu cations[†]

illustrative (Fig. 1). Collectively, the chemical shift ranges for N- and C-metalated nitriles provide diagnostic signals for identifying the location of the metal in solution without the challenge of crystallizing air and moisture sensitive organometallics.

Fewer ¹³C NMR chemical shifts are available for metalated nitriles having Li, Mg, Zn, and Cu counter ions.⁵ For N-lithiated phenylacetonitrile (3), the ¹³C NMR resonances of the nitrile carbon vary modestly from δ = 146.2 to 152.7 depending on the solvent.¹² In contrast, the chemical shifts of the nitrile carbon in the equilibrating lithiated acetonitriles **5** and **6** (–100 °C, Et₂O) are δ 155.3 for the N-lithiated nitrile **5** and δ 148.5 for the C-lithiated nitrile **6** (Fig. 1).^{9b}

Solution and solid state structures of two zincated acetonitriles show coordination of the metal to the nucleophilic carbon (Fig. 2). A crystallographically determined structure of the zincated acetonitrile **7a** bearing a pyrazolylborate ligand crystallizes with zinc bound to the nucleophilic carbon.¹³ In solution, the parent C-zincated acetonitrile **7b** exhibits a ¹³C NMR chemical shift of δ 131.8 for the nitrile

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Fig. 2 ¹³C NMR of metalated nitriles containing Zn, Cu, and Mg.

carbon (Fig. 2).¹⁴ The metal coordination site of cuprated nitriles is less secure. The solution NMR of the C-cuprated nitrile **8** exhibits a resonance for the nitrile carbon that lies toward the upper chemical shift limit for C-metalated nitriles, at δ 137.8.¹⁵

Structural analyses of magnesiated nitriles are lacking.¹⁶ A rare exception is the magnesiated alkenenitrile 9^{17} which exhibits a ¹³C NMR resonance for the nitrile carbon at δ 129.6. In contrast to the C-magnesiated nitrile 9, diphenylacetonitrile affords a magnesiated nitrile whose infra-red signals are consistent with an N-magnesiated nitrile structure.¹⁶ The ambiguity surrounding the location of magnesium in magnesiated nitriles is compounded by reactivity trends that correlate with C-magnesiation¹⁸ and a configurationally labile C–Mg bond.¹⁹ The dearth of structural information for metalated nitriles, and the structural ambiguity of magnesiated nitriles, stimulated an NMR investigation into a series of lithiated, magnesiated, and cuprated nitriles.

Metalated arylacetonitriles are attractive for NMR analyses because the highly acidic methylene protons are readily deprotonated by a range of bases.¹ Phenylacetonitrile was readily deprotonated by i-PrMgCl in THF to afford the corresponding magnesiated nitrile **10**. Spectra obtained at -20 °C show one aliphatic resonance at $\delta = 31.3$ ppm and five resonances between $\delta = 113-148$ ppm (Fig. 3). Comparing the ¹³C NMR chemical shifts of **10** with those of N-lithiated phenylacetonitrile **11**¹² indicate a close structural correspondence consistent with **10** having magnesium coordinated to the nitrile nitrogen (Fig. 1).

Donor groups adjacent to the nitrile in lithiated alkylnitriles⁹ can override the normal preference for lithium to coordinate to the nitrile nitrogen to favour C-lithiated structures. If the coordination of magnesium to the nitrile nitrogen in magnesiated phenylacetonitrile and diphenylacetonitrile is weak, then C-magnesiated nitriles might be accessed with an appropriately positioned chelating group. 2-(2-Methoxyphenyl)acetonitrile was selected for deprotonation to determine whether an adjacent methoxy group could redirect the preference of magnesium to coordinate to carbon instead of nitrogen.

As a point of reference, the lithiated nitrile was first generated from 2-(2-methoxyphenyl)acetonitrile (Fig. 4). Adding BuLi to a -78 °C, THF solution of 2-(2-methoxyphenyl)acetonitrile readily afforded the lithiated nitrile 12 which gave a resonance for the nitrile carbon at δ 142.1. In the ¹H NMR, the methine proton at δ 2.86 experiences an upfield shift of δ 0.84 which parallels a similar δ 0.85 upfield shift on deprotonating acetonitrile.⁶ An analogous deprotonation in Et₂O generates a signal for the nitrile carbon at δ 151.9, suggesting a tighter CN-Li association than in THF. The



Fig. 3 ¹³C NMR shift comparison of metalated phenylacetonitrile.



nucleophilic carbon ¹³C resonance for **12** was assigned to the signal at δ = 26.1 ppm in THF (and δ = 25.9 in Et₂O) through a strong, single bond correlation with the signal for the methine hydrogen at δ = 2.86 ppm. In THF and Et₂O the ⁶Li NMR shows a single resonance consistent with formation of a symmetrical N-lithiated dimer.

Deprotonating 2-(2-methoxyphenyl)acetonitrile with i-PrMgCl affords 13 that has a ¹³C NMR signal for the nitrile carbon at δ 147.6 (Fig. 4). The ¹³C NMR chemical shifts of the magnesiated nitrile 13 closely correlate with the analogous signals for the magnesiated nitrile 10 and the lithiated nitriles 11 and 12. Collectively the ¹³C chemical shift similarities between 10–13 imply that the nitrile is N-metalated in each case. Extensive attempts to crystallize 13 provided low quality crystals whose X-ray crystallographic structure was consistent with the N-magnesiated structure 13 but the *R* value was unable to be refined below 15%.²⁰

Although the presence of the 2-methoxy group in **12** and **13** was insufficient to promote C-metalation, less electropositive metals may prefer C-metalation. Consequently, the cuprated nitrile **14** was prepared by adding CuI to the lithiated nitrile **12**.²¹ Cuprated nitrile **14** has a diagnostic nitrile carbon resonance at δ 131.2 (Fig. 4), similar to that of the C-cuprated nitrile **8** and distinctly different from the N-lithiated nitriles **11** and **12**, and the N-magnesiated nitriles **10** and **13**.²²

Collectively, the metalations are consistent with lithiated and magnesiated arylacetonitriles favoring N-metalated structures whereas the less electropositive copper favors a C-cuprated nitrile. Although magnesiated arylacetonitriles favor coordination of magnesium to the nitrile nitrogen, the stereodivergent alkylations¹⁸ and cyclizations^{1a} of some magnesiated and lithiated *alkyl*nitriles suggest that the preference for C- or N-metalation may be strongly influenced by the carbon scaffold.

Cyclohexanecarbonitrile was chosen as a representative alkylnitrile to investigate the influence of the carbon skeleton on the coordination preferences of metalated nitriles because alkylations¹⁸ and cyclizations^{1a} implicating C-metalated nitriles have featured in mechanistic analyses of conformationally constrained, 6-membered carbonitriles.¹⁹ As a point of reference, cyclohexanecarbonitrile was deprotonated with LDA (1.1 equiv.) to afford the N-lithiated nitrile **15** (Fig. 5). Although the upfield signals of the ring carbons were obscured by signals from other components, a broad signal for the nitrile carbon was observed at δ 163.6.²³ The nitrile carbon resonance is further upfield than the arylacetonitriles **11** and **12**, consistent with the influence of the aromatic system,²⁴ and is similar in frequency to the signal for lithiated acetonitrile in THF, δ 157.3.¹⁰

Access to the corresponding magnesiated and cuprated nitriles employed a facile bromine-metal exchange with 1-bromocyclohexanecarbonitrile.²⁵ Halogen-metal exchange methods carry the



Fig. 5 ¹³C NMR chemical shifts of metalated cyclohexanecarbonitriles.

advantage of accessing metalated nitriles in the absence of a conjugate acid that might function as a ligand. Although i-PrMgCl is typically employed in the exchange, the i-PrBr complicates NMR analyses requiring long acquisition times at ambient temperatures because competitive alkylation occurs. Consequently the magnesiated nitrile **16** was prepared by treating a d^8 -THF solution of bromocyclohexanecarbonitrile²⁵ with MesMgBr (1.2 equiv.). Subtracting the signals for MesBr identifies the nitrile carbon chemical shift at δ 126.6 (Fig. 5), a similar chemical shift to that of the C-magnesiated alkenenitrile **9** (Fig. 2). Surprisingly, the chemical shift of the nitrile carbon changes only modestly on addition of two equivalents of DME (δ_{CN} 126.7), TMEDA (δ_{CN} 126.7), or DMPU (δ_{CN} 126.6). The preference of the magnesium to coordinate to carbon in the cyclohexylcarbonitrile **16** is consistent with the greater covalency of the C-Mg bond compared to the C-Li bond.²⁶

The preference of copper to form the C-cuprated arylacetonitrile 14 suggested forming the corresponding C-cuprated cyclohexylcarbonitrile to provide a direct comparison with the lithiated and magnesiated nitriles 15 and 16, respectively. Access to the cuprated nitrile 17 was achieved through a bromine-copper exchange between 1-bromocyclohexanecarbonitrile and Me₂CuLi (1.2 equiv.).²⁵ The cuprated nitrile **17** exhibits a chemical shift for the nitrile carbon at δ 123.5 in a 2:1 THF: Et₂O mixture (Fig. 5). Performing the exchange in pure Et₂O shifts the nitrile carbon resonance of the cuprated nitrile to δ 125.1. The ¹³C nitrile carbon resonance of 17, in THF and Et₂O, lies in the mid-range of the chemical shifts of neutral, quaternary cyclohexanecarbonitriles.¹¹ As further support for the structure of 17, propargyl bromide was added to the solution employed for the NMR analysis (eqn (1)). Alkylation with propargyl bromide smoothly formed the allene 18 which provides a signature of a C-cuprated nitrile.²⁵



Metalated nitriles are complex organometallics whose precise structural identity intimately depends on the nature of the cation and the nature of the substituents on the nucleophilic carbon. Solvent effects appear to play a lesser role in determining the structure of metalated nitriles. NMR analyses of metalated arylacetonitriles and metalated cyclohexanecarbonitriles demonstrate that Lewis acidic lithium preferentially coordinates to the nitrile nitrogen in both structural types. Magnesiated nitriles exhibit greater coordination changes, preferring N-magnesiation with arylacetonitriles and C-magnesiation with cyclohexanecarbonitrile. The less electropositive metal, copper prefers C-metalation with both arylaceto- and alkylnitriles. The solution NMR analyses correlate with the reactivity, and stereoselectivity trends implied by divergent alkylations of N- and C-metalated nitriles, and demonstrate the profound influence of the metal and carbon scaffold on the coordination site of metalated nitriles. Financial support for this research from NSF (CHE 1111406, 0904393 and CHE 0614785 for NMR facilities) and the Swedish research council (GH) are gratefully acknowledged.

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