Zincation

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Structurally Defined Reactions of Sodium TMP–Zincate with Nitrile Compounds: Synthesis of a Salt-Like Sodium Sodiumdizincate and Other Unexpected Ion-Pair Products**

William Clegg, Sophie H. Dale, Eva Hevia, Lorna M. Hogg, Gordon W. Honeyman, Robert E. Mulvey, Charles T. O'Hara, and Luca Russo*

The recent development of modern alkali-metal ate reagents has provided a passport to previously unconquered areas of metalation chemistry.[1] Thus the less-electropositive metal (Mg, Al, Zn, or Mn[2]) anionically activated within the ate reagent can be transformed into a super metalating agent, making possible *direct* low-polarity metal–hydrogen exchange reactions with aromatic compounds. As the alkali metal is essential (on their own low-polarity organometallic complexes are generally weak bases) but does not actually perform the deprotonation, these reactions are best interpreted as alkali-metal-mediated metalations. TMP–zincates (TMP is 2,2,6,6-tetramethylpiperidide) of lithium[3] and sodium[4] have been demonstrated to be excellent reagents for triggering direct zincation of a wide range of activated,[5] and most spectacularly, non-activated aromatic compounds.[4g,h] Herein we present the first systematic study and structural definition of the reactivity of a TMP–zincate towards nitrile compounds (Scheme 1). Each of the three nitriles investigated reveals a new unexpected aspect of TMP–zincate chemistry, collectively establishing for the first time the existence and importance of Lewis base separated ion-pair structures within this emerging topic.

There is only one report[3a] of a reaction of this type, namely between the simplest aromatic nitrile, benzonitrile, and lithium TMP-zincate "Li[tBu$_2$Zn(TMP)]", in THF solution (that is, in a bulk Lewis basic solvent). Excellent yields of *ortho*-metalation (up to 96 %) were realized, though the reaction remained structurally opaque as its outcome was determined indirectly by electrophilic interception with iodine and benzaldehyde. A subsequent computational (DFT) study[3f] theorized that *ortho*-zincation is favored over the commonly observed 1,2-addition reaction to $C\equiv N$ owing to a lower energy transition state in which the Zn atom is not involved in activation of the cyano function. For our first study we chose the methyl-substituted benzonitrile, *m*-tolunitrile, since it is an important molecular building block in biomedicinal chemistry[6] and its potential metalation invokes issues of regioselectivity. To our knowledge *m*-tolunitrile has never been metalated, let alone zincated directly. We sought to zincate it by subjecting it to sodium TMP–zincate [(TMEDA)Na(tBu)(TMP)Zn(tBu)] in bulk hexane solution containing excess TMEDA (*N,N,N′,N′*-tetramethylethylenediamine). Zincation was achieved (Scheme 1) but in an unexpected way as the isolated product of the reaction, **1**, has the extraordinary ion-pair composition [(3-Me-C$_6$H$_4$CN)$_2$Na(TMEDA)$_2$]$^+$ [{6-Zn(tBu)$_2$-3-Me-C$_6$H$_3$CN}$_2$Na(TMEDA)$_2$]$^-$.[7] In explanation, two nitrile ligands regioselectively zincated *ortho* to the cyano function (*para* to the methyl group) are found in the anionic moiety, while two neutral, nonmetalated nitrile ligands are found in the cationic moiety. Ionic zincate **1** was obtained initially from a 1:1, zincate base:*m*-tolunitrile stoichiometry, but commensurate with the formula of **1** the yield was improved (from 29.3 to 48.9 %) on changing to a 1:2 stoichiometry with an extra equivalent of TMEDA. Retention of both tBu groups on the newly developed arylzinc units suggested that the TMP–zincate reagent functions as an amido (TMP) base with elimination of TMPH and this was confirmed by detection of TMPH in the filtrate of the reaction. Though such TMP basicity has been postulated theoretically to be kinetically preferable,[3e] this is the first structurally authenticated experimental example found for a reaction performed in hexane or indeed any other solution. It can be reasoned that the released TMPH cannot reaminate the Zn center with concomitant tBuH elimination owing to the absence of an attached Na (Lewis acidic) site (i.e. consistent with a separated ion-pair structure) to which it could "precoordinate", coupled with the fact that other stronger Lewis bases (metalated and non-metalated nitriles; TMEDA) compete with/win against sterically restricted TMPH for the coordination sites around Na. This finding is important as it shows that the basicity of TMP–zincate reagents can be controlled by modulation of ligand coordination. Crystallographic characterization of **1**[7] showed that the dominating feature of the structure of this first ever "sodium sodiumdizincate" complex (Figure 1) is a salt-like N_6 octahedral coordination of the central Na atom in both cationic and anionic moieties.

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[*] Dr. E. Hevia, L. M. Hogg, Dr. G. W. Honeyman, Prof. R. E. Mulvey, Dr. C. T. O'Hara
WestCHEM
Department of Pure and Applied Chemistry
University of Strathclyde
Glasgow, G1 1XL (UK)
Fax: (+44) 141-552-0876
E-mail: r.e.mulvey@strath.ac.uk

Prof. W. Clegg, Dr. S. H. Dale, Dr. L. Russo
School of Natural Sciences (Chemistry)
Newcastle University
Newcastle upon Tyne, NE1 7RU (UK)

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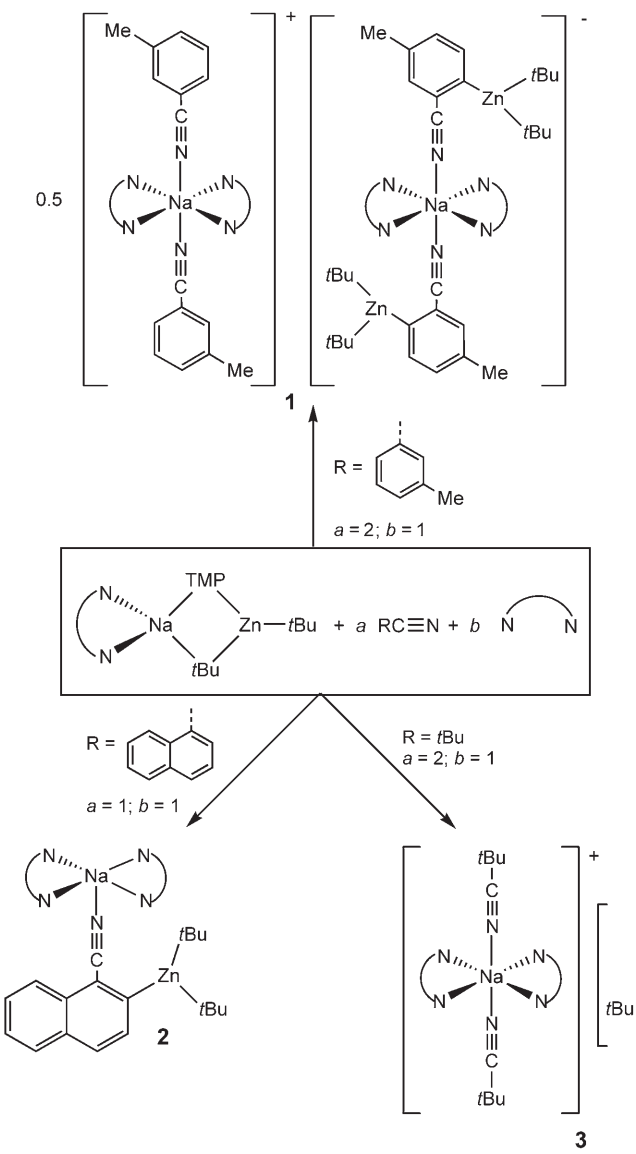

Scheme 1. Reactions of sodium TMP–zincate with aromatic and aliphatic nitriles in the presence of additional *N,N,N′,N′*-tetramethylethylenediamine (TMEDA; $\overset{\frown}{\text{NN}}$) that give isolated crystalline products.

Except for substitution of one H by a tBu$_2$Zn unit in each of the two nitrile ligands of the anion, both ions exhibit near-identical structures with the nitriles occupying *trans* (N-Na-N angle, 180°) positions. Perfect octahedral symmetries are prevented only by the restricted bite angle of the TMEDA ligands (mean N-Na-N, 72.8°) which occupy the four remaining octahedral sites.

Endeavoring to extend the concept of alkali-metal-mediated zincation to polycyclic aromatic nitriles, we next subjected 1-cyanonaphthalene to the same sodium TMP–zincate reagent (Scheme 1). Synergic zincation was successfully accomplished but again it was manifested in a surprising and different way. Thus the isolated product was not an ionic zincate, but the discrete molecular species [(TMEDA)$_2$Na{2-Zn(tBu)$_2$-1-N≡C-C$_{10}$H$_6$}] (**2**).[7] Similar to that in **1**, zincation is delivered through amido (TMP) activity of the base which leaves a Zn(tBu)$_2$ unit at the deprotonated site *ortho* to the cyano function. The molecular structure of **2** (Figure 2) establishes its contacted ion-pair nature, with the bis(TMEDA) chelated Na datively bound to the cyano N atom, making Na five coordinate overall.

Six-coordination of Na (as in **1**), and therefore the opportunity for an ionic zincate structure may not necessarily be prohibited by the large steric demands of the cyanonaphthyl ligand as the reaction producing **2** is not totally clean and other products are formed (see the Supporting Information). Kinetic factors are presumably responsible for this mixture as also observed in reactions of sodium TMP–zincate with anisole.[4f]

To attempt to gain more understanding of the structural maneuvers taking place prior to zincation of the nitrile, we studied the reaction between sodium TMP–zincate and aliphatic trimethylacetonitrile, tBuC≡N, the hydrogen atoms of which are generally not accessible to metalation.[8] Maintaining the trend of surprising outcomes seen with **1** and **2**, this reaction (Scheme 1) also afforded an unexpected crystalline product in the sodium trialkylzincate [{(tBuCN)$_2$Na(TMEDA)$_2$}$^+$(tBu$_3$Zn)$^-$] (**3**).[7] This was produced initially from a 1:1:2 mixture of the TMP–zincate, tBuCN, and TMEDA, but repeating the preparation with a 1:2:2 stoichiometry (matching that in the cationic moiety) improved the yield. The Lewis base separated ion-pair structure of **3** (Figure 3) was confirmed by X-ray crystallography. Mimicking **1**, the cation of **3** exhibits N$_6$ octahedral coordination of Na with *trans*-disposed, neutral tBuCN ligands and equatorially disposed TMEDA ligands. In contrast to the dizincate of **1**, the anion of **3** is a simple monozincate, but its

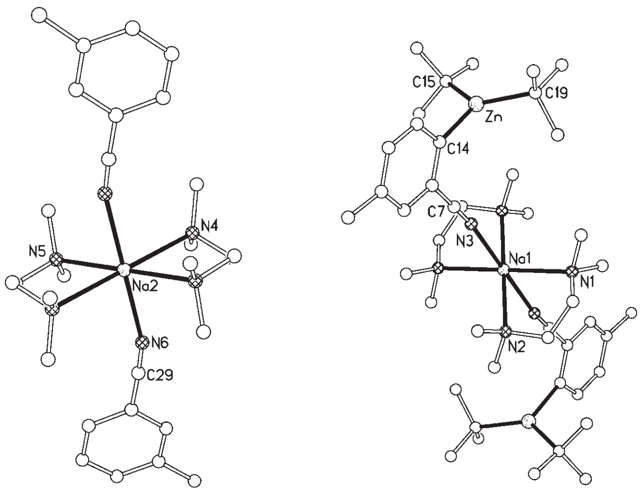

Figure 1. Ion-pair structure of **1** showing cation (left) and anion (right). Hydrogen atoms and minor disorder components are omitted for clarity.

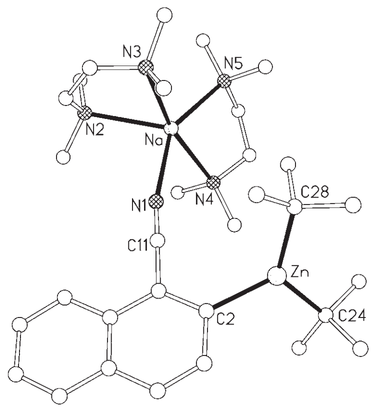

Figure 2. Molecular structure of **2**. Hydrogen atoms and minor disorder components are omitted for clarity.

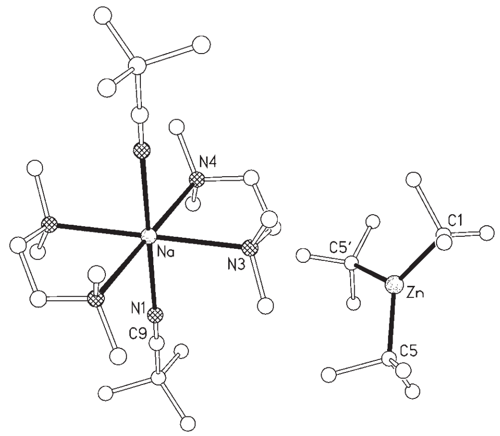

Figure 3. Ion-pair structure of **3** showing cation (left) and anion (right). Hydrogen atoms and second disorder components are omitted for clarity.

composition is not heteroleptic $[t\mathrm{Bu}_2(\mathrm{TMP})\mathrm{Zn}]^-$, which would signify a straightforward scission of sodium TMP–zincate, but the homoleptic trialkylzincate $[t\mathrm{Bu}_3\mathrm{Zn}]^-$, indicating that dismutation has occurred.

Taken together, the three new crystal structures are highly illuminating. They establish that 1) nitrile molecules coordinate preferentially to the Na centers of these bimetallic Na/Zn reagents, and can do so even in the company of TMEDA; 2) Lewis base separated ion pairs play a prominent part in TMP–zincate chemistry; and most significantly, 3) the free zincate anions can engage in complicated dismutation processes.

To conclude, by structurally defining the metal containing products of these reactions with nitriles, a new category of zincate, a sodium sodiumdizincate, has been uncovered, which would have been otherwise missed if the reaction had been investigated indirectly through electrophilic trapping methods. This salt-like organic compound establishes a link between air-sensitive heterometallic organozinc chemistry and air-stable (aqueous-based) heterometallic inorganic zinc chemistry, which is currently attracting attention in areas such as hydrogen adsorption.[9] These findings provide yet more evidence of chemists' continued fascination for zinc chemistry as recently highlighted in a review.[10]

Experimental Section

1: BuNa (2 mmol, 0.16 g) was suspended in hexane (10 mL) and sonicated for 10 min to form a fine dispersion. TMPH (2 mmol, 0.34 mL) was added and the creamy, white suspension formed was stirred for 1 h. $t\mathrm{Bu}_2\mathrm{Zn}$ (2 mmol, 0.36 g) in hexane was then added followed by TMEDA (2 mmol, 0.3 mL) to give a yellow solution which was stirred for around 45 min before *meta*-tolunitrile (2 mmol, 0.24 mL) was introduced. The solution became red and slightly cloudy. Approximately 5 mL toluene was added to give a red/orange homogeneous solution. Crystallization occurred at −24 °C (orange crystals, yield 0.39 g, 29.3 %).

2: BuNa (2 mmol, 0.16 g) was suspended in hexane (10 mL) and sonicated for 10 min to form a fine dispersion. TMPH (2 mmol, 0.34 mL) was added and the creamy, white suspension formed was stirred for 1 h. $t\mathrm{Bu}_2\mathrm{Zn}$ (2 mmol, 0.36 g) in hexane was then added followed by TMEDA (4 mmol, 0.6 mL) to give a yellow solution which was stirred for around 45 min before 1-cyanonaphthalene (2 mmol, 0.3 g) was introduced. The solution became red and a dark precipitate formed almost immediately. Hexane was removed from the mixture in vacuo and 7 mL of toluene was added to give a dark red solution which was stirred for around 45 min. A dark red crystalline solid formed (0.45 g) at −24 °C which was used for the NMR spectroscopic analysis and the X-ray crystallographic study. No absolute yield can be given as this solid contained more than one metallo product (see NMR analysis in the Supporting Information).

3: BuNa (2 mmol, 0.16 g) was suspended in hexane (10 mL) and sonicated for 10 min to form a fine dispersion. TMPH (2 mmol, 0.34 mL) was added and the creamy, white suspension formed was stirred for 1 h. $t\mathrm{Bu}_2\mathrm{Zn}$ (2 mmol, 0.36 g) in hexane was then introduced followed by two molar equivalents of TMEDA (4 mmol, 0.6 mL) to give a yellow solution which was stirred for around 45 min before cooling to −20 °C. *tert*-Butylcyanide (2 mmol, 0.18 mL) was then added to the solution. The solution became orange/red and a dark precipitate formed immediately. The solution was allowed to come to room temperature slowly (over 2 h). 10 mL of toluene were added to give a dark red solution with some fine precipitate. On removing some solvent in vacuo to make the solution more polar, the precipitate dissolved, leaving a dark red/orange solution. A large crop (0.45 g, 35 %) of small, red, needle-like crystals formed overnight (at room temperature) which were employed for the X-ray crystallographic study and characterized by NMR spectroscopy.

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[7] For synthetic details and NMR spectroscopic characterization see the Supporting Information. Crystal data for **1**: $C_{28}H_{46}N_6Na^+C_{44}H_{80}N_6NaZn_2^-$, $M_r = 1336.6$, triclinic, space group $P\bar{1}$, $a = 10.187(3)$, $b = 12.209(4)$, $c = 17.637(5)$ Å, $\alpha = 73.426(5)$, $\beta = 87.412(5)$, $\gamma = 76.154(5)°$, $V = 2041.0(11)$ Å^3, $Z = 1$ (both ions on inversion centers), $\rho_{calcd} = 1.087\ g\,cm^{-3}$, $T = 150$ K, $\mu(Mo\ K\alpha) = 0.64\ mm^{-1}$ ($\lambda = 0.71073$ Å); 14870 reflections measured, 6448 unique, $R_{int} = 0.015$; R (F, $F^2 > 2\sigma$) = 0.045, wR (F^2, all data) = 0.128, S (F^2) = 1.026, 493 refined parameters and 433 restraints, constrained H atoms, difference map extremes +1.12 and −0.62 e Å^{-3}. Crystal data for **2**: $C_{31}H_{56}N_5NaZn$, $M_r = 587.2$, monoclinic, space group $P2_1/c$, $a = 12.1597(14)$, $b = 13.6753(17)$, $c = 21.433(4)$ Å, $V = 3550.7(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.098\ g\,cm^{-3}$, $T = 150$ K, $\mu(Mo_{K\alpha}) = 0.73\ mm^{-1}$; 37071 reflections measured, 6851 unique, $R_{int} = 0.054$; R (F, $F^2 > 2\sigma$) = 0.046, wR (F^2, all data) = 0.111, S (F^2) = 1.031, 459 refined parameters and 626 restraints, constrained H atoms, difference map extremes +0.69 and −0.53 e Å^{-3}. Crystal data for **3**: $C_{22}H_{50}N_6Na^+C_{12}H_{27}Zn^-$, $M_r = 658.4$, monoclinic, space group $C2/c$, $a = 19.018(4)$, $b = 11.656(2)$, $c = 20.795(4)$ Å, $\beta = 94.58(3)°$, $V = 4595.0(15)$ Å^3, $Z = 4$ (cation on an inversion center, anion disordered on a twofold rotation axis), $\rho_{calcd} = 0.952\ g\,cm^{-3}$, $T = 150$ K, $\mu(Mo_{K\alpha}) = 0.57\ mm^{-1}$; 26012 reflections measured, 4018 unique, $R_{int} = 0.049$; R (F, $F^2 > 2\sigma$) = 0.056, wR (F^2, all data) = 0.134, S (F^2) = 1.050, 250 refined parameters and 132 restraints, constrained H atoms, difference map extremes +0.34 and −0.18 e Å^{-3}. CCDC 661569 (**1**), 661570 (**2**) and 661571 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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