Salt Effects

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Split Personality of Lithium Chloride: Recent Salt Effects in Organometallic Recipes

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Mirroring its Jekyll-and-Hyde nature in human health, salts when added intentionally or unintentionally to reactions of organometallic reagents can have either positive or negative effects. "Salt effects" are common especially in the mechanistic labyrinth of organolithium chemistry[1] (Figure 1) where the effects refer to changes in reactivity and/or selectivity in a multitude of reactions (e.g., ortholithiations, enolizations, nucleophilic additions) compared to "salt-free" protocols, but their influence extends wider into other important areas of organometallic chemistry.[2] While decades of chemical, spectroscopic, and theoretical investigation have elaborated salt effects in specific systems the reasons for them are often couched in vague terms and the structures and mechanisms involved are generally cloaked in mystery. However, a scan of the recent literature reveals that the dragnet is beginning to close in on this complex subject with spectacular progress on a number of fronts, both in the fundamental understanding of salt effects and on new ways to exploit them in stoichiometric and catalytic reactions with implications for laboratory and process chemistry.

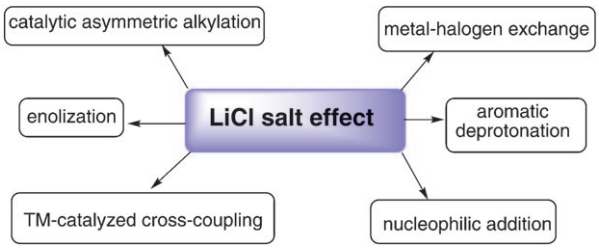
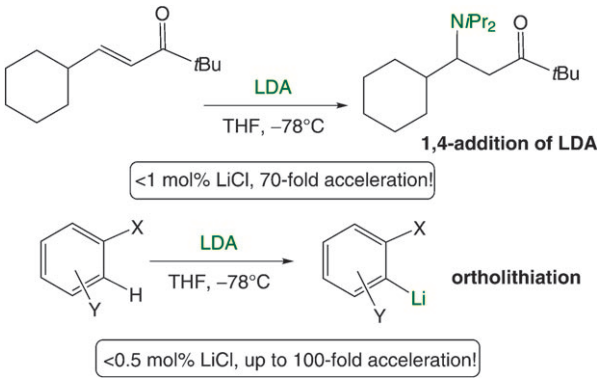


Figure 1. Selected reactions exhibiting salt effects.

Considering first organolithium chemistry, Collum et al.'s meticulous attention to detail uncovered the remarkable fact that minute quantities of lithium chloride (as small as 0.5 mol%) can greatly accelerate ortholithiation reactions of arenes (Scheme 1) containing halogen-based directing groups (F, Cl, or CF_3) using the protocol commonly practiced by organic chemists (lithium diisopropylamide (LDA), THF, −78 °C).[3] The unexpectedly high magnitude of this lithium chloride catalysis is astonishing and considering that LDA made from commercial *n*-butyllithium is contaminated with sufficient LiCl to catalyze such reactions, it may have been an unrecognized factor in the results of previously reported lithiations. Collum et al. wisely caution all users of commercial lithium reagents to be alert to the possible influence of LiCl contamination stressing that source and batch dependency could be a problem and potentially costly in larger-scale process chemistry. In a subsequent study significantly not probing deprotonation but nucleophilic addition reactions of LDA (with unsaturated esters),[4] Collum et al. detected similar rate enhancements caused by as little as 1.0 ppm of LiCl. This same occurrence in two distinct types of LDA-executed reaction focuses thoughts on the likelihood of a shared substrate-independent process at least in part, which Collum et al.'s rigorously conducted kinetic measurements suggest could involve rate limiting deaggregation of an LDA dimer. Mixed aggregation (or more strictly cocomplexation as individual components may be present as single entities) between LDA, LiCl, the organic substrate, and THF, and the rates by which such mixed aggregates exchange, especially if comparable to the rate of the deprotonation or nucleophilic addition reaction, shrouds this issue in dense fog and a lot more painstaking physical-organic work is needed to clear it. How LiCl catalyzes the deaggregation of LDA remains a mystery, though Collum envisages either a LDA rung breaking away from a mixed $(LDA{\cdot}LiCl)_2$ ladder or a



Scheme 1. Collum's LiCl-catalyzed reactions of LDA.[3,4]

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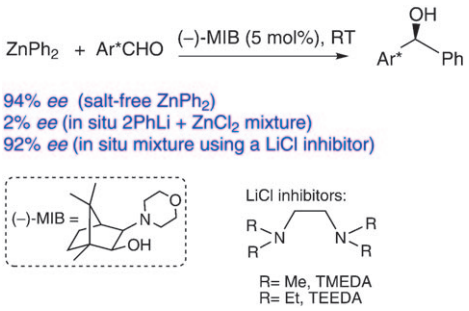
$(LDA{\cdot}THF)_2Cl^-$ 'ate releasing monomeric $LDA{\cdot}(THF)_2$ and $(LDA)Cl^-$.[5]

Inhibitions of RLi by molar excesses of LiCl are also noted by Collum who stresses that the amount of LiCl is a critical factor in the outcome of organolithium reactions. Compelling solution evidence for LiCl-mediated deaggregation of RLi (R = Me) comes from the combined NMR (including DOSY)/DFT study by Maddaluno et al.[6] They contend that mixing tetrameric methyllithium with dimeric lithium chloride in THF solution produces a solitary new species in dinuclear (MeLi·LiCl) in the equilibrium mixture. A suspected tris-THF solvate, this cocomplex contains a monomeric fragment of MeLi.

Looking beyond organolithium horizons, seminal advances have also recently been made in exploiting salt effects for improved synthetic performance. Knochel et al. have been championing these developments with stoichiometric lithium chloride, a staple diet and modifying ingredient in his turbo Grignard/Hauser reagents [e.g., (TMP)MgCl·LiCl; $(TMP)_2MgCl{\cdot}2\,LiCl$],[7] which exhibit enhanced magnesiating power towards many aromatics and heterocycles generally inert towards non-turbo prototypes (TMP is 2,2,6,6-tetramethylpiperidide). Turbo magnesiating reagents exhibit a greater functional-group tolerance (e.g., to esters, ketones, nitriles) than conventional organolithium reagents but are intolerant of more sensitive groups (e.g., aldehydes, nitro). Tolerance thresholds are further raised by incorporating a zinc component as in $(TMP)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ which can metallate oxadiazoles and triazoles without fragmenting them.[8] The combination of salts promotes solubility and high zinc amide reactivity. Order of addition is important with such multicomponent bases as adding $ZnCl_2$ first to the substrate (e.g., quinoxaline) followed by $(TMP)_2Mg{\cdot}2\,LiCl$ produces faster deprotonation reactions than those with the reverse order of addition or with preformed $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2\,LiCl$.[9] This hints at a two-step magnesiation and fast magnesium to zinc transmetalation process. 'Ate species are implicated in turbo reagent chemistry from DOSY NMR and X-ray diffraction studies though evidence is circumstantial.[9]

Salt effects can also surface unexpectedly in cases where LiCl is not added deliberately, but forms as a byproduct of a metathesis. Walsh et al. document a nice example in catalytic enantioselective phenylations of aldehydes (Scheme 2).[11] Prepared from ArLi and ZnX_2, diarylzincs add to aldehydes in the presence of an asymmetric catalyst, but the Lewis-acidic LiX byproduct promotes an achiral background reaction, which is suppressed by a Lewis base. Marder and Lei[12] have noted similar detrimental effects in Ni-catalyzed oxidative homocouplings of PhZnCl, generated in situ through salt-metathesis (yield is quantitative using PhMgCl but a miserly 13% using PhLi). Mixed-metal salt intermediates (Mg–Zn) are implicated in this study and in related Negishi couplings.[13]

All this chemistry could be designated "molecular salt" chemistry. Intrinsic to its complexity, molecular LiCl is both Lewis acidic and Lewis basic, and this amphoteric character makes it excel at cocomplexing other components (starting organometallic reagent, organic substrate, organometallic product, polar solvent). While the Lewis acidity of LiCl is often quoted, its Lewis basicity is often ignored. Yet in a polar solvent (commonly THF) with Li^+ fully or partially solvated this is likely to be a significant factor, and indeed Collum pictures the Cl anion as a "sterically unhindered hexamethylphosphoramide analog" in binding to the terminal Li^+ of an $(LDA{\cdot}THF)_2$ open dimer.[5] The take home message is if LiCl is present in reaction solutions, whether intentionally or unintentionally (e.g., as an impurity in a commercial reagent) added, or forms as a seemingly innocent byproduct, then its possible influence must be explicitly explored before the chemistry can be confidently considered fully understood. Moreover future studies are needed to investigate the potential transformational chemical properties that LiCl and other salts can exert in other areas of solution chemistry. Molecular salt chemistry is certain to be a hot topic for many years to come.



Scheme 2. LiCl-inhibited catalytic phenylations of aldehydes. TMEDA = tetramethylethylenediamine, TEEDA = tetraethylethylenediamine.

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