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Accessible heavier s-block dihydropyridines: structural elucidation and reactivity of isolable molecular hydride sources

Samantha A. Orr, Alan R. Kennedy, John J. Liggat, Ross McLellan, Robert E. Mulvey* and Stuart D. Robertson*

The straightforward metathesis of 1-lithio-2-*t*butyl-1,2-dihydropyridine using metal tert-butoxide (Na/K) has resulted in the first preparation and isolation of a series of heavier alkali metal dihydropyridines. By employing donors, TMEDA, PMDETA and THF, five new metallodihydropyridine compounds were isolated and fully characterised. Three distinct structural motifs have been observed; a dimer, a dimer of dimers and a novel polymeric dihydropyridylpotassium compound, and the influence of cation π-interactions therein has been discussed. Thermal volatility analysis has shown that these complexes have the potential to be used as simple isolable sodium or potassium hydride surrogates, which is confirmed in test reactions with benzophenone.

Introduction

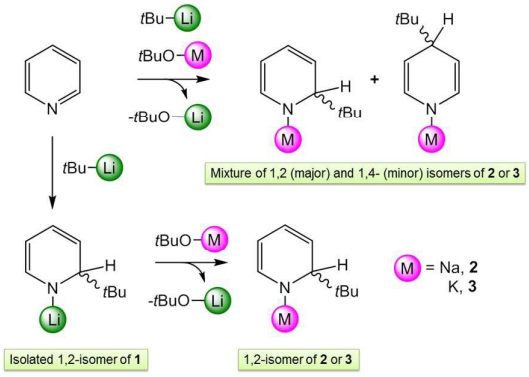
Thirty years after the mid 1800's discovery of pyridine and related aromatic CN heterocycles in Glasgow by Anderson,[1] Hantzsch serendipitously prepared 1,4-dihydropyridines (DHPs) during his seminal development of a suite of substituted pyridines.[2] Today the landscape of DHP chemistry[3] is panoramic extending into areas such as biochemistry,[4] pharmacology,[5] agrochemistry[6] and synthesis.[7] The unearthing of the naturally occurring coenzyme nicotinamide adenine dinucleotide (NADH) highlighted the biological activity of DHPs and stimulated more interest in their isolation and redox chemistry. 1,4-DHP isomers have also commanded attention due to their prevalence in cardiovascular pharmaceuticals, for example, Nifedipine, a calcium channel blocker used to treat hypertension. Additionally, antihypertensive 1,4-DHPs have also been reported as successful cystic fibrosis transmembrane conductance regulator (CFTR) correctors.[8] Whilst the pharmacologically active 1,4-scaffold is well-documented, the 1,2-isomer is also a fundamental synthetic precursor to more sophisticated scaffolds, for example, participating as a diene in Diels-Alder reactions to construct isoquinuclidines and intermediates to anti-cancer agents and flu remedies (e.g., Tamiflu).[9]

Reflecting the importance of DHPs, there are over 4000 entries of 1,2 and 1,4-isomers in the Cambridge Structural Database (CSD).[10] However it is somewhat surprising that less than 3% of these are metallodihydropyridines (MDHPs). The reported MDHP structures contain a range of p-, d- and f-block metals. Contrastingly, those of s-block metals have been largely neglected with only two Li 1,4 DHPs representing group 1.[11] While no Na or K examples are known, a zinc DHP containing K in the outer sphere that stabilises the complex via π-contacts is known.[12] Similarly, Group 2 DHP chemistry has been little studied though recently Mg[13] and Ca[14] DHPs have been structurally characterised and investigated in hydroboration and hydrosilylation reactions. In a previous report we shed new light on the long studied 1,2 nucleophilic addition of alkyllithium compounds to pyridine.[15] Modifying the stoichiometry from excess pyridine to unity led to the discovery of a hexane soluble, isolable lithium 1,2-DHP (1-lithio-2-*t*butyl-1,2-dihydropyridine) **1**, that could be recrystallized, isolated and crystallographically characterised as a monomer through complexation by tetradentate Me_6TREN [tris(*N*,*N*-dimethyl-2-aminoethyl)amine]. A successful extension of this route to isolate *s*- and *i*-butyl LiDHP derivatives followed, along with theoretical studies supporting the original *t*butyl experimental findings.[16] This background coupled with the dual σ/π bonding potential of 1,2-DHPs prompted us to consider whether it would be possible to synthesise, isolate and crystallographically characterise presumably more challenging, less stable DHP complexes of more π-philic[17] alkali metals. This would enable the first systematic study of a congeneric series of Li, Na and K DHPs, allowing the exploration of any significant changes in σ and π metal-DHP interactions on descending group 1, which we have carried out and herein report.

Results and discussion

Initially we probed the direct 1,2 addition of typical alkyl sodium and potassium reagents, such as *n*BuNa and KCH_2SiMe_3, to pyridine. However, given the limited scope for varying the alkyl group on heavier alkali metals and that the initial reactions produced intractable black solids, this route was abandoned.

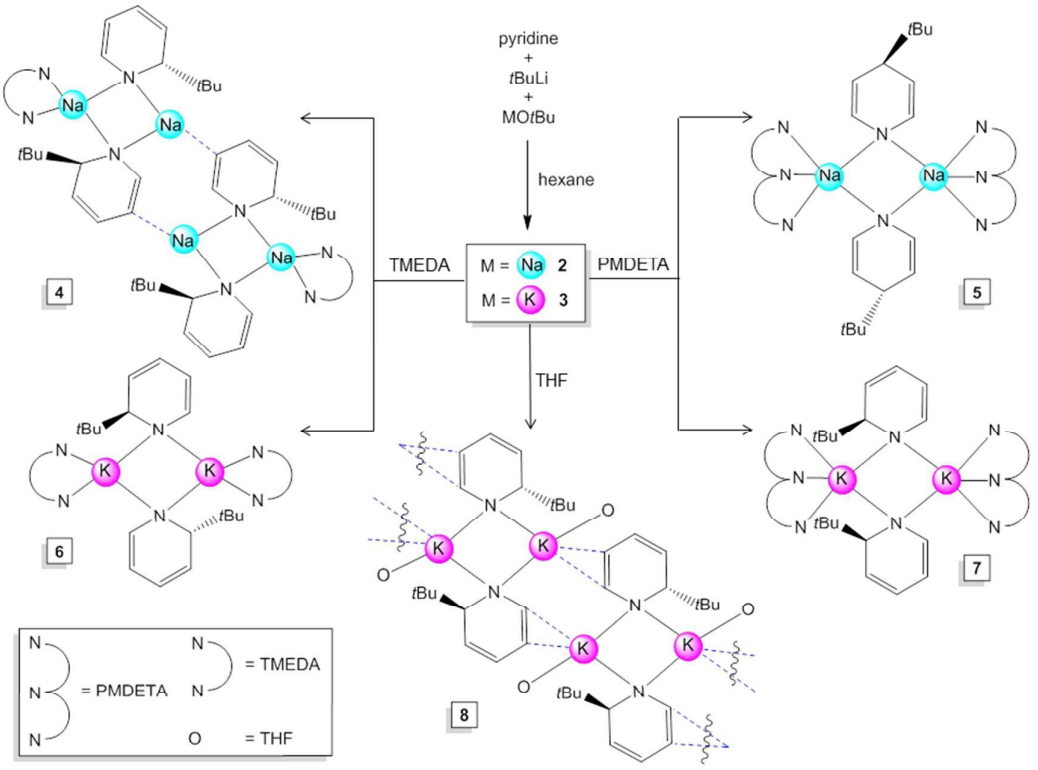
Consequently, this work describes a successful straightforward route via s-block metathesis of our 1-lithio-2-*t*butyl-1,2-dihydropyridine, **1**, to novel, isolable heavier alkali metal DHPs (scheme 1). The resulting products exhibit remarkable structural diversity, presenting to the best of our knowledge, the first crystallographically characterised sodium and potassium DHPs including an unprecedented example of a polymeric metallodihydropyridine.



Scheme 1: Metathetical synthesis of heavier s-block metallodihydropyridines **2** and **3** via an *in-situ* or isolated route to **1**.

The 1,2 LiDHP [1-Li-2-*t*Bu(NC_5H_5)] **1**, can be selectively crystallised and isolated in an 80% yield, although the *in situ* mixture interestingly contains both 1,2 and 1,4-isomers in a 4:1 respective ratio. Initially **1** was made *in situ* and reacted with MO*t*Bu (M= Na, K) accessing the Na and K metallodihydropyridines, [1-Na-2-*t*Bu(NC_5H_5)] and [1-Na-4-*t*Bu(NC_5H_5)] **2** and [1-K-2-*t*Bu(NC_5H_5)] and [1-K-4-*t*Bu(NC_5H_5)] **3,** as insoluble powders which precipitated from hexane. These were isolated in yields of 87 and 93% respectively and characterised by NMR spectroscopy. In each case ^{1}H NMR spectra in d_8-THF (figures S2 and S6) shows the presence of both 1,2 and 1,4 isomers, with 5 equal intensity resonances for the asymmetric 1,2-isomer and 3 resonances corresponding to the symmetric 1,4-isomer in a 2:2:1 ratio. The 1,2-isomer is the major product, again in a 4:1 ratio. When starting with recrystallized **1** (that is, pure 1,2-isomer), the metathesis reactions result only in 1,2 isomers being formed. Solution NMR spectroscopic studies of the Na and K 1,2-isomers were carried out, to determine if there is a conversion from the 1,2 isomer to the 1,4 isomer over time. However, even with prolonged heating, no sign of this alkyl transfer was seen.

Next we attempted to make Lewis donor adducts of these non-crystalline materials in order to divulge more structural information. X-ray quality crystals were grown by slowly adding the polydentate donors TMEDA (*N,N,N',N'*-tetramethylethylenediamine), PMDETA (*N,N,N',N'',N''*-pentamethyldiethylenetriamine), or monodentate donor THF to suspensions of **2** or **3** in hexane until homogeneity was obtained. X-ray crystallographic studies of the resulting crystalline products revealed five new metallodihydropyridine structures (Scheme 2): [{{Na(1,2-*t*Bu-DHP)}$_2$(TMEDA)}$_2$] **4**, [{Na(1,4-*t*Bu-DHP)(PMDETA)}$_2$] **5**, [{K(1,2-*t*Bu-DHP)(TMEDA)}$_2$] **6**, [{K(1,2-*t*Bu-DHP)(PMDETA)}$_2$] **7** and [{K(1,2-*t*Bu-DHP)(THF)}$_\infty$] **8**.



Scheme 2: CHEMdraw representation of the crystallographically characterised Na and K DHPs in the presence of donors, TMEDA, PMDETA and THF. For clarity only interdimer cation-π interactions are shown. Only a single enantiomer is shown for clarity although racemic mixtures were obtained.

Adducts **5**, **6** and **7** are discrete dimers, a common motif in alkali metal chemistry[18] (fig. 1). Each has a four atom $(MN)_2$ ring, where the bridging amide is a *t*Bu substituted dihydropyridyl unit, and the metal coordinated by either TMEDA or PMDETA. However, **5** is anomalous in having its *t*Bu located at the 4-position (C3), compared with **6** and **7** where it is at the 2-position, C5. We note however that the ~~re~~crystallized product **5** was a microcrystalline solid which contained a few larger, X-ray quality crystals. A ^{1}H NMR study of this bulk product in cyclo-C_6D_{12} showed only the 1,2-isomer, suggesting the major, microcrystalline material was 1,2-, though it is clearly also possible to recrystallize a donor stabilised 1,4 isomer starting from *in-situ* prepared **2**. As the only complex soluble in non-donating solvent, **5** was also subjected to a DOSY NMR study[19] in an attempt to determine its solution structure (fig S22). Such a technique has seen considerable use recently for the determination of solution structures of organometallic (particularly alkali-metal) species.[20] This revealed that the molecular weight is higher than that of the largest internal standard (1,2,3,4-tetraphenylnaphthalene, 432.55) and so the results must be treated with caution. That said, the estimated molecular weight, as determined from a logarithmic plot of diffusion coefficient versus formula weight (graph S1, table S1), is calculated as being 633.28, based on the well isolated and resolved dihydropyridyl ring proton resonances. This value represents an error of less than 5% from the molecular weight of dimeric [{Na(1,2-*t*Bu-DHP)(PMDETA)}$_2$] (MW = 665.02), although we acknowledge that an unsolvated tetrameric complex [{Na(1,2-*t*Bu-DHP)}$_4$] is an even better fit (636.84, 0.56% error). However, two further pieces of evidence allow us to conclude that the solvated dimer arrangement is likely the true solution structure; firstly, the PMDETA resonances do not correlate with free PMDETA in the same solvent (fig S23), suggesting that it is still bound to the Lewis acidic metal and secondly an unsolvated complex is unlikely to be soluble in such a medium (c.f. complex **2**, which requires Lewis donating THF to solubilize it for NMR studies). We note that PMDETA has a different diffusion coefficient than the organometallic fragment to which it is bound, however, this has frequently been witnessed previously for Lewis donor:acceptor adducts through DOSY NMR whereby the dissociation/association of the neutral donor to the metal is occurring.[21] In this instance the calculated molecular weight of PMDETA is 260.25, noticeably larger than that in its free state (173.3) and indicative of being loosely coordinated in solution.

Comparing the structures of dimers, **5**, **6** and **7**, the location of the *t*Bu has a strong influence on the bond lengths of the $(MN)_2$ ring (table 1). In **5**, the Na1-N1 and Na1-N1', [2.4204(2) and 2.4511(2)] respectively, are very similar. However in **6** and **7** when the *t*Bu group is at the 2-position, a distinction between the two types of M-N bonds in the $(MN)_2$ ring can be made. For example, in **6**, K1-N1', [2.7492(1)] is shorter than K1-N1 [3.0014(1)], a trend also seen in **7**, [K1-N1' and K1-N1; 2.774(13) and 3.056(16) respectively]. This difference in bond lengths indicates a shorter σ-bond and longer π-interaction which can be attributed to **6** and **7** having a conjugated C=C-C=C π system interacting with the second metal cation unlike **5**. The π-interaction within the dimer is emphasised when the M1-N1-M1' bond angles are compared. Typically, amido dimers such as $(D{\cdot}MTMP)_2$ and $(D{\cdot}MHMDS)_2$ (TMP = 2,2,6,6-tetramethylpiperidide; HMDS = 1,1,1,3,3,3-hexamethyldisilazide; D = THF/TMEDA) display an acute bond angle in the region 75-85°, which **5** obeys [84.92(2)°].[22] However, **6** and **7** do not conform to this trend, instead they expand into obtuse bond angles [94.91(1) and 96.2(4)°], respectively, as a consequence of these intramolecular cation π-interactions. Interestingly, alongside the difference in M-N distances and bond angles, the influence of dimerization interactions in **6** and **7** is manifested in a tilting of the dihydropyridyl ring towards one metal centre, which is supported by the difference in M-C and M-C' bond lengths (table 1). In the case of **5**, where we don't observe any interactions between Na and the dihydropyridyl ring, the values are fairly similar. However, in the potassium dimers, **6** and **7**, where there are K-π interactions, some values are over 1 Å in difference due to the tilting of the ring. In order to quantify this tilting further we have measured the N-N-C_{para} angle. For **5**, the angle is 163.11(3)°, suggesting no significant ring tilting towards the metal, whereas in **6** and **7**, the rings are tilted considerably closer to the metal [109.21(1) and 115.1(5)° respectively] presumably to maximise the stabilising cation-π-interactions. Although **6** and **7** display a similar $(KN)_2$ ring motif, the overall structures differ due to the influence of the donors; TMEDA or PMDETA. Their bridging dihydropyridyl moieties adopt a conventional *trans*oid and a more unusual *cis*oid geometry, respectively.[23] $(MN)_2$ dimeric rings also feature in **4** (fig. 2) and **8** (fig. 3), but interestingly reducing the number of donor atoms (i.e. for sodium changing from the tridentate donor PMDETA to the bidentate donor TMEDA and for potassium moving to the monodentate donor THF from bidentate TMEDA) means discrete ring dimers are no longer observed. Instead they act as the basic building blocks of higher aggregated, intricate assemblies, each of which is distinct.

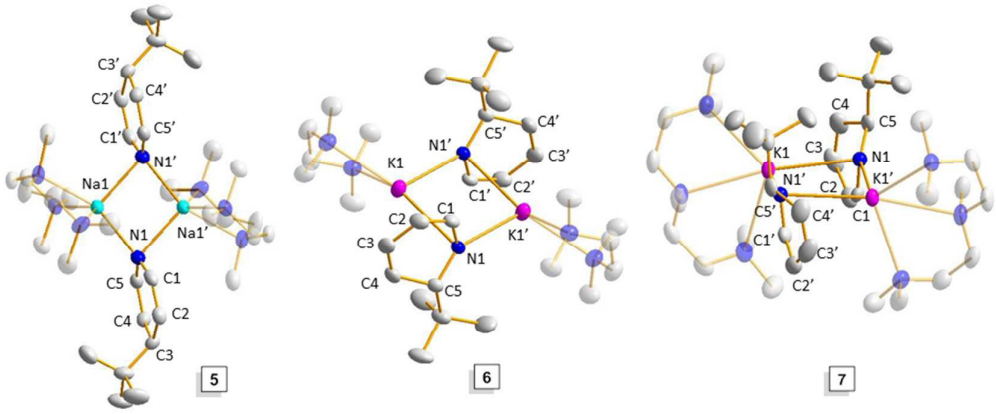


Fig 1. Molecular structure of **5**, **6** and **7** with thermal ellipsoids drawn at the 50% probability level and hydrogen atoms and minor disordered component omitted for clarity. Symmetry transformations used to generate equivalent atoms labelled ': (**5**) -x, -y, 1-z, (**6**) 0.5-x, 1.5-y, -z and (**7**) 1.5-x, y, 1.5-z. π-interactions of **6** and **7** have been omitted for the sake of clarity, a figure showing them is included in the Supporting Information (fig S24).

Table 1. Bond distances [Å] and angles [°] for **5, 6** and **7** compared with typical amido dimer bond parameters

	5	**6**	**7**
M1-N1	2.4204(2)	3.0014(1)	3.056(16)
M1-N1'	2.4511(2)	2.7492(1)	2.774(13)

M1-	C1	C1'	3.2105(2)	2.9452(2)	2.9532(1)	3.2447(1)	3.122(7)	3.193(7)
	C2	C2'	4.4538(3)	4.0334(4)	3.2257(1)	4.6165(2)	3.479(5)	4.559 (5)
	C3	C3'	5.1915(4)	4.8529(4)	3.1939(1)	5.3856(3)	3.416(6)	5.385(6)
	C4	C4'	4.6351(4)	4.3195(4)	3.2796(2)	5.1315(3)	3.423(6)	5.191(6)
	C5	C5'	3.4470(3)	3.3015(2)	3.6589(2)	4.0529(2)	3.722(3)	4.096(3)
M1-N1-M1'			84.92(2)		94.91(1)		96.2(4)	

X-ray crystallographic studies revealed adduct **4**, $[Na_4(1,2\text{-}t\text{Bu-DHP})_4(TMEDA)_2]$, to be a discrete, centrosymmetric tetranuclear dimer of dimers (fig. 2). It consists of two simple (NaNNaN) dimeric rings within which the nature of the bonding is distinguishable. The bond lengths of Na1-N2, Na2-N1 and Na2-N2, [2.4465(15), 2.343(2) and 2.4472(14) Å], are consistent with typical σ Na-N(amide) bonds.[22] The anomaly is Na1-N1 with an extended length of 2.631(2) Å, which is more characteristic of Na being engaged in a π-interaction with the ring (*vide supra*).[24] This side-on bonding mode exhibits Na1-C_{ring} interactions spanning 2.710(3)-2.996 (3) Å which are in agreement with reported Na-C π-interactions.[25] These dinuclear subunits are stitched together by further cation-π interactions between Na1 and the dipyridyl moiety of the neighbour, Na1-C11' 2.6055(17) Å, to form a central 8-atom $(NaNCC)_2$ ring. This ring is essentially planar through 6 atoms, Na1-C10-C11-Na1'-C10'-C11', with the N2 puckered out of the ring, residing 1.038 Å above the plane. Both the μ_2-bridging and μ_3-bridging dihydropyridyl groups are analogous to the reported LiDHP in showing loss of aromaticity, and an sp^3-αC which is corroborated by the bond lengths of the dihydropyridyl ring, [N1-C5, 1.467(3); C4-C5, 1.508(3) and N2-C14, 1.475(2); C13-C14, 1.503(3) Å]. The molecular structure is completed by a TMEDA molecule chelating the outermost Na atom.

In contrast to LiDHP, **4** exhibits poor solubility in arene solvents so its NMR spectra were recorded in d_8-THF ~~which confirmed its empirical formula~~. The ^{1}H NMR spectrum revealed five equal intensity resonances attributable to the asymmetric dihydropyridyl ring H atoms (3.21, 3.84, 4.17, 5.91 and 6.80 ppm) and a singlet (0.84 ppm) concordant with addition of the *t*Bu at the 2-position. The 1:2 ratio of TMEDA to dihydropyridyl rings was also confirmed in solution.

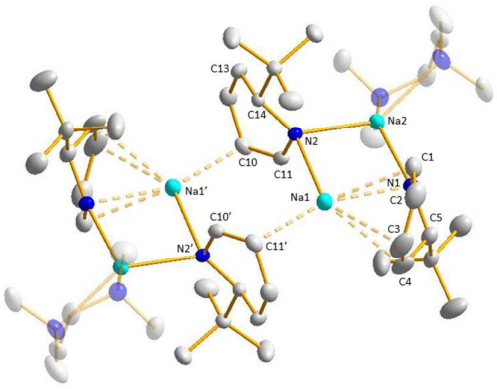


Fig. 2 Molecular structure of $[Na_4(1,2\text{-}t\text{-Bu-DHP})_4(TMEDA)_2]$, **4** with thermal ellipsoids drawn at the 50% probability level and hydrogen atoms and minor disordered component omitted for clarity. Dashed bonds represent bonds with significant π-character. Symmetry transformations used to generate equivalent atoms labelled ': 1-x, 2-y, 1-z.Selected bond lengths (Å) and angles (°): Na1-N1, 2.631(2); Na1-N2, 2.4465(15); Na2-N1, 2.343(2); Na2-N2, 2.4472(14); Na1-C1, 2.710(3); Na1-C3, 2.834(3); Na1-C4, 2.825(2); Na1-C11', 2.606(2); Na1-C10', 3.193(2); Na1-N2-Na2, 86.92(5); N2-Na2-N1, 97.66(7); Na2-N1-Na1, 84.98(6); N1-Na1-N2, 90.43(6); C11-Na1-N2, 109.18(6).

Deaggregation to a dimer could also be suppressed in the K analogue by switching to the non-chelating monodentate donor THF. An unprecedented polymeric potassium dihydropyridine $[\{K(1,2\text{-}t\text{Bu-DHP})(THF)\}_\infty]$ **8**, was produced (fig. 3).

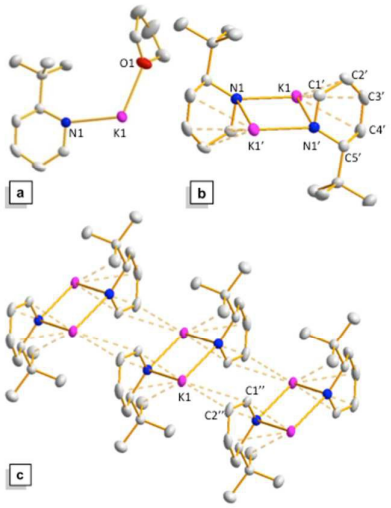


Fig. 3 Molecular structure of [{K(1,2-*t*-Bu-DHP)(THF)}$_\infty$] **8** with thermal ellipsoids drawn at the 50% probability level and hydrogen atoms, minor disordered component and THF molecules (in b and c) have been omitted for clarity. a) monomeric unit, b) dimeric unit, and c) polymeric assembly. Dashed bonds represent bonds with significant π-character. Symmetry transformations used to generate equivalent atoms labelled ': 1-x, 2-y, 1-z, labelled '': -1+x, y, z. Selected bond lengths (Å) and angles (º): K1-N1, 2.7220(14); K1-C1', 2.9897(15); K1-C2', 3.1939(17); K1-C3', 3.0986(17); K1-C4', 3.2543(18); K1-O1, 2.7171(14); K1-N1', 3.1128(13); K1-C1'', 3.1188(17); K1-C2'', 3.3500(15); N1-K1-O1, 116.86(5); K1-N1-K1', 97.58(4); N1-K1-N1', 82.42(4).

Its basic monomeric unit (fig 3a.) contains one K atom engaging in a K-N bond with the dihydropyridyl ring and a K-O(THF) bond. These monomeric units aggregate into $(KN)_2$ dimers (fig. 3b) in a similar manner as **4**, with K1-N1', 3.1128(13) deviating considerably from K1-N1, 2.7220(14) owing to increased π-character in the dimerization interaction, with the K-C distances suggesting a η^4 manner, (K1-C1'/C2'/C3'/C4') mean length 3.1342 Å,[12,25f,g,26] The dimers then link up through intermolecular η^2 π- type interactions between K and the olefinic C1'' and C2'' atoms (at lengths 3.3498(15) and 3.1190(19) Å) of a neighbouring dihydropyridyl ring (fig 3c.). Thus the propagation of this polymeric motif relies solely upon these modest K-π interactions. Unique in DHP chemistry, this polymeric structure can be compared with a select few K polymers of other amido and related groups,[27] though these generally exhibit zigzag arrangements.[28]

Thermal volatility analysis (TVA) studies were performed on the donor-free molecular Na and KDHP solids **2** and **3**, for comparison with that previously carried out on LiDHP, to gain insight on their stability as well-defined Na and K hydride surrogates.[29] Upon heating the sample the decomposition volatiles were collected and identified. In the case of NaDHP, **2**, the maximum rate of NaH loss occurred at 124ºC (fig. 4a) producing the alkylpyridine, 2-*t*butylpyridine, whereas for KDHP, **3**, this maximum rate of loss occurred at a noticeably lower temperature of 99ºC (fig 4b). Note that LiDHP **1** has a maximum rate of loss at 120ºC, similar to NaDHP. These results reflect the lower thermal stability of the K complex compared with those of the two smaller alkali metals Li and Na. The collected decomposition products were analysed by NMR spectroscopy which confirm the loss of metal hydride and concomitant gain of aromaticity forming 2-*t*-butylpyridine.[15] The thermogram of complex **3** also shows an additional peak at around 50ºC. The experiment was repeated with heating stopped at 55ºC so that this fraction could be isolated. ^{1}H NMR studies confirmed this to be hexane. Despite rigorous drying *in vacuo*, this could not be prevented and is likely trapped in the lattice when the product precipitates.

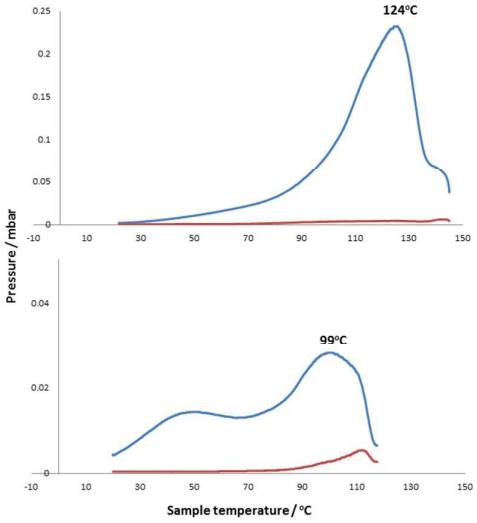


Fig. 4 Thermal volatility analysis thermogram for (a, top) NaDHP, **2** and (b, bottom) KDHP, **3**. The blue line represents total volatile products and the red line non-condensable volatile products.

To demonstrate their ability as potential MH reagents we studied the simple reduction of benzophenone. Reacting isolated **3** with benzophenone in hexane resulted in a white precipitate, in 76% yield, analogous to the LiDHP **1.**[15] The ^{1}H NMR in d_8-THF confirmed the solid to be the hydropotassiated product, potassium diphenylmethoxide. However for **2**, no precipitate formed due to the highly soluble nature of the product.[30] An internal standard was employed to quantify the hydrometallation of benzophenone with **2**, a yield of 48% was calculated.

Conclusions

The effective metathesis reaction of our 1-lithio-2-*t*butyl-dihydropyridine using cheap, commercially available metal tert-butoxides has resulted in the isolation of heavier alkali metal dihydropyridines in excellent yields. A structural study has revealed three distinct motifs that these unsaturated molecules can adopt when combined with an alkali metal with a greater propensity for cation-π interactions. Along with structural insights, we have revealed a straightforward one pot synthesis at room temperature to prepare isolable well-defined NaH and KH surrogates, which was verified by thermal volatility studies and hydrometallation of the representative ketone benzophenone.

Acknowledgements

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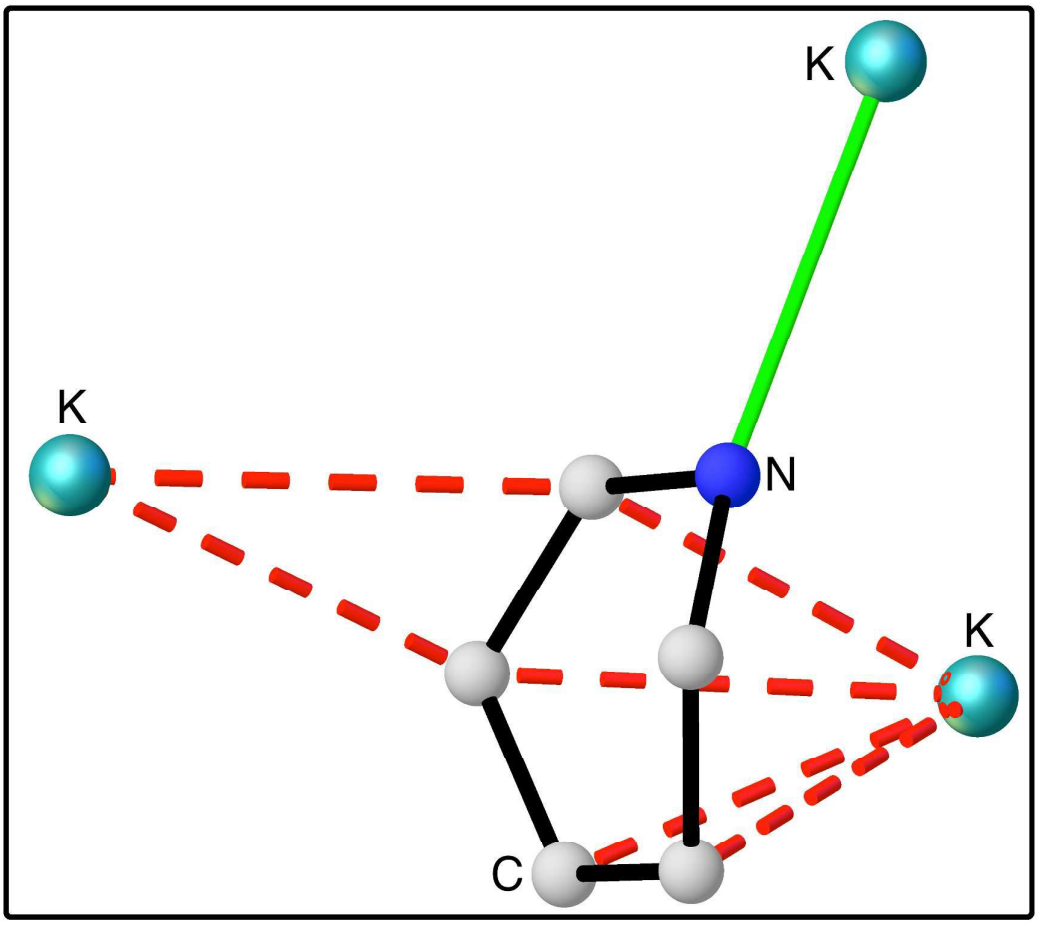

Transmetallation of 1-lithio-2-alkyl-1,2-dihydropyridines with heavier alkali-metal alkoxides provides facile access to reactive MH (M = Na, K) sources, which show significant diversity in their structures due in part to the distinct ways that Na and K can engage with the σ (green bond) and π (red bonds) donor systems of the dihydropyridyl ligands.