Nitrogen Ylides

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Sixty Years after Wittig: Gas-Phase Synthesis of Lithium Trimethylammonium Methylide, $[(CH_3)_3NCH_2Li]^{+}$**

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Dedicated to Professor Charles DePuy on the occasion of his 80th birthday

Wittig's work on ylides culminated in the 1979 Nobel Prize for Chemistry in recognition of "the discovery of the synthetic method which bears his name".[1] The Wittig reaction and variants involving other ylides continue to play important roles in organic synthesis.[2,3] Although best known for his work on phosphorus ylides, Wittig discovered in 1947, as part of the quest for pentavalent nitrogen compounds, that the reaction of phenyllithium with tetramethylammonium bromide led to the formation of benzene and the lithium bromide complex of trimethylammoniummethylide [Eq. (1)].[4,5]

$$C_6H_5Li + (CH_3)_4N^+Br^- \rightarrow C_6H_6 + (CH_3)_3N^+CH_2^- \cdot LiBr \qquad (1)$$

Reactivity studies revealed that this complex behaves like a typical carbanion, an example being the deprotonation of water [Eq. (2)]. Coordination of lithium bromide appears to be vital for the stability of the ylide; for example, by changing the alkali metal to sodium, the "free" ylide is formed, which undergoes either polymerization [Eq. (3)][5] or a Stevens rearrangement [Eq. (4)].[5,6] Herein we report the gas-phase synthesis, characterization, and preliminary reactivity studies of the gas-phase ylide $[(CH_3)_3NCH_2Li]^+$ (**3**), sixty years after Wittig's original report of the equivalent neutral salt complex $(CH_3)_3N^+CH_2^-{\cdot}LiBr$.[4,5]

$$(CH_3)_3N^+CH_2^- \cdot LiBr + H_2O \rightarrow (CH_3)_4N^+OH^- + LiBr \qquad (2)$$

$$(CH_3)_3N^+CH_2^- \rightarrow (CH_3)_3N + (CH_2)_{polymer} \qquad (3)$$

$$(CH_3)_3N^+CH_2^- \rightarrow (CH_3)_2NCH_2CH_3 \qquad (4)$$

Remarkably little is known about the stability and fundamental reactivity of nitrogen ylides in the gas phase.[7,8] As part of our studies into the gas-phase synthesis and reactivity of organometallic ions,[9] it occurred to us that decarboxylation of the lithium complex of betaine, $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**), would yield the hitherto unknown *gas-phase* lithium trimethylammonium methylide ion $[(CH_3)_3NCH_2Li]^+$ (**3**).[4,5] Herein we report mass-spectrometry experiments and density functional theory (DFT) calculations that examine the formation of **3** and its gas-phase reaction with water [cf. Eqs. (1), (2)]. An examination of key bond lengths from DFT calculations on **3** suggest that it is closely related to Wittig's salt complex $(CH_3)_3N^+CH_2^-{\cdot}LiBr$ as well as the free ylide $(CH_3)_3N^+CH_2^-$ (Figure 1).

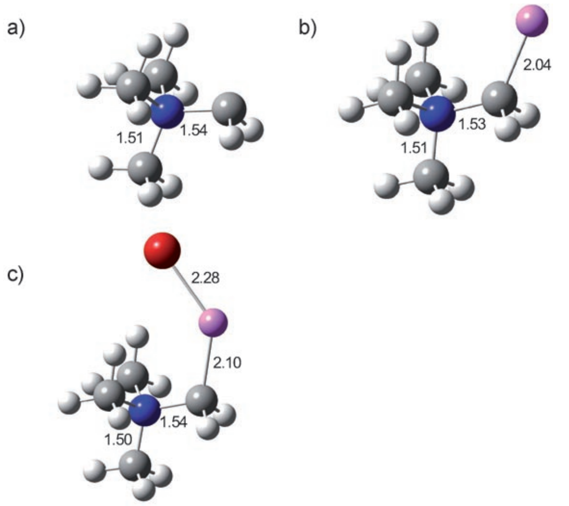

Figure 1. Comparison of DFT-calculated structures of a) $(CH_3)_3NCH_2$, b) $[(CH_3)_3NCH_2Li]^+$ (**3**), and c) Wittig's salt complex, $(CH_3)_3NCH_2{\cdot}LiBr$. Selected bond lengths in [Å]; blue N, purple Li, red Br.

Electrospray ionization mass spectrometry (ESI/MS) of an acetonitrile solution containing betaine and lithium iodide provided access to the cationic lithiated betaine complex $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**, m/z 124). Collisional activation of **1** resulted in decarboxylation to give the lithium trimethylammonium methylide cation $[(CH_3)_3NCH_2Li]^+$ (**3**) [Eq. (5a);

$$[(CH_3)_3NCH_2CO_2Li]^+ (\mathbf{1}) \rightarrow [(CH_3)_3NCH_2Li]^+ (\mathbf{3}) + CO_2 \qquad (5a)$$

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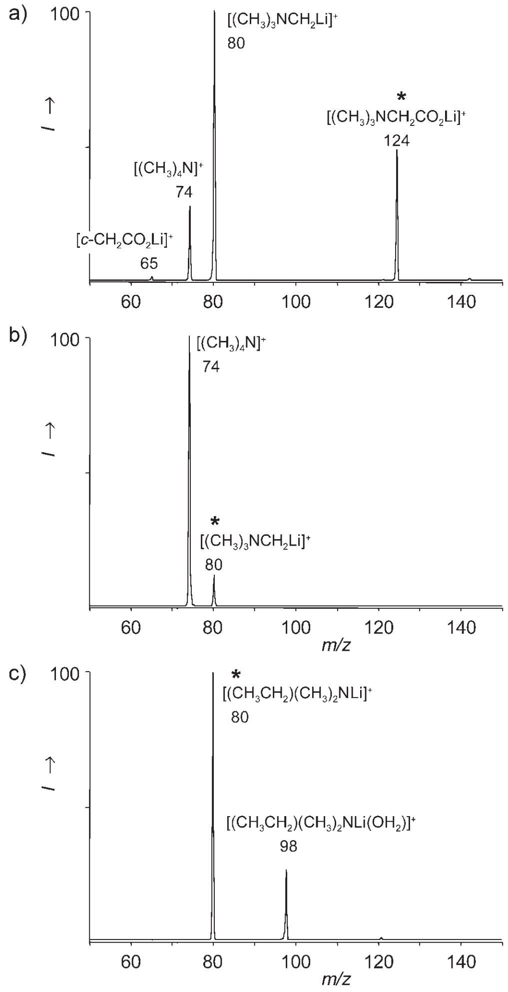

Figure 2. Mass spectra of a) collisional activation of $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**; *m/z* 124) to give $[(CH_3)_3NCH_2Li]^+$ (**3**; *m/z* 80) and neutral CO_2, b) the reaction of $[(CH_3)_3NCH_2Li]^+$ (**3**; *m/z* 80) with H_2O to give $[(CH_3)_4N]^+$ (*m/z* 74) and neutral LiOH, and c) the reaction of $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**; *m/z* 80) with H_2O to give $[(CH_3CH_2)(CH_3)_2NLi(OH_2)]^+$ (*m/z* 98). The mass-selected precursor ion is marked with an * in each case.

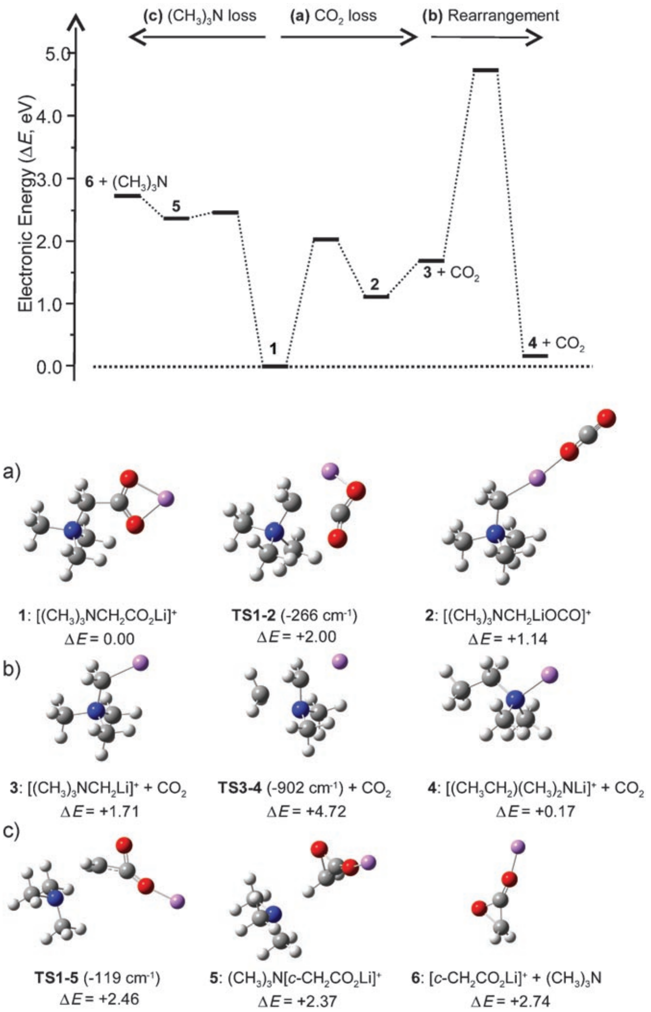

Figure 3. DFT-calculated structures and relative energies for key intermediates involved in a) decarboxylation of $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**) to form the ylide $[(CH_3)_3NCH_2Li]^+$ (**3**) and CO_2, b) rearrangement of the ylide to the amine $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**), and c) elimination of $(CH_3)_3N$ from $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**) to form $[c\text{-}CH_2CO_2Li]^+$ (**6**). Energies are relative to the reactant ion $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**); blue N, purple Li, red O.

Figure 2a, *m/z* 80]. Additional weaker product ions were also observed at *m/z* 65 and 74. The species with *m/z* 65 corresponds to the metalated α-lactone $[c\text{-}CH_2CO_2Li]^+$ (**6**), which most likely arises from intramolecular nucleophilic displacement of trimethylamine by the carboxylate group [Eq. (5b)].

$$[(CH_3)_3NCH_2CO_2Li]^+\ (\mathbf{1}) \rightarrow [c\text{-}CH_2CO_2Li]^+\ (\mathbf{6}) + (CH_3)_3N \qquad (5b)$$

The *m/z* 74 corresponds to $[(CH_3)_4N]^+$, which forms from further reaction of product $[(CH_3)_3NCH_2Li]^+$ with background water, and is described in more detail below.

Calculations indicate that the decarboxylation reaction is endothermic by 1.71 eV, with a transition state 2.00 eV above that of the reactant $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**; Figure 3), consistent with it requiring collisional activation to proceed. The reaction proceeds through exit-channel $[(CH_3)_3NCH_2LiOCO]^+$ (**2**), with the outgoing CO_2 coordinated to the lithium atom. The second primary product observed was assigned to the metalated α lactone $[c\text{-}CH_2CO_2Li]^+$ (**6**). Calculations indicate that this product was formed by intramolecular nucleophilic displacement of trimethylamine by the carboxylate group of $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**; via **TS1-5**, Figure 3c). This pathway was predicted to be endothermic by 2.74 eV, which is above the transition state and the products from decarboxylation (Figure 3a), and is consistent with loss of $(CH_3)_3N$ being observed as only a minor channel in the collision-induced dissociation (CID) experiment (Figure 2a). The mechanism of this latter reaction is related to previous studies on the loss of halide ions from α-haloacetate anions to generate α lactones.[10,11]

An important question concerns the structure of the decarboxylated product observed at *m/z* 80 and assigned to the $[(CH_3)_3NCH_2Li]^+$ ion: Is it indeed the lithiated ylide $[(CH_3)_3NCH_2Li]^+$ (**3**) as assigned above, or has it undergone an ionic Stevens rearrangement to form the isomeric lithiated tertiary amine *N*,*N*-dimethylethylamine complex, $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**)?[8] We investigated this question by 1) DFT calculations, 2) comparison of the collisional activation spectrum of $[(CH_3)_3NCH_2Li]^+$ (**3**) with that of the authentic isomeric amine $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) generated independently by electrospray, and 3) comparison of the reactivity of $[(CH_3)_3NCH_2Li]^+$ (**3**) and $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) with water.

The lithiated *N*,*N*-dimethylethylamine complex **4** is predicted to be thermodynamically more stable than the ylide isomer by 1.54 eV (**3**, Figure 3). However, the calculations indicated a large barrier of 3.01 eV for isomerization of **3** to **4**, which is 4.72 eV above the reactant ion $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**; Figure 3b). The rearrangement process requires migration of the CH_3 group from nitrogen to carbon as well as the lithium from carbon to nitrogen, and is predicted to occur via a concerted transition state (**TS3-4**, Figure 3b).[12] Since CID in the quadrupole ion trap is a slow heating process,[13] and product ions do not undergo further activation, it seems unlikely that collisional activation of the parent $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**) would provide sufficient internal energy to convert the initial product ylide $[(CH_3)_3NCH_2Li]^+$ (**3**) into the thermodynamically favored metalated amine isomer $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**). This finding supports the assignment of *m*/*z* 80 as the authentic ylide $[(CH_3)_3NCH_2Li]^+$ (**3**).

The authentic amine complex $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) was independently generated by electrospray of an acetonitrile solution containing $(CH_3CH_2)(CH_3)_2N$ and lithium iodide. This approach allowed its fragmentation under collisional activation to be compared with that of the ion assigned to the ylide $[(CH_3)_3NCH_2Li]^+$ (**3**). Spectra are included in the Supporting Information (Figure S2). Collisional activation of $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) only resulted in the loss of ion signal, presumably owing to dissociation to $(CH_3CH_2)(CH_3)_2N$ and Li^+, the latter being too light to be detected by the mass spectrometer used. In contrast, collisional activation of the ylide $[(CH_3)_3NCH_2Li]^+$ (**3**) resulted in loss of a methyl radical, methyllithium, and ethane. The differing fragmentations of the authentic amine isomer $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) and of the ion generated by decarboxylation of $[(CH_3)_3NCH_2CO_2Li]^+$ (**1**) supports the assignment of the ion coming from **1** being the ylide $[(CH_3)_3NCH_2Li]^+$ (**3**).

The structure of the decarboxylation product at *m*/*z* 80 was also investigated by ion–molecule reactions, since our previous studies have demonstrated that reactions with water are an experimental probe of organometallic structure.[9b,d] For example, the organomagnesates $[CH_3MgL_2]^-$ (L = Cl, O_2CCH_3) react with water to yield $[HOMgL_2]^-$ and methane [Eq. (6)].[9b]

$$[CH_3MgL_2]^- + H_2O \rightarrow [HOMgL_2]^- + CH_4 \qquad (6)$$

Mass selection and reaction of the ion having *m*/*z* 80 with water resulted in formation of $[(CH_3)_4N]^+$ (*m*/*z* 74) and neutral lithium hydroxide [Eq. (7), Figure 2b]. This

$$[(CH_3)_3NCH_2Li]^+ (\mathbf{3}) + H_2O \rightarrow [(CH_3)_4N]^+ + LiOH \qquad (7)$$

reaction is related to that observed previously for organomagnesates [Eq. (6)], but with a neutral metal hydroxide formed instead. The equivalent reaction with D_2O resulted in formation of $[(CH_3)_3NCH_2D]^+$ (*m*/*z* 75, see Supporting Information).[14] This reactivity is consistent with that expected for $[(CH_3)_3NCH_2Li]^+$ (**3**) [see, for example, Eqs. (2), (7)]. In contrast, the metalated amine isomer $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) reacted with water by addition only to form $[(CH_3CH_2)(CH_3)_2NLi(OH_2)]^+$ (**10**) [Eq. (8), Figure 2c].

$$[(CH_3CH_2)(CH_3)_2NLi]^+ (\mathbf{4}) + H_2O \rightarrow [(CH_3CH_2)(CH_3)_2NLi(OH_2)]^+ (\mathbf{10}) \qquad (8)$$

The reaction energetics of both $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) and $[(CH_3)_3NCH_2Li]^+$ (**3**) with water were explored by DFT calculations (Figure 4). These results indicated that reaction of the lithiated ylide **3** with water is exothermic by 0.99 eV, with the transition state below the entrance channel, and therefore *should* be observed experimentally [Eq. (7), Figure 4a]. In contrast, the equivalent reaction with the lithiated amine isomer is endothermic by 0.44 eV [Eq. (9),

$$[(CH_3CH_2)(CH_3)_2NLi]^+ (\mathbf{4}) + H_2O \rightarrow [(CH_3CH_2)(CH_3)_2NH]^+ (\mathbf{12}) + LiOH \qquad (9)$$

Figure 4b], and therefore *should not* be observed experimentally. Instead, addition of water to form $[(CH_3CH_2)(CH_3)_2NLi(OH_2)]^+$ (**10**) is energetically favored [Eq. (8), Figure 4b]. Accordingly, the observed reactivity of the

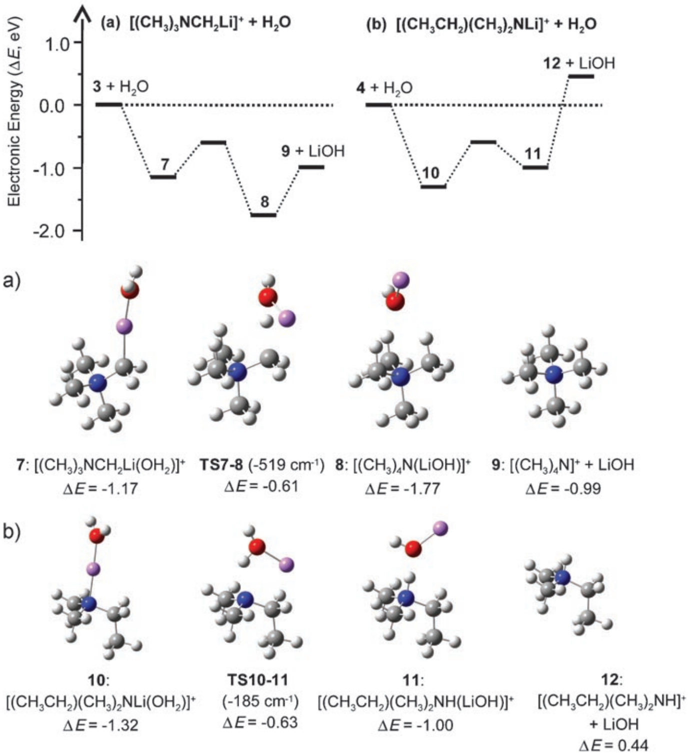

Figure 4. DFT-calculated structures and relative energies for intermediates involved in a) reaction of $[(CH_3)_3NCH_2Li]^+$ (**3**) with H_2O to form $[(CH_3)_4N]^+$ (**9**) and LiOH [Eq. (7)], and b) reaction of $[(CH_3CH_2)(CH_3)_2NLi]^+$ (**4**) with H_2O to form $[(CH_3CH_2)(CH_3)_2NH]^+$ (**12**) and LiOH. Structures of **3** and **4** are given in Figure 3b; blue N, purple Li, red O.

decarboxylation product at *m*/*z* 80 with water further supported its assignment as the authentic ylide $[(CH_3)_3NCH_2Li]^+$ (**3**).

Further preliminary studies suggest that decarboxylation of other metal salts of fixed-charge zwitterions, such as betaine, appears to be a general synthetic route to metalated ylides, such as $[(CH_3)_3NCH_2M]^+$ (M = Li, Na, K, Ag). Recent theoretical studies demonstrate that the leaving group, X, can have profound effects on the reactivity of the ylides $X^+CH_2^-$ ($X = (CH_3)_2O$, $(CH_3)_2S$, $(CH_3)_3N$, and $(CH_3)_3P$).[15] The general technique described herein to generate such gas-phase ylides should allow future gas-phase experiments on these species to be carried out, providing valuable insights into the reactivity of this important class of compounds in the absence of solvation. Future studies will probe the role of the metal and the leaving group on the generation of such gas-phase metalated ylides and examine their reactivity towards a range of neutral reagents, including water, aldehydes, ketones, and alkyl halides.

Experimental Section

Methods. Mass Spectrometry: Experiments were conducted using a modified Finnigan LCQ quadrupole ion-trap mass spectrometer equipped with a Finnigan electrospray ionization source. $[(CH_3)_3NCH_2CO_2Li]^+$ was generated by electrospray of acetonitrile solutions containing betaine and lithium iodide (both ca. 0.1 mg mL^{-1}). $[(CH_3CH_2)(CH_3)_2NLi]^+$ was generated by electrospray of a 90:10 CH_3CN:Me_2EtN solution containing lithium iodide (ca. 0.1 mg mL^{-1}). Ion–molecule reactions were carried out as previously described.[16]

Theoretical Calculations: Density Functional Theory (DFT) calculations were carried out at the B3LYP/6-311+G* level of theory[17] using the Gaussian 03 program.[18a] Stationary points were characterized by frequency calculations, and unscaled zero-point energies are included for all species. Structures were visualized using GaussView.[18b] Intrinsic reaction coordinate (IRC) calculations were carried out to confirm that transition states connected to the appropriate minima.

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