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Turbo-Grignard Reagents

Diisopropylamide and TMP Turbo-Grignard Reagents: A Structural Rationale for their Contrasting Reactivities**

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A century on since Grignard won the Nobel Prize in Chemistry for their development, Grignard reagents "RMgX" are still widely utilized today and still stand at the cutting edge of synthetic research. Current innovation centers on Knochel's exciting 21st century models "turbo-Grignard reagents" especially those formulated as "$R_2NMgCl{\cdot}LiCl$".[1] Equipped with enhanced kinetic basicity, these commercially available turbo-Grignard reagents can outperform their illustrious ancestors by executing magnesiation reactions of excellent regioselectivity and high functional group tolerance upon a large number of aromatic and heteroaromatic substrates. Since the exceptional reactivities of these special bases must be dictated by cooperative effects between their different component parts (Li, Mg, R_2N, Cl, any solvent ligands), it is important to understand how these components organize and interact with each other, both in solid state and most importantly in solution where they operate. To date, little structural information has been gathered and, what is more, only in the solid state through one X-ray crystallographic study of the TMP (2,2,6 6-tetramethylpiperidide) turbo-Grignard reagent or Knochel–Hauser base "(TMP)MgCl·LiCl" (turbo-TMP). It exists in the crystal as the tris(THF)-solvated contact ion pair $[(THF)_2Li(\mu\text{-}Cl)_2Mg(THF)TMP]$ (**1**).[2] A terminal (TMP)N−Mg bond is its salient feature. Here we present a more detailed characterization, in both the solid state and solution, of "(TMP)MgCl·LiCl" and its DA (diisopropylamide, $i\text{Pr}_2\text{N}$) analogue, the turbo-Grignard reagent "(DA)MgCl·LiCl" (turbo-DA). A complementary combination of X-ray crystallographic and NMR spectroscopic studies [including diffusion-ordered (DOSY) and exchange (EXSY) experiments] reveals that both in its crystalline form, $[\{(THF)_2Li(\mu\text{-}Cl)_2Mg(\mu\text{-}DA)\}_2]$ (**2**), and most significantly in solution turbo-DA differs markedly from turbo-TMP, enabling a rationalization of their markedly different observed reactivities.[1c] Furthermore, looking more generally across the whole field of modern metalation chemistry, these results allow a key distinction to be drawn between TMP-magnesiation reactions performed by these halide-activated regents and by mixed alkyl-amido formulations that dispense alkali metal mediated magnesiation (AMMMg).[3]

In a variation of the original literature synthesis,[1c] we prepared turbo-DA by mixing LDA ($i\text{Pr}_2\text{NLi}$) with magnesium chloride in THF.[4] The crystalline form of turbo-DA **2** (60% yield) came from a hexane/THF mixture. Dimeric aggregation is the main feature of the centrosymmetric molecular structure of **2** (Figure 1). Its tetranuclear arrangement consists of a central $(MgN)_2$ planar ring, lying orthogonal to and separating two $(LiCl)_2$ non-planar outer rings. The Li atoms carry two THF ligands. All four metal atoms and N atoms of the amido bridges exhibit distorted tetrahedral geometries, while the chloro bridges have two-coordinate bent geometries. The THF ligands, one *i*Pr arm of each DA ligand, and the chloride atoms Cl2/2a are disordered over two positions, ruling out discussion of metrical parameters associated with them though the connectivity of **2** is unequivocal.

Searching the Cambridge Crystallographic Database[5] emphasized the general novelty of the turbo-DA structure **2** as no hits were found for an alkali metal/magnesium/DA/halide composition, and the $[Li(\mu\text{-}Cl)_2Mg]$ ring is only precedented in turbo-TMP **1**. Widening the search to tetranuclear motifs of composition "$AM(\mu\text{-}X)_2Mg(\mu\text{-}X)_2Mg(\mu\text{-}X)_2AM$" (where AM = Li or Na; X = any ligand) revealed only four hits.[6,7] Poorly soluble in nonpolar solvents, **2** was dissolved in $[D_8]$THF solution (0.23 M)[4] for NMR spectroscopic characterization to attempt to reconstruct the actual conditions employed when turbo-DA is utilized in synthesis. Two different species labeled **2a** and **2b** were discernible from routine ambient-temperature ^1H and $^{13}C\{^1H\}$ NMR spectra

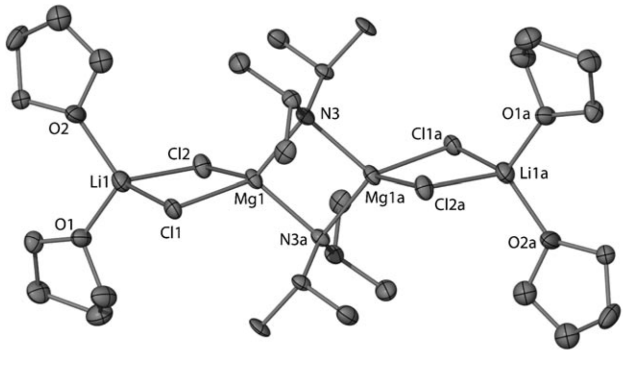

Figure 1. Molecular structure of $[\{(THF)_2Li(\mu\text{-}Cl)_2Mg(\mu\text{-}DA)\}_2]$ (**2**) with hydrogen atoms and disorder omitted for clarity.[4]

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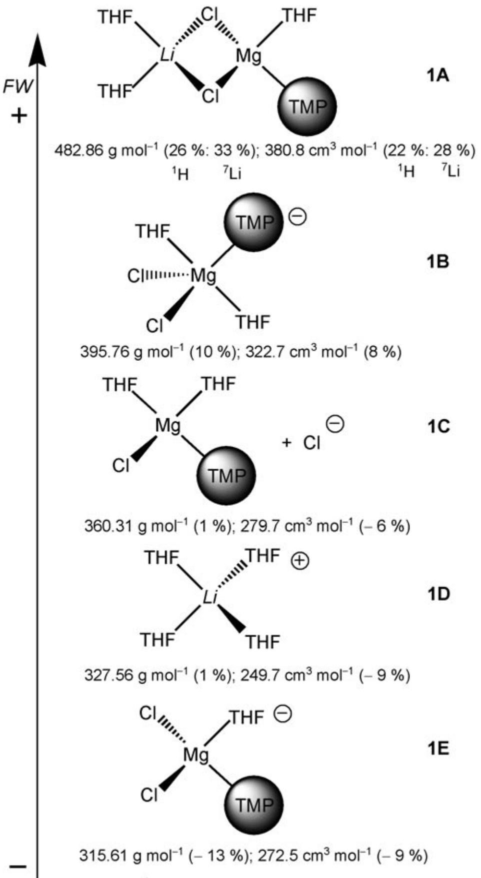
through two distinct types of DA ligand in a 2:1 ratio (^1H spectrum: **2a** $\delta = 3.41/1.32$ ppm; **2b** $\delta = 2.91/1.02$ ppm for CH/CH_3).[4] This complication contrasts with the apparent simplicity of turbo-TMP **1** which under the same conditions shows only one type of TMP resonance (^1H spectrum: $\delta = 1.57/1.17/1.16$ ppm for γ-CH_2/β-CH_2/CH_3). The presence of lithium in **2** was confirmed by a singlet in the ^7Li NMR spectrum (at $\delta = 0.25$ ppm),[4] with a similar chemical shift to that observed for **1** ($\delta = 0.27$ ppm). Note that typical resonances of LiTMP and LiDA in [D$_8$]THF are not present in solutions of **1** and **2**, respectively. If **2a** and **2b** contain lithium in their structures two distinct resonances are expected at different chemical shifts, but the possibility of coincident resonances cannot be discarded. Since a standard of LiCl (0.23 M in [D$_8$]THF solution) reveals a singlet at 0.51 ppm, this a priori rules out the possibility that **2a** and **2b** are monometallic magnesium species and that LiCl is "swimming" free in solution (unless the chemical shift difference is due to the dielectric constant varying between solutions[8]). Knochel hypothesized the ionic formula "$[Li(THF)_4]^+$-$[i$PrMg(THF)$Cl_2]^-$" to account for the high reactivity of the alkyl turbo-Grignard reagent "*i*PrMgCl·LiCl",[1a,b] and this known solvent-separated cation would fit ^7Li NMR data for **2a**/**2b**. As ^1H and ^{13}C resonances of **2** appeared broad, hinting at fluxional processes, a variable-temperature study (from −78 °C to 40 °C)[4] was undertaken. Revealing an even more complex picture, the former spectra catalog the gradual decrease in concentration of **2a** and **2b** and the emergence of a third species **2c** ($\delta = 3.07/1.04$ ppm at −78 °C for CH/CH_3 of DA), which is the major component at −78 °C. Significantly ^7Li spectra show only a singlet throughout the whole temperature window with modest variations in chemical shift ($\delta = 0.25$ ppm at 20 °C; $\delta = 0.30$ ppm at −78 °C). This is again consistent with one lithium-containing species common to **2a** and **2b**, and now to **2c**. A ^1H-^1H EXSY NMR[9] experiment confirmed dynamic equilibria between all three species.[4] In addition, ^1H and ^7Li spectra run at 25 °C on three different concentrations (0.46 M, 0.23 M, and < 0.10 M) of **2** in [D$_8$]THF established that **2a** predominates at higher concentrations whereas **2b** predominates at lower concentrations, suggestive of a possible dimer (**2a**)–monomer (**2b**) equilibrium. The same singlet ^7Li resonance was seen during these variable-concentration studies.[4] To gain further information about the solution chemistry of **1** and **2**, we studied their diffusion properties using diffusion-ordered NMR spectroscopy (DOSY). DOSY techniques can be used to identify individual components of solution mixtures (comparable to chromatography in NMR terms), and to estimate their sizes, which are inversely proportional to their diffusion coefficients (*D*).[4,10]

^1H and ^7Li DOSY NMR spectra were recorded in [D$_8$]THF at −50 °C. TMP ligand signals (γ-CH_2, β-CH_2, CH_3) show a single cross point with the same diffusion coefficient ($D = 1.63 \pm 5 \times 10^{-10}\,m^2 s^{-1}$) in ^1H DOSY spectra. The ^7Li DOSY shows also a single aggregate ($D = 1.68 \times 10^{-10}\,m^2 s^{-1}$).[4] The similar diffusion coefficients obtained in the ^1H and ^7Li experiments a priori indicate that proton- and lithium-containing molecules are linked together into a single species, possibly the X-ray structure $[(THF)_2Li(\mu\text{-}Cl)_2Mg(THF)TMP]$ (**1**).[2] However, if solvent separation takes place giving $[\{Li(THF)_4\}^+]$ and $[\{(Cl)_2Mg(THF)TMP\}^-]$, which have similar sizes, similar results would be seen in the diffusion experiment. Accurate determination of species sizes became necessary to resolve this dilemma. Thus ^1H and ^7Li diffusion measurements were recorded with internal references present. The sizes inferred [expressed in formula weight (*FW*) and volume (*V*)] for different solution concentrations are always in the same range, giving as average: ^1H-TMP $357 \pm 12\,g\,mol^{-1}$, $297 \pm 9\,cm^3\,mol^{-1}$; ^7Li $326 \pm 12\,g\,mol^{-1}$, $273 \pm 9\,cm^3\,mol^{-1}$.[4] From these estimated sizes comparisons can be drawn between these unknowns and plausible species.

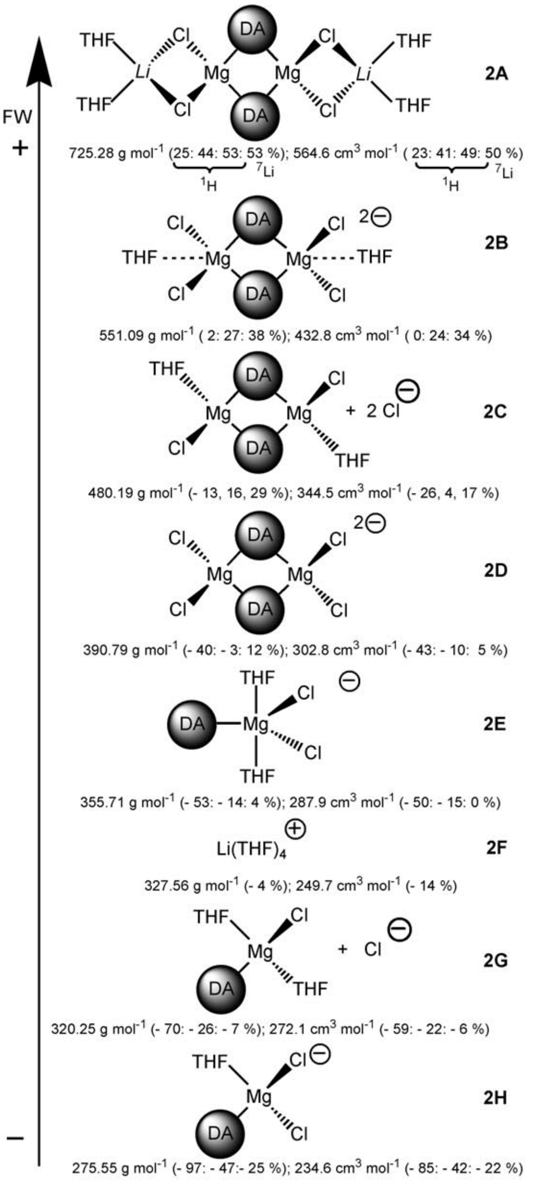
Figure 2 depicts some possible candidates with their respective *FW* and *V* values and the error for every considered structure with respect to the average sizes predicted through the DOSY study.[4] The contact ion pair $[(THF)_2Li(\mu\text{-}Cl)_2Mg(THF)TMP]$ (**1**) is our starting point. Dissolved in [D$_8$]THF it can retain its integrity (**1A**) or solvent-separate to smaller ionic molecules (**1B**–**1E**). The cation would be a known lithium–THF solvate, most probably $[Li(THF)_4]^+$ (**1D**). The anion could be a magnesiate type $[(THF)_nMg(Cl)_2TMP]^-$ (**1B**, $n = 2$; **1E**, $n = 1$) or neutral



	FW and *V* predicted of TMPMgCl·LiCl species in [D$_8$]THF	
Species	^1H-TMP	^7Li
FW [g mol^{-1}]	*357 ± 12*	*326 ± 12*
V [cm^3 mol^{-1}]	*297 ± 9*	*273 ± 9*

Figure 2. Possible species of (TMP)MgCl·LiCl in [D$_8$]THF solution and errors (in brackets) for every consideration respect to the average *FW* and *V* values predicted through the DOSY study.

$[(THF)_2Mg(Cl)TMP]$ (**1C**) with concomitant Cl^- swimming free in solution. Key conclusions reached, using either the *FW* or *V* approach are: firstly, the molecular structure in the crystal $[(THF)_2Li(\mu\text{-}Cl)_2Mg(THF)TMP]$ (**1**) is not retained in $[D_8]$THF solution as no species near its size (**1A**) appears in solution (error range 22–33 %); and secondly a solvent-separated situation described by an appropriate combination of possible species **1B**–**1E** (error range 1–13 %) seems most probable. The accuracy of the method is not enough to clearly establish the exact nature of the solution species,[4] but clearly indicates that lithium- and magnesium-containing species, although inevitably interacting, do not form strongly contacted ion pairs.



	FW and *V* predicted of DAMgCl·LiCl species in $[D_8]$THF			
Species	$[^1H]$**2a**	$[^1H]$**2c**	$[^1H]$**2b**	^{7}Li
FW (g mol^{-1})	*543 ± 13*	*404 ± 16*	*343 ± 11*	*340 ± 40*
V (cm^3 mol^{-1})	*433 ± 9*	*332 ± 12*	*287 ± 8*	*285 ± 30*

Figure 3. Possible species of (DA)MgCl·LiCl in $[D_8]$THF solution with errors (in brackets respect to **2a**/**2c**/**2b** when applicable) respect to average *FW* and *V* values predicted through the DOSY study.

^{1}H and ^{7}Li DOSY NMR spectra were recorded in $[D_8]$THF at −50 °C.[4] ^{1}H DOSY spectra show that **2a**, **2b**, and **2c** have different diffusion coefficients $[D(\mathbf{2a}) = 1.67 \times 10^{-10}\ m^2 s^{-1}$; $D(\mathbf{2c}) = 1.91 \times 10^{-10}\ m^2 s^{-1}$; $D(\mathbf{2b}) = 2.08 \times 10^{-10}\ m^2 s^{-1}]$ which indicates a relative size sequence of $\mathbf{2a} \gg \mathbf{2c} > \mathbf{2b}$. ^{7}Li DOSY, in accordance with its simplicity, shows a single aggregate ($D = 2.00 \times 10^{-10}\ m^2 s^{-1}$), suggesting that its size is similar to that of **2b** or **2c** but much smaller than that of **2a**.[4] The fact that ^{1}H DOSY shows three different DA-containing species and ^{7}Li DOSY just one lithium aggregate, indicates that at least two DA–magnesium complexes do not contain lithium in their compositions, making again solvent separation most plausible. The use of internal standards became necessary to obtain more information about the complicated nature of (DA)MgCl·LiCl in THF solution so the procedure carried out with the TMP complex was repeated. *FW* and *V* values for the "^{1}H-DA" and "^{7}Li" species lie in the same range at different concentrations. The averages values are: ^{1}H-DA(**2a**) = 543 ± 13 g mol^{-1}, 433 ± 9 cm^3 mol^{-1}; ^{1}H-DA(**2c**) = 404 ± 16 g mol^{-1}, 332 ± 12 cm^3 mol^{-1}; ^{1}H-DA(**2b**) = 343 ± 11 g mol^{-1}, 287 ± 8 cm^3 mol^{-1}; ^{7}Li = 340 ± 40 g mol^{-1}, 285 ± 30 cm^3 mol^{-1}.[4] Figure 3 depicts some possible molecules that can form in a $[D_8]$THF solution of (DA)MgCl·LiCl (considering what would require the least reorganization from the solid-state structure) with their respective *FW* and *V* values and the error for every considered structure respect to the average sizes predicted through the DOSY study.[4] If the contacted ion-pair $[\{(THF)_2Li(\mu\text{-}Cl)_2Mg(\mu\text{-}DA)\}_2]$ (**2**) dissolved in $[D_8]$THF retains its integrity, a species with a *FW* of 725.28 g mol^{-1} (**2A**) should be visible in the second dimension; however, the heaviest species *FW* predicted is only 543(13) g mol^{-1}, which implies a 25 % error using ^{1}H DOSY data. Also considering the heaviest and unique lithium species in solution has a predicted *FW* of 340(40) g mol^{-1}, the error of considering the existence of **2A** would be around 50 % from ^{7}Li DOSY. The *D*–*V* approach exhibits the same results. Thus consistent with the TMP derivative, it appears that the solid-state structure $[\{(THF)_2Li(\mu\text{-}Cl)_2Mg(\mu\text{-}DA)\}_2]$ (**2**) is not retained in $[D_8]$THF solution. A solvent-separated situation implies the existence of a THF-solvated lithium cation species, most probably $[Li(THF)_4]^+$ (**2F**) although a higher THF solvation cannot be ruled out. Anionic counterions range from dimeric (**2B**–**2D**), in which different THF solvation and Cl^- coordination are considered, to monomeric **2E**, **2G** and **2H**. The method is not accurate enough[4] to unequivocally establish the exact nature of **2a**, **2b**, and **2c** but clearly indicates that **2a** fits the dimer category and **2b** is a monomer (as suggested by the concentration study), and **2c** is in an intermediate situation. They all are "DAMgCl"-containing species in equilibria affected by concentration and temperature.

These results show how changing the steric bulk and electronic properties of the amide controls not only the turbo-Grignard bases' structural features (in solid state and solution), but also changes strongly their reactivity characteristics. For example, whereas (TMP)MgCl·LiCl selectively magnesiates ethyl-3-chlorobenzoate in the C2 position,[1d,2] with (DA)MgCl·LiCl only addition–elimination is observed.[4] Although not definitive about the exact solution nature of turbo-TMP and turbo-DA in THF, these NMR studies clearly indicate their solid-state structures are not retained. Compared against the uniformity of a single solution species with a solitary terminal Mg–N(amido) bond, the DA turbo-base exhibits a dynamic mixture of species, complicated by the presence of both bridging and terminal amido ligands, which in combination with the inherent lower basicity of DA versus TMP can explain, at least in part, the different observed reactivities of turbo-DA and turbo-TMP. This established solvent-separated nature of these chloride-based magnesiating agents distinguishes them from the contact ion-pair arrangements generally found for related alkyl amido species such as [(TMEDA)Na(μ-TMP)(μ-*n*Bu)Mg(TMP)] (**3**), a mitigating factor being the former are used in THF solution, while the latter are generally used in hydrocarbon solution. Therefore distinct mechanisms must be open to each type of Mg base. Intermolecular processes not directly involving the alkali metal should be common with the former, whereas intramolecular processes in which the alkali metal could act as a Lewis acidic coordination point for an incoming aromatic substrate within a pre-magnesiation complex are probable with the latter. This distinction may explain why turbo-Grignard reagents tend to manifest their enhanced magnesiating power in usual *ortho* positions (conforming to directed *ortho*-metalation, D*o*M principles),[11] whereas favorable stereochemical dispositions in base–substrate complexes enable **3** to perform deprotonations in extraordinary positions, typified by the *meta*-magnesiation of toluene.[12]

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