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Structure – Reactivity Relationship of Organo-zinc and -zincate Reagents: Key Elements towards Molecular Understanding

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Abstract: The main parameters that influence the structure-reactivity relationship of ZnR_2 and $ZnRX$ types of organozinc and organozincate reagents are gathered in this perspective article. Influences of substituents, inorganic salts, and solvents are discussed and illustrated with examples from the literature. Based on the peculiarities of this chemical system, the perspective is enlarged by molecular modelling considerations to raise the comprehension at the molecular scale of structure-activity relationships of organozinc and organozincate reagents in solution.

Introduction

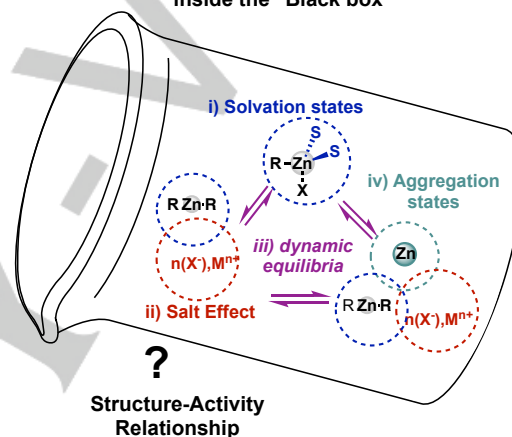
Since their discovery by Edward Frankland in 1848,^[1] organozinc compounds have found broad interest in organic chemistry. Organozinc reagents feature at least one Zn-C bond,^[2] as in the homoleptic diorganozinc reagents (ZnR_2) or in the heteroleptic reagents ($ZnRX$: R = Alk, Ar; X = Hal). They are often compared to the magnesium-based Grignard reagents as they share similar reactivity trends. In particular, organozinc reagents promote C-C bond formation under mild conditions, such as in cyclopropanation,^[3] nucleophilic addition,^[4] carbozincation,^[5] halogen-zinc exchange^[6] or Negishi cross-couplings.^[7]

In 1859, Frankland observed that dimethylzinc is more easily obtained from zinc diiodide when coordinating solvents are used.^[8] To our knowledge, this is the first report of the influence of specific solvation effect in organozinc chemistry. In the presence of Y⁻ anion originating from salt additives, organozincs can yield mono- and di-anionic species respectively named low- ($[ZnRXY]^-$) and high-order ($[ZnRXY_2]^{2-}$) organozincates. In many cases, the reactivity, and the selectivity of organo-zincs and -zincates are driven by the choice of solvent(s) and salt additive(s). To date, the influence of such additives on the exact structure, and consequently on the reactivity of organozinc and organozincate reagents, remains a black box due to the lack of understanding at the molecular level (**Scheme 1**).

In this perspective, we first propose a rapid overview of the structural diversity of mono- and poly-nuclear organo-zinc and -zincate reagents in polar and non-polar solutions. A more complete survey of the structure of organozinc reagents is already available from Van Kotten and co-workers in a dedicated book chapter.^[9] Then, the tuning of the reactivity of organozinc reagents by means of LiCl salt addition to reach a desired reactivity is illustrated. Only the global aspects of these salt additives on the reactivity are reviewed here. On this specific topic, we redirect the reader to discussions provided by the groups of Organ^[10] and Hevia.^[11] Finally, the technical difficulties

related to the adequate modelling of the structure and reactivity of organozinc reagents in solution are discussed.

Structure of Organozinc and Organozincates: inside the "Black box"



Scheme 1. Key concepts for an in-depth elucidation of the structure-reactivity of organozinc reagents. R = Alk, Ar; X = Alk, Ar or Hal; M = Li, Na, Mg or Ca; S = solvent molecule. ii) Salt Effects avec un s ! Homogénéité des majuscules i), ii) iii) et iv).

Solvation and aggregation states of organozinc compounds in solution

Structure, bonding, and properties of solvent-free ZnR_2 .

Bis-alkylated organozinc compounds, ZnR_2 , have been well-characterized as pure compounds by IR-Raman and electron diffraction in both solid, liquid or gaseous states.^[12] These data have been complemented by photoelectron spectroscopy and theoretical calculations performed at the DFT level.^[13] In terms of bonding and electronic structure, $ZnMe_2$ in gas phase is linear and has two pure σ C-Zn bonds that can freely rotate; in this complex the 3d electrons of Zn should be regarded as non-bonding. In agreement with this bonding scheme, $ZnMe_2$ stays linear and monomeric in its pure liquid form.^[12]

In contrast, due to the ability aryl groups to form μ -bridge, diarylzinc compounds $ZnAr_2$ show a different behavior and lead to the formation of polynuclear structures. For instance, the XRD structure of $ZnPh_2$ ^[14] reveals characteristic $[ZnPh_2]_2$ dimers. Similarly, mixed $ZnRX$ alkylzinc compounds tend to aggregate to form dimers (R = *t*Bu, X = *Ot*Bu),^[15] trimers (X = NPh₂),^[16] tetramers (X = Cl, Br),^[17] or coordination polymers (X = I).^[18]

The parameters that qualitatively influence the aggregation state of organozinc compounds were discussed by Bell and Moseley. It was proposed that the entropy of the system, the steric

hindrance of the substituents, the saturation of the coordination sphere to reach a coordination number of 4 and the nature of X can, among other parameters, control the aggregation state of the reagent.^[19]

Structure of organozincs in non-coordinating solvents.

In organic synthesis, organozinc reagents are usually used as a solution in either coordinating or non-coordinating solvents. To date, details concerning the determination of the exact structure of ZnRX reagents in non-coordinating solvents remain scattered and elusive. An in-depth comprehension of how these species form, interact, and rearrange in solution is yet not documented. In this outlook, additional *in situ* characterization experiments based for instance on the method of continuous variations *via* Job plots analysis would be desirable for the progress of the field.^[20]

Structure of organozincs in coordinating solvents.

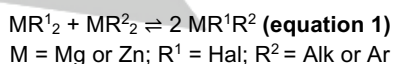
Very little is known about the exact structure of organozinc reagents in coordinating solvents. Alkylzinc compounds show relatively weak interaction between Zn and coordinating solvent molecules,^[21] and have as well as a limited propensity to oligomerize in solution in agreement with the structure of the pure compounds. In a series of seminal works, Thiele studied the coordination of solvent molecules to ZnMe₂ using a set of cyclic mono-ethers.^[21] He reported that up to two solvent molecules bind ZnMe₂. To complement, Smets reported that the addition of small amounts of THF or Et₂O to a benzene solution of ZnEt₂ has no influence on its NMR spectra. This may be indicative of a rapid equilibrium between the different solvation states of ZnEt₂.^[22] Recently, the monitoring by microcalorimetry experiments of stoichiometric mixtures of ZnMe₂ and THF has been reported by the group of Espinet.^[23] It reveals that the solvation of ZnMe₂ by two THF solvent molecules is exothermic by 7.9 ± 0.2 kcal mol⁻¹ (ΔH value).

Rare crystallizations from solution enabled to resolve structures by solid-state X-ray diffraction (XRD). In these cases, monomer^[24] and dimer^[25] structures of organozinc species coordinated to solvent molecules have been reported. The solvation of diarylzinc reagents was never studied,^[25a] but as many structures of organo-magnesium,^[26] -aluminum^[27] and -copper^[28] show μ -aryl bridges, the formation of diarylzinc dimer in solution cannot be excluded.

From these solid-state structures, the following general trends can be delineated: *i*) alkyl organozinc reagents are essentially monomeric in coordinating solvent, *ii*) organozinc compounds are likely coordinated by two ethers molecules and *iii*) they have a distorted tetrahedral geometry.

Dynamic structure of ZnRX type of reagents

In the field of organomagnesium chemistry, Grignard reagents MgRX are in equilibria with MgR₂ and MgX₂ accordingly to the Schlenk equation (**equation 1**). The mechanism of this equilibrium has only been recently elucidated by Cascela and Eisenstein by means of metadynamic simulations performed at the DFT level using explicit solvent cages.^[29] In addition to the speciation of organomagnesium dimer species, this computational study has revealed the role played by the solvation dynamics of Mg to promote the Schlenk equilibrium.



Similarly, organozinc reagents are involved in the Schlenk equilibrium.^[30] Rolfe and co-workers estimated the thermodynamic of the Schlenk equilibrium of ZnEtI in THF.^[31] In this case, the equilibrium is displaced toward the formation of ZnRI with a reaction constant $K_{\text{eq}} = [\text{ZnRX}]^2/[\text{ZnR}_2][\text{ZnI}_2] \geq 100$ at room temperature. Analogous value was later estimated from ¹H-NMR for ZnMeI in THF solution ($K_{\text{eq}} = [\text{ZnMeI}]^2/[\text{ZnMe}_2][\text{ZnI}_2] \geq 500$ at -90°C).^[32] Evans and co-workers also reported IR and Raman spectra of mixtures of ZnR₂ and ZnX₂ (R = Me or Et, X = Cl, Br or I) in coordinating solvents.^[33] The data collected suggests the formation of monomeric species. This contrasts with the chemistry of organomagnesium reagents in which dimer structures have been reported as stable intermediates along the Schlenk equilibrium.^[26a,29]

Again the picture depicted above changes when considering apolar solvents. For instance, the ¹H-NMR monitoring of mixtures of ZnEtX and ZnEt₂ (X = Cl or Br) in toluene solution exhibits a linear relationship between the ¹H-NMR shift of methylene group $\delta(\text{CH}_2)$ and the organozinc molar fraction $x(\text{ZnEtX})$, undependably of its value.^[34] This demonstrates that the equilibrium is strongly displaced toward the formation of ZnEtX. For X = I, a similar linear relationship between $\delta(\text{CH}_2)$ and $x(\text{ZnEtI})$ is obtained till $x(\text{ZnEtI}) < 0.19$, but $\delta(\text{CH}_2)$ is constant for higher molar fraction along with the apparition of a colorless precipitate.^[18] This originates from the formation of a non-soluble coordination polymer and highlights differential solubilities of organozincs in solution.^[18]

By analogy with Grignard reagents, a unified molecular model in which organozinc intermediates in solution are identified and their structure-activity relationships are understood at the molecular level would be beneficial for further developments in organic synthesis and catalysis. More precisely, this would contribute to the design of sets of experimental conditions that promote the formation of the most reactive species toward a desired selectivity.

Salt and additive effects on structures and reactivities of organozinc reagents

In organic synthesis, organozinc reagents are often employed in the presence of salts. The presence of these salts stems either from the preparation method of the organozinc reagent,^[35] or from the addition – on purpose – of the salt additives to promote the reaction. To date, very little is known about the exact role, at the molecular scale, of these additives on the synthesis,^[36] and on structure-reactivity relationship of the organozincates.^[10]

Structure-reactivity relationship of lithium-organozincates. Organozincates can be straightforwardly and quantitatively obtained by transmetalation between dialkylzinc and organolithium reagents. The formation of aggregates from mixtures of ZnEt₂ and LiEt was early established in 1930 by cryoscopic measurements.^[21b] The first preparation of Li₂Zn(Me)₄ was reported by Hurd in 1948.^[37] This formation of this complex was later monitored by ⁷Li- and ¹H-NMR and a mechanism was suggested for the methyl group exchange between ZnMe₂ and (MeLi)₄.^[38] The rate determining step was attributed to the dissociation of (MeLi)₄. Later on, Smets and co-workers established that ZnEt₂ and LiEt form 1:1 adducts in benzene.^[22] Upon addition of various amounts of THF, they noticed the

formation of aggregates having a ratio 1:1:1.7 in LiEt:ZnEt₂:THF. Replacing THF by Et₂O or DME (DME = 1,2-dimethoxyethane) resulted in the formation of 1:1:1 LiEt:ZnEt₂:solvent complexes. EXAFS spectra of ZnMe₃Li and Li₂Me₃Zn(R) (R = Me, CN or SCN) have been reported by Sakamoto and co-workers.^[39] They showed that within these high-order organozincates, Zn adopt a tetrahedral geometry.

The situation becomes more intricate when organolithium are replaced by lithium halides. In these cases, and as a general trend, the diversity of structures and reactivities of organozinc reagents are significantly enlarged, as recently computationally clarified in the case of the interaction between LiCl and isoelectronic Pd(0) complexes.^[40] Indeed, as underlined by Hevia and co-workers, lithium halides exhibit an amphoteric character.^[11] Therefore, both their Lewis acid and base properties should be considered to describe the structure and reactivity of organozinc reagent mixture, though the exact nature of lithium organozincates formed remains unknown.

The group of Koszinowski has used electrospray ionization mass spectrometry (ESI-MS) to probe the ability of organo-zinc and -zincate compounds to aggregate in THF solution.^[41] From ESI-MS spectra, it was shown that the nature of the halide has a strong influence on association state of the zinc complex, Cl being more prone to yield organozincate aggregation.^[41a,41b] They detected the putative soluble intermediate RZnHal·LiCl formed by zinc metal insertion into the carbon-halide bond of the electrophile in presence of LiCl. This structure was previously proposed, in its dissociated form [Li]⁺[RZnHalCl]⁻ by Knochel and co-workers.^[35d,42] By combining ESI-MS, conductimetry and ¹H- and ⁷Li-NMR spectroscopies, the group of Koszinowski established that the addition of 1 equivalent of LiCl to ZnBuCl quantitatively leads BuZnCl₂⁻ (*K*_{Ass} = 113). In this case, the formation of higher-order organozincate BuZnCl₃²⁻ was found disfavored. As compared to mixed organozinc halides ZnRX and in line with previous reports from Knochel,^[43] diorganoalkylzinc reagents such as ZnBu₂ are less prone to form organozincate in the presence of LiCl.

From the literature, low- and high-order lithium organozincates have different reactivities relative to their neutral form. For example, depending on the structure of the organozincate, selectivities in epoxide-opening or Br-Zn exchange have been tuned as reported by Sakamoto.^[39,44] Additionally, in a series of articles, the group of Organ extensively studied the influence of additives and solvent mixtures on the Pd catalyzed Negishi coupling between ZnRBr (R = *n*Bu or Ph) and alkylzinc halides in THF:DMI mixture (DMI = 1,3-dimethyl-2-imidazolidinone).^[45] As established by titration experiments (Figure 1), the reaction remains dormant until 1.0 equivalent of LiBr is added to ZnBuBr, and becomes optimal with a slight excess of LiBr (ca. 1.4 equivalent).^[45d] In line with a previous report by Vicić,^[46] the reaction is inhibited by the addition of zinc bromide^[45d] which likely acts as a bromide scavenger.^[45e] From MS and NMR spectrometry, it was found that DMI stabilizes high-order organozincates such as ZnBuBr₃²⁻.^[45e] Full conversion for the Negishi coupling of alkylbromides was reached when crystalline ZnRBr₃²⁻(Bu₄N)₂⁺ (R = Et, Bu) was used to replace ZnBuBr, in THF and without any additives. This led to the suggestion that ZnRBr₃²⁻ is the species that undergoes transmetalation.^[45f,47] Once again, the case of arylzinc reagents is different. Whereas diarylzinc can directly transmetalate in absence of salts and in low-dielectric solvent such as THF,

transmetalation from arylzinc halide requires the addition of LiBr or the use of more polar solvent to avoid organozincate aggregation, as postulated.^[45g] The work of Organ illustrates the tunability of the reactivity of organozinc reagents based on their inherent dynamic equilibria, the nature of Zn substituent, the presence of additives and the choice of the solvent.

Though a large amount of data has been collected on salt effects in this field of chemistry, it remains too fragmented to allow a coherent representation and a molecular scale understanding. This is a global challenge of current organometallic chemistry and would specifically allow a rational use of salt effects in organozinc chemistry.

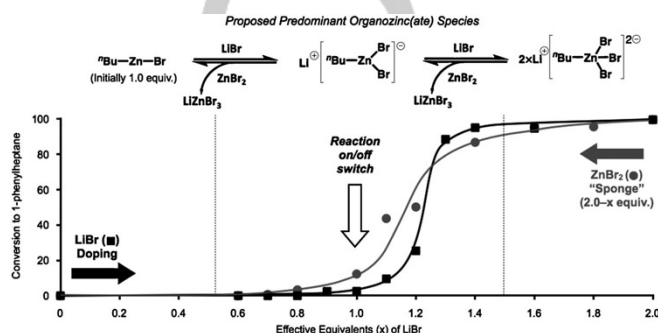


Figure 1. Titration experiments for the Negishi coupling of *n*BuZnBr with 3-bromo-1-phenylpropane by Pd-PEPPSI-IPr ([1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium) in THF:DMI (2:1) mixture, the presence of varying amounts of LiBr or ZnBr₂.^[45d]

Structure-reactivity relationship of magnesium and calcium/sodium/potassium organozincates.

Lei and Bedford underlined that organozinc reagents prepared from Grignard reagents showed a totally different reactivity compared to those prepared from organolithium.^[48] In a series of articles, the group of Hevia provided interesting insight on the formation of Zn-Mg heterobimetallic species.^[49] They reported that efficient Zn-I exchange reaction occurs in THF when 4-iodoanisole is in the presence of *i*) Mg^tBuCl/Zn^tBu₂ (1:1) or *ii*) Mg^tBuCl/ZnCl₂ (3:1), but the reaction is inhibited with *iii*) Mg^tBuCl/ZnCl₂ (1:1). Based on NMR/ESI-MS analysis and XRD structure characterization, they unambiguously attributed the observed activity to the formation of the solvent-separated ion pair Mg₂Cl₃(THF)₆⁺·Zn^tBu₃⁻. Under the inhibiting conditions (*iii*), the formation of the contacted ion pair (THF)₄Mg(μ²-Cl)₂Zn(^tBu)Cl and solvent separated ion pair MgTHF₆²⁺·Zn₂Cl₆²⁻ were observed. This suggest that halide concentration strongly influences the aggregation state and reactivity of organozincate and is in line with earlier contributions from Koszinowski.^[41a,41b] Concerning the structure of Mg/Zn heterobimetallic complex, in 2011, the group of Hevia characterized the complex [THF₂Mg(μ-Cl)₃ZnEt]₂ (Figure 2). It has a double heterocubane geometry in which two corners are missing. It was obtained from equimolar reaction between ZnCl₂ and ZnR₂.^[50]

Other alkali organozincates have been also reported. For example, Maillard and co-workers reported the synthesis and the characterization of tetraethylzincates MZnEt₄ (M = Ca, Sr or Ba).^[51] Joint cryoscopic, NMR and UV experiments showed that diethylzinc and divalent cation M²⁺ form solvated ion pairs M²⁺·ZnEt₄²⁻ in THF or Et₂O. While dialkylzinc are unreactive towards saturated ketones,^[52] it has been reported that up to 2 alkyl groups from calcium tetraalkylzincates can react with ketones.^[53] Recently, sodium organozincates have also been synthesized and characterized by the group of Hevia.^[54]

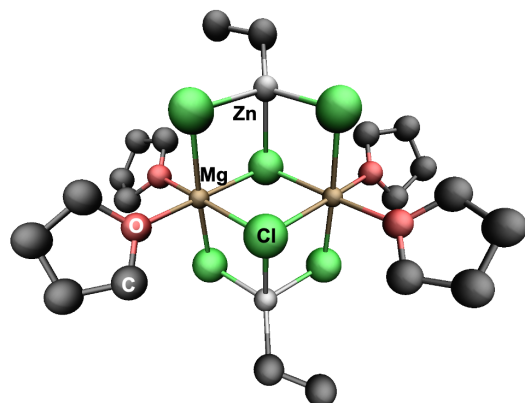


Figure 2. XRD-structure of $[(\text{THF})_2\text{Mg}(\mu\text{-Cl})_3\text{ZnEt}]_2$.^[50] All hydrogen atoms have been removed for clarity purposes.^[55]

Modelling organozinc compounds in solution: a computational challenge

To get relevant information from molecular modelling on organozinc compounds, it is essential to properly describe solvent effects.^[23] Indeed, calculation results can be strongly affected by the solvation model that is used.^[56] On the one hand, the widely used polarization continuum models (PCM) were several times proved non-suitable to reproduce organozinc solvation.^[23,57] On the other hand, the micro-solvation approach that combine an implicit solvent model in addition with some few explicit solvent molecules are delicate to handle since the number of solvent molecules coordinated to intermediates and transition states cannot be straightforwardly determined. Additionally, this approach raises the critical point of structural sampling. Finally, in all cases, the entropic effects related to the solute-solvent system are roughly estimated though many tailored corrections have been proposed.^[58]

An approach that considers at least two shells of solvent molecules and their dynamics is therefore required to adequately represent the solvated solute. In this vein, molecular dynamic simulations would be optimal to study the structure-activity relationship of organozinc reagents at the DFT level.^[59] In order to enhance the conformational sampling and to promote the exploration of rare events such as transition states, the use of biased molecular dynamics simulations is appealing. This, by means of metadynamics simulations, proved efficient in elucidating the mechanism of the Schlenk equilibrium of Grignard reagents (**Figure 3**) and the solvation of Na^+ ion in THF solution^[29a,60] or the speciation of ZnCl_2 in water.^[61]

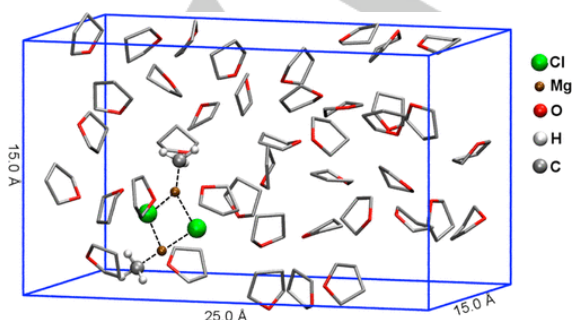


Figure 3. Cell of $[\text{MgMeCl}]_2$ dimer with explicit solvation model used to elucidate the Schlenk equilibrium of Grignard reagents.^[31a]

Perspectives: how to tame organozinc reagents?

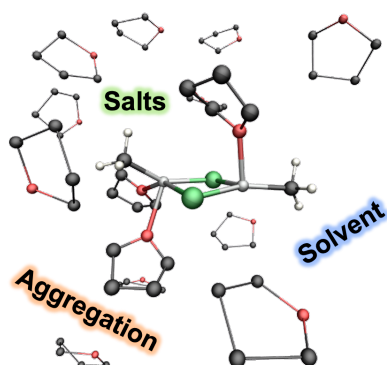
The survey of the literature reveals that the exact structure of organozinc halides in solution is not yet fully established and it is a missing link in the field. It has been highlighted that the nature of the substituents and of the solvent, as well as the presence of inorganic salts have a strong influence on organo-zinc and -zincate structure-activity relationships. Though an appreciable amount of experimental data concerning the solvation and aggregation states of organo-zinc and -zincate reagents in polar or apolar solvents is currently available, an effort to provide a rational picture – at the molecular scale – is still needed to understand how organo-zinc and -zincate react within complex reactive media. Addressing this intricate topic by molecular modelling would contribute to push further the limit of state-of-the-art in computational chemistry dedicated to the fine depiction of complex organometallic systems in solution. More generally, the identification the active species and the understanding of how-to promote their formation through a set of additive and solvent will enable organozinc chemistry to enter a new era.

Keywords: Zincates • Salt effect • Solvent effects • Computational Chemistry • Structure-activity relationship

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The reactivity of organozinc reagents is dictated by a subtle choice of reaction conditions (solvents, additives, concentration). In this perspective article, some of the key parameters that allow an efficient control of the structure - activity relationship of organozinc and organozincate reagents in solution are reviewed. The appropriate modeling strategies to address these complex chemical systems are discussed.

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