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Supramolecular Metallocycle

Dizincation of a 2-Substituted Thiophene: Constructing a Cage with a [16]Crown-4 Zincocyclic Core**

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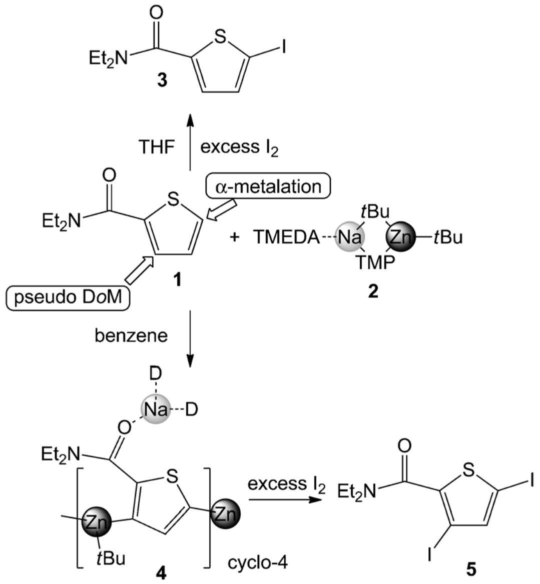
The heterocyclic thiophene (SC_4H_4) ring is one of the most fundamentally important molecular scaffolds. It is incorporated within a plethora of structures used in applications ranging from medicinal chemistry[1] to materials science.[2] Data from 2011 reveal that five of the top one hundred best selling pharmaceuticals in the USA feature a thiophene scaffold.[3] Polythiophenes and oligothiophenes are extensively researched as these conjugated systems make excellent environmentally and thermally stable materials that can be employed as, for example, electrical conductors, light-emitting diodes (LEDs), batteries, and solar cells.[2] Synthetic chemistry plays a vital role in all of these applications in constructing the substituted thiophenes needed for such applications starting from the parent heterocycle or simple derivatives. Lithiation is a common tool for executing regioselective C–H to $C^{\delta-}$–$Li^{\delta+}$ transformations in thiophene rings to facilitate tandem substitution reactions. A pertinent example to the present work is lithiation of *N*,*N*-diethylthiophene-2-carboxamide (**1**) by using *s*BuLi/TMEDA (*N*,*N*,*N′*,*N′*-tetramethylethylenediamine) in THF solution.[4] This illustrates the competition between α-lithiation (at the 5-position) and (pseudo) directed *ortho*-metalation (D*o*M) mediated by the carboxamide arm (at the 3-position; Scheme 1), with the former winning out on adding one equivalent of the base. More recently, thiophene and derivatives have been metalated by the original Hauser base “(*i*Pr$_2$N)MgCl”,[5] Knochel’s new Turbo model “(TMP)MgCl·LiCl”,[6] and Mongin’s cadmate “LiCd(TMP)$_3$” (TMP = 2,2,6,6-tetramethylpiperidide)[7] benefiting from ambient temperature protocols (cf., low-temperature lithiation) and direct magnesiation or cadmation (without the need for an additional transmetalation step).



Scheme 1. Solvent-dependent reactions of thiophene **1** with sodium TMP–zincate **2**.

Stimulated by the intriguing lithiation patterns established for **1**, we wanted to test the regioselectivity of our zincate base [(TMEDA)Na(TMP)(*t*Bu)Zn(*t*Bu)] (**2**)[8] and rather than assuming the intermediacy of the metalated thiophene, go a step further by seeking its isolation and full characterization. Reported herein, this study illustrates how an unwanted complication to a synthetic chemist can turn out to be an unearthed treasure to a supramolecular chemist. Thus the 1:1 reaction between **1** and **2** in benzene solution “failed” in that it never gave a selective single-site deprotonation as anticipated but rather gave a much more challenging to achieve 3,5-double deprotonation through dual TMP/*t*Bu basicity. However, from a structural/supramolecular perspective the reaction proved a great success as the double zinc–hydrogen exchange was manifested in a new type of metallacrown cage compound, a remarkable find that would have remained hidden if the metallothiophene intermediate had been used in situ in tandem bond-forming applications.

To establish an exact comparison with the aforementioned metalation studies, we initially tested a 1:1 mixture of carboxamide **1** with base **2** at ambient temperature in THF solution (Scheme 1). ^{1}H NMR monitoring of an NMR scale reaction over time revealed the complete consumption of **2**

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and the emergence of one major metalated thiophene product. Repeating the reaction on the bench and performing an iodine quenching in tandem confirmed it as *N*,*N*-diethyl-5-iodothiophene-2-carboxamide (**3**, isolated in 79 % yield). Thus base **2** executes deprotonation selectively at C(5) (α-metalation) in THF in concordance with the previously reported but low-temperature regime organolithium-mediated transformations. Unable to grow crystals of any metalated thiophene intermediate from this polar medium, we repeated the reaction of **1** and **2** in benzene solution, obtaining the final pure product (**4**) as yellow crystals (47 %).

To our surprise characterization of these crystals revealed not—as anticipated—a monozincated thiophene, but rather the dizincated thiophene of composition [{$D_2Na[\mu\text{-}3,5\text{-}[2\text{-}C(O)NEt_2]\text{-}C_4H_1S]Zn(t\text{Bu})\}_4$] (**4**; where D represents donor sites on sodium occupied by either bidentate TMEDA or two monodentate THF ligands).[9] Moreover, X-ray crystallographic studies heightened the surprise by revealing an octanuclear (made up of 4 Zn and 4 Na atoms), tetrameric molecular structure (Figure 1) that establishes a new type of zincocycle. Its cyclic framework consists of four doubly deprotonated (at 3- and 5-positions) thiophene subunits linked by the newly formed carbanionic C centers to four zinc atoms in a tetramer with crystallographically imposed C_2 symmetry. Arranged in two distinct sets, the four zinc atoms form a distorted tetrahedron that helps give the core metalacycle an irregular bowl shape. By exhibiting this $(ZnCCC)_4$ cyclic framework, the dizincated thiophene can be considered a polarity-reversed analogue of the [16]crown-4 macrocycle where $Zn^{\delta+}\text{–}C^{\delta-}$ ring links replace $O^{\delta-}\text{–}C^{\delta+}$ ring links (Figure 2 a). Endocyclic C-Zn-C angles within the 16-atom ring of **4** are distorted from 120° [C(23)-Zn(1)-C(1), 111.85(15)°; C(3)-Zn(2)-C(21), 109.36(15)°]. In addition to linking C atoms of two individual thiophene molecules [bond lengths: Zn(1)–C(1), 2.036(4) Å; Zn(1)–C(23), 2.023(4) Å; Zn(2)–C(3), 2.021(4) Å, Zn(2)–C(21), 2.047(4) Å], each Zn carries a terminal *t*Bu ligand. Distances between adjacent Zn atoms are 6.2218(8) Å and 6.2254(6) Å, while transannular Zn···Zn distances are 7.7644(8) Å [Zn(1)–Zn(1′)] and 7.7990(6) Å [Zn(2)–Zn(2′)], hinting at a larger cavity than that in Saalfrank and Waldmann's [Zn_4(picoline-tetrazolylamide)$_8$] cluster in which a [16]MC-4 (MC represents metallacrown) is apparent where Zn ions link through N-C-N bridges with adjacent and diagonal distances of 5.658 and 7.349 Å, respectively (Figure 2 b).[10] Sodium atoms in **4** are primarily bound to two donor solvent atoms and the carbonyl O atom, although there are also secondary Na···C_{aryl} interactions one of which [Na(1)–C(21)] is anomalously short [2.647(5) Å]. Thiophene rings tilt 46.1(1)° and 51.7(1)° relative to each other [S(1)–S(2′) and S(1)–S(2), respectively] and with distances in the range 16–17 Å from diagonally opposite ethyl arms, which allows **3** to be classed as a nanomolecule.

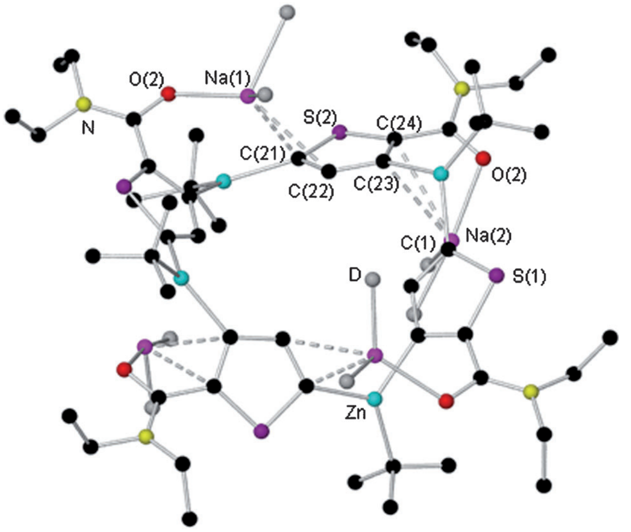

Figure 1. Molecular structure of **4** with selective atom labeling. Hydrogen atoms and donor solvent backbone are omitted for clarity. The long Na···C_{aryl} contacts are highlighted by dashed lines. Selected bond lengths [Å]: Na(1)···C(3) 3.050(4), Na(1)···C(21) 2.647(5), Na(1)···C(22) 2.923(4), Na(1)–O(1) 2.276(3), Na(2)···C(1) 3.027(4), Na(2)···C(23) 2.999(4), Na(2)···C(24) 3.053(4), Na(2)–O(2) 2.311(4).

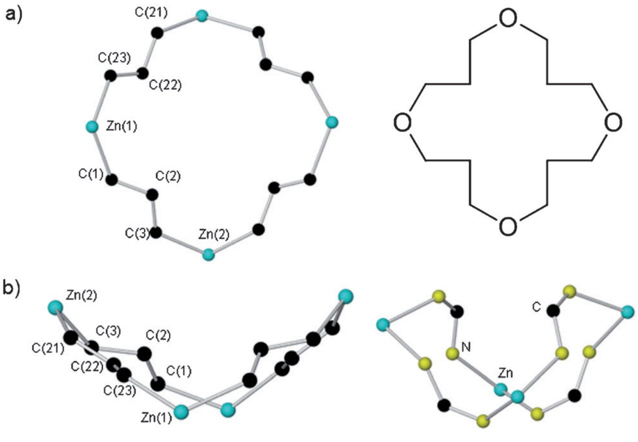

Figure 2. a) "Anti-crown" core of **4** from top face view (left) with selective atom labeling and the [16]crown-4 ether architecture (right). b) Side edge view of the core of **4** with selective atom labeling, illustrating its bowl conformation (left) and the less open structure of the previously reported [16]MC-4 zincocycle with N-C-N bridges (right). Selected bond lengths [Å] and angles [°]: Zn(1)–C(1) 2.036(4), Zn(1)–C(23) 2.023(4), Zn(2)–C(3) 2.021(4), Zn(2)–C(21) 2.047(4); C(1)-Zn(1)-C(23′) 111.85(15), C(3)-Zn(2)-C(21) 109.36(15).

Recalling that **4** was produced from a 1:1 mixture of base to substrate, coupled with the retention of only one basic arm of **2** in its structure, suggests that the zincate has acted as a dual base. While poly-deprotonation of a single substrate has precedence in sodium TMP–zincate chemistry, for example where **2** has previously effected bis-deprotonation with benzene[11] or naphthalene,[12] two equivalents of the base have been necessary as it has acted in a monobasic capacity and moreover the bis-deprotonations have been executed symmetrically as opposed to the unsymmetrical situation expressed in **4**. In contrast, in constructing **4**, zincate **2** functions as an ambi (alkylamido) base.[13] Note that the net effect of the reaction sequence producing **4** represents the first example in TMP–zincate chemistry where polybasicity of the initial reagent (through two arms of the base) and polymetalation of a single substrate have been achieved simultaneously. It is significant that the dimetalation occurred in benzene but not in THF solution.[14] The solvating, structure-stabilizing ability of each solvent may hold the key to this reactivity distinction.[15] In polar, strongly coordinating THF solution, the strong solvation should coordinatively saturate and hence stabilize the monometalated thiophene intermediate, diminishing its reactivity and precluding it from executing a second metalation. However, in poorly solvating benzene, the weaker solvation would lessen the stability of the zincate, make it more reactive and thus primed to deprotonate the thiophene ring of an adjacent molecule at the inductively/coordinatively acidified 3-position, rather than at the 4-position which would result in adjacent carbanions. Another way to view this is that in benzene the monozincated intermediate is more prone to aggregation and so, as two molecules attempt to combine intermolecularly, a second deprotonation of the thiophene ring can ensue.

Schlosser et al. have previously assessed the practicality of dimetalations, studying alkyl-substituted benzenes and *N*,*N*-crowded anilines.[16] Dimetalation was found to occur only with excess of highly concentrated Lochmann–Schlosser *n*BuLi/*t*BuOK superbasic mixtures in hydrocarbon media, and even then it occurred only incompletely in a moderate best yield of 41 %. Dimetalation was considered kinetically, but not thermodynamically favored over monometalation, and thought to proceed by an aggregation phenomenon with evidence suggesting that the second deprotonation is accomplished within a tightly packed mixed aggregate (comparable to the benzene case in our zincate system). Significantly, in THF no trace of dimetalated species was found, although such species are stable in this solvent at −75 °C by generating a 5-monometalated intermediate and then introducing a second metal separately.[4c]

New zincate **4** was also characterized by NMR spectroscopy in [D$_8$]toluene solution (see Supporting Information). Most informative is the sole aromatic singlet at 7.84 ppm in the ^{1}H spectrum providing a diagnostic marker for bis-deprotonation and its placement between two zincated carbons is reflected in its downfield shift relative to those in starting thiophene **1** (7.08, 6.90 and 6.65 ppm). Further confirmation of the di-deprotometalation within **4** came from treating it in situ with a THF solution of iodine. Sensitive to the dryness of the THF, the reaction carried out with care produces *N*,*N*-diethyl-3,5-diiodothiophene-2-carboxamide (**5**) quantitatively (see Supporting Information).

A search of the Cambridge Crystallographic Database revealed no hits for a zincated, mono- or di-deprotonated thiophene structure.[17] The one magnesiated example, $[(\mathrm{TMEDA})\mathrm{Na}(\mu\text{-}2\text{-}\mathrm{C_4H_3S})_3\mathrm{Mg}(\mathrm{TMEDA})]$,[18] contrasts with **4** in having three α-monodeprotonated thiophenes bridging Mg to Na, accomplished through monometalation as opposed to polymetalation. Furthermore, to the best of our knowledge, **4** represents the first crystallographically characterized [16]MC-4 complex of any metal where the organic constituents of the hexadecanuclear ring are all C atoms. Given this surprising find of **4**, we now plan to initiate a research project to establish how many other unprecedented structures are hidden in the literature on "unwanted" dimetalated or polymetalated heterocyclic or other organic substrates.

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[9] Single-crystal X-ray diffraction revealed the original product to be a TMEDA-solvated tetramer as described ($D_2 = $ TMEDA). However, the quality of the refined structure was low. This material was recrystallized from a hexane/THF mixture and gave a better crystal structure as shown in Figure 1 [$D_2 = $ TMEDA/2 THF modeled in a 41:59 ratio at Na(1) and a 75:25 ratio at Na(2)]. The original TMEDA solvate was used as **4** in all future reactions. Crystal data for **4**: $\mathrm{C_{87.36}H_{160}N_{8.64}Na_4O_{9.36}S_4Zn_4}$; a colorless block gave monoclinic space group $C2/c$, $a = 32.9619(8)$, $b = 12.4438(3)$, $c = 29.2420(7)$ Å, $\beta = 118.645(3)°$, $V = 10526.2(4)$ Å^3, $T = 123(2)$ K, $Z = 4$, $r_{\mathrm{calcd}} = 1.239$ Mg m^{-3}, $\lambda(\mathrm{Mo_{K\alpha}}) = 0.71073$ Å, $R1 = 0.0586$ [for 8830 reflections with $I > 2\sigma(I)$] $\omega R2 = 0.1770$ and $S = 1.075$ for 622 parameters and 12035 independent reflections. Max/min residual electron density 0.851/−0.677 e Å^{-3}. Structures were solved and refined to convergence on F^2 (SHELXS and SHELXL-97; G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122). CCDC 878393 contains 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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