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 "R2NMgCl·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, R2N, 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(µ-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, iPr₂N) 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, $[{(THF)_2Li(\mu-Cl)_2Mg(\mu-DA)}_2]$ (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

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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*Pr₂NLi) 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(μ -Cl)₂Mg] ring is only precedented in turbo-TMP **1**. Widening the search to tetranuclear motifs of composition "AM(μ -X)₂Mg(μ -X)₂Mg-(μ -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 [D₈]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 ¹³C{¹H} NMR spectra



Figure 1. Molecular structure of $[{(THF)_2Li(\mu-Cl)_2Mg(\mu-DA)}_2]$ (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/CH₃).^[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 -CH₂/ β -CH₂/CH₃). 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 [D₈]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 $(0.23 \text{ M in } [D_8]$ 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)Cl₂]⁻" to account for the high reactivity of the alkyl turbo-Grignard reagent "iPrMgCl·LiCl",[1a,b] and this known solvent-separated cation would fit 7Li NMR data for 2a/2b. As ¹H and ¹³C 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/CH₃ 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 [D₈]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 variableconcentration 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 [D₈]THF at -50 °C. TMP ligand signals (γ -CH₂, β -CH₂, CH₃) show a single cross point with the same diffusion coefficient ($D = 1.63 \pm 5 \times 10^{-10} \text{ m}^2 \text{s}^{-1}$) in ¹H DOSY spectra. The ⁷Li DOSY shows also a single aggregate ($D = 1.68 \times 10^{-10} \text{ m}^2 \text{s}^{-1}$).^[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(μ -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 $357 \pm 12 \text{ gmol}^{-1}$, $297 \pm 9 \text{ cm}^3 \text{mol}^{-1}$; ⁷Li $326 \pm 12 \text{ gmol}^{-1}$, $273 \pm 9 \text{ cm}^3 \text{mol}^{-1.[4]}$ 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 $[(THF)_2Li(\mu-Cl)_2Mg(THF)TMP]$ (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



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(μ -Cl)₂Mg(THF)TMP] (**1**) is not retained in [D₈]THF solution as no species near its size (**1A**) appears in solution (error range 22–33%); and secondly a solventseparated 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.

¹H and ⁷Li DOSY NMR spectra were recorded in $[D_8]$ THF at -50 °C.^[4] ¹H DOSY spectra show that **2a**, **2b**, and 2c have different diffusion coefficients $[D(2a) = 1.67 \times$ $10^{-10} \text{ m}^2 \text{s}^{-1};$ $D(2c) = 1.91 \times 10^{-10} \text{ m}^2 \text{s}^{-1};$ $D(2b) = 2.08 \times 10^{-10} \text{ m}^2 \text{s}^{-1};$ $10^{-10} \text{ m}^2 \text{s}^{-1}$ which indicates a relative size sequence of $2a \gg$ 2c > 2b. ⁷Li DOSY, in accordance with its simplicity, shows a single aggregate ($D = 2.00 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$), suggesting that its size is similar to that of **2b** or **2c** but much smaller than that of 2a.^[4] The fact that ¹H DOSY shows three different DAcontaining species and ⁷Li 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 "¹H-DA" and "⁷Li" species lie in the same range at different concentrations. The averages values are: ${}^{1}\text{H-DA}(2a) = 543 \pm 13 \text{ gmol}^{-1}, 433 \pm 9 \text{ cm}^{3}\text{mol}^{-1}; {}^{1}\text{H-}$ $DA(2c) = 404 \pm 16 \text{ gmol}^{-1}$, $332 \pm 12 \text{ cm}^3 \text{mol}^{-1}$; ¹H-DA- $(2b) = 343 \pm 11 \text{ gmol}^{-1}, \qquad 287 \pm 8 \text{ cm}^3 \text{ mol}^{-1};$ $^{7}Li = 340 \pm$ 40 gmol^{-1} , $285 \pm 30 \text{ cm}^3 \text{ mol}^{-1}$.^[4] Figure 3 depicts some possible molecules that can form in a [D₈]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 $[{(THF)_2Li(\mu-Cl)_2Mg(\mu-DA)}_2]$ (2) dissolved in $[D_8]THF$ retains its integrity, a species with a FW of 725.28 gmol^{-1} (2A) should be visible in the second dimension; however, the heaviest species FW predicted is only $543(13) \text{ gmol}^{-1}$, which implies a 25% error using ¹H 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 ⁷Li 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



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.

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

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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 $[(TMEDA)Na(\mu-TMP)(\mu-nBu)Mg(TMP)]$ (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, DoM 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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