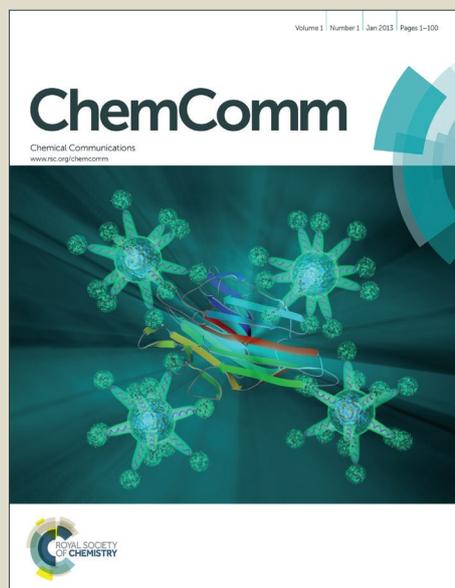


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COMMUNICATION

## Ammonium Catalyzed Cyclitive Additions: Evidence for a Cation- $\pi$ Interaction with Alkynes<sup>†</sup>

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Edith Nagy,<sup>a</sup> Elijah St.Germain,<sup>a</sup> Patrick Cosme,<sup>a</sup> Pradip Maity,<sup>a,‡</sup> Andrew C. Terentis,<sup>a</sup> and Salvatore D. Lepore<sup>\*a</sup>

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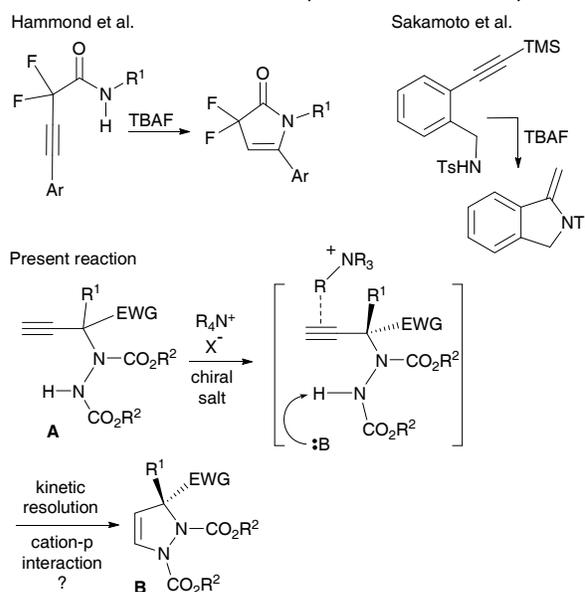
**The addition of carbamate nitrogen to a non-conjugated carbon-carbon triple bond is catalyzed by an ammonium salt leading to a cyclic product. Studies in homogeneous systems suggest that the ammonium agent facilitates nitrogen-carbon bond formation through a cation- $\pi$  interaction with the alkyne unit that, for the first time, is directly observed by Raman spectroscopy.**

Over the past two decades, cation- $\pi$  interactions have been characterized and identified in numerous biological and host-guest systems.<sup>1</sup> More recently, this relatively new intermolecular force has found application in organic synthesis playing a key role in a variety of stereoselective reactions.<sup>2</sup> A few conspicuous examples include the development by Dougherty of cyclophane hosts that catalyse alkylation reactions leading to ammonium cations,<sup>3</sup> face-selective additions by Yamada to pyridinium/arene complexes,<sup>4</sup> and intramolecular Schmidt reactions with regiocontrol via diazonium/phenyl interactions by Aubé.<sup>5</sup> While these and other examples demonstrate a cation binding force in aromatic systems, analogous cation interactions with other  $\pi$ -systems have only rarely been reported.<sup>6</sup> In this communication, we describe our discovery of a cation- $\pi$  interaction with alkynes as part of our mechanistic investigation of a cyclization reaction involving propargyl hydrazines.

We have previously reported a cyclization reaction of  $\beta$ -alkynyl hydrazines to give azaprolines derivatives in high enantiomeric excesses under kinetic resolution conditions.<sup>7</sup> Notably, these reactions were catalyzed by ammonium and phosphonium salts. While heteroatom additions to unactivated alkynes are well known in the presence of transition metal catalysts such as palladium<sup>8</sup> and gold,<sup>9</sup> there are only a few reports of such

reactions involving non-metal catalysts. Hammond and co-workers demonstrated that gem-difluoro propargyl amides undergo 5-endo-dig cyclization to give the  $\gamma$ -lactam in the presence of stoichiometric tetrabutylammonium fluoride (TBAF).<sup>10</sup> This same reagent was also shown by Jacobi<sup>11</sup> and later by Sakamoto and coworkers<sup>12</sup> to efficiently give isoindole products via a 5-exo-dig cyclization (Scheme 1). These previous studies pointed to TBAF as a soluble source of fluoride thought to be an ideal mild base for this transformation. However, our previous success<sup>7</sup> in the synthesis of non-racemic azaprolines **B** from propargyl hydrazines **A** using chiral ammonium catalysts suggested a more discriminating interaction with the substrate (Scheme 1). In this communication, we put forward the first direct evidence for an ammonium cation- $\pi$  interaction with the triple bond of alkynes.

### Scheme 1. Ammonium-mediated cyclitive additions to alkynes.



<sup>a</sup> Department of Chemistry, Florida Atlantic University, Boca Raton, FL 33431-0991 (USA); e-mail: slepore@fau.edu

<sup>‡</sup> Current address: Organic Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India

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Our initial hypothesis for the role of ammonium salts in our reaction was that these act as phase transfer agents serving to solubilize weaker bases such as fluoride.<sup>13</sup> To examine this hypothesis, we employed soluble weak bases with basicities within several log units of fluoride. For this, we chose 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and sodium phenoxide which were entirely soluble in several common organic reaction solvents.<sup>14</sup> To our surprise, we observed a substantial rate enhancement with these bases in the presence of tetrabutylammonium bromide (TBAB) whose counter anion is essentially non-basic. For example, the reaction of substrate **1** in MeCN in the presence of stoichiometric DBU gave product **2** in 50% yield in 722 min ( $t_{1/2}$ ). This same reaction gave a  $t_{1/2}$  of 196 min in the presence of added TBAB (1 eq) for a relative rate of 3.7 (Table 1, entry 1). Interestingly, the ionic base NaOPh led to much higher relative rates in MeCN (22) and other solvents.<sup>15</sup> Several other ammonium bromide salts also catalyzed the cyclization under homogeneous conditions (entries 3 – 5). The most significant rate enhancement was measured in tetrahydrofuran (THF) (entry 6). The reaction was very slow in the absence of TBAB and product decomposition was observed after long reaction times. It is possible that the differences in relative rates (Table 1) are a function of the degree of dissociation of the TBAB ion pair in the solvents examined.<sup>16</sup> Nevertheless, considering the complete solubility of the bases used in this study, it appears that the ammonium salt enhanced these cyclization reactions by something other than a phase transfer mechanism.

**Table 1.** Role of base in TBAB catalyzed cyclization of **1** under homogeneous conditions.

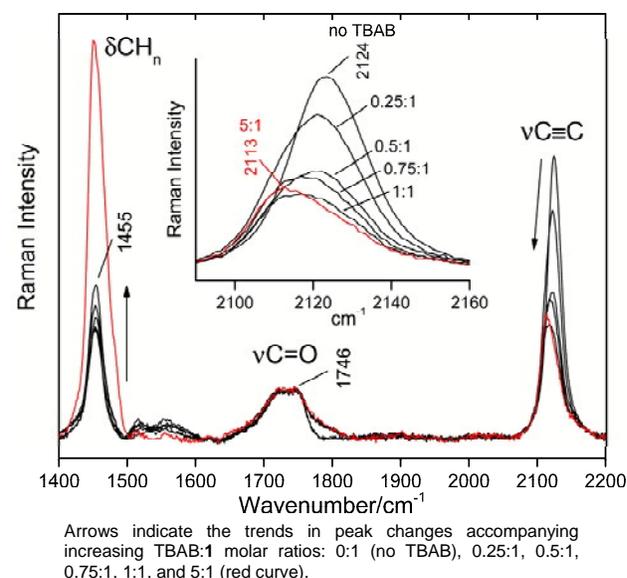
Entry	Base	Solvent	Salt	$t_{1/2}$ (min) <sup>a</sup>		Rel Rate <sup>b</sup>
				No Salt	Salt	
1 <sup>c</sup>	DBU	MeCN	Bu <sub>4</sub> NBr	722	196	3.7
2	NaOPh	MeCN	Bu <sub>4</sub> NBr	1140	52	22
3	NaOPh	MeCN	Et <sub>4</sub> NBr	1140	54	21
4	NaOPh	MeCN	<sup>n</sup> Pr <sub>4</sub> NBr	1140	52	22
5	NaOPh	MeCN	Oct <sub>4</sub> NBr	1140	46	25
6	NaOPh	THF	Bu <sub>4</sub> NBr	7515	33	228
7	NaOPh	pyridine	Bu <sub>4</sub> NBr	360	125	2.9
8	NaOPh	DMF	Bu <sub>4</sub> NBr	70	1	70

<sup>a</sup> $t_{1/2}$  represents time required for 50% conversion of the starting material into product determined using NMR. Reactions performed at 0.1 M. <sup>b</sup>Relative rate =  $t_{1/2}(\text{no } R_4\text{NBr}) / t_{1/2}(R_4\text{NBr})$ . <sup>c</sup>Reaction performed at 0.025 M to ensure solubility.

Based on these homogeneous reaction data, we surmised that an alternative pathway for ammonium salt involvement in the aforementioned cyclization reactions (and those of Hammond<sup>10</sup> and Sakamoto<sup>12</sup>) could be through a cation- $\pi$  association with the carbon-carbon triple bond in the substrate. To our

knowledge, ammonium- $\pi$  interactions have not been demonstrated with alkynes. Such an interaction should be theoretically possible here since they are thought to be largely electrostatic,<sup>17</sup> which is not exclusive to aromatic systems. Indeed, in our initial report, we put forward indirect evidence for an association of chiral ammonium cations with a  $\pi$ -bond in **A** by noting a complementarity between the size of the ammonium catalyst and steric congestion at the propargylic chiral center.<sup>7</sup>

To directly observe this interaction, we turned to Raman spectroscopy (RS) since the polarizable carbon-carbon triple bond appears as an intense band (more so than IR) that is easily recognizable in an uncrowded region of the spectrum. Moreover, RS has been used to elucidate metal-tryptophan interactions in a periplasmic protein (CusF)<sup>18</sup> and, more recently, to understand conformational changes in small molecules induced by ammonium/indole associations.<sup>19</sup> Thus a series of spectra of **1** were measured using RS in the absence or presence of varying amounts of TBAB noting especially the alkyne stretching ( $\nu_{C\equiv C}$ ), carbonyl stretching ( $\nu_{C=O}$ ), and  $\text{CH}_2/\text{CH}_3$  deformation ( $\delta_{\text{CH}_n}$ ) regions (Figure 1). In these experiments, TBAB was mixed in a dichloromethane solution of compound **1** and then drops of this homogeneous mixture were deposited onto a slide for analysis. Spectral intensities were normalized so that all spectra have the same carbonyl stretching band intensity (Figure 1). The inset provides a detailed view of the alkyne stretching band of **1**, showing a peak shift to lower wavenumber and intensity decrease as increasing amounts of TBAB were added. Critically, other vibrational modes showed no shift in wavenumber in the presence of TBAB.<sup>20</sup> Similar trends were also observed in different solvents using the RS method described above. Thus when compound **1** was mixed with TBAB (5 eq), a shift of  $-11 \text{ cm}^{-1}$  was observed in THF and  $-8 \text{ cm}^{-1}$  in DMF (see Supporting Information).



**Figure 1.** Raman titration of **1** with added Bu<sub>4</sub>NBr (TBAB).

Other alkynes, including one bearing no other functional group (compound **7**), also exhibit a down-shift of the C-C triple bond wavenumber in the presence of TBAB. Using the same TBAB titration experiments as described above for compound **1**, five other terminal alkynes exhibited wavenumber shifts ranging from 4 to 12 cm<sup>-1</sup> (Table 2). There appears to be no correlation of the C-C triple bond shift with other functional groups present in the molecule. Raman measurements of alkyne **3** in the presence of KBr gave no significant shift (Table 2, entry 7).

**Table 2.** Raman measurements of alkynes with added TBAB.

Entry	Alkyne	TBAB (0 eq) (cm <sup>-1</sup> )	TBAB (5 eq) (cm <sup>-1</sup> )	Δ (cm <sup>-1</sup> ) <sup>a</sup>
1	<b>1</b>	2124	2113	11
2	<b>3</b>	2125	2114	11
3	<b>4</b>	2124	2117	7
4	<b>5</b>	2121	2109	12
5	<b>6</b>	2114	2110	4
6	<b>7</b>	2120	2108	12
7 <sup>b</sup>	<b>3</b> with KBr (5 eq)	2125	2125	<1

<sup>a</sup>Represents the change in wavenumbers in the sample measured with TBAB (5 eq) relative to the sample containing no TBAB. <sup>b</sup>No TBAB was added.

We propose that these data indicate an interaction between the tetrabutylammonium cation and the carbon-carbon triple bond of alkynes, and that this is best explained by a cation- $\pi$  interaction. The direction of the shift towards lower wavenumber suggests that electron density from the triple bond is drawn towards the cation, slightly decreasing the bond order of the alkyne though the maximum limit of this shift is well below the change in bond order seen in transition metal alkyne interactions.<sup>21</sup>

The primary goal of the present study was to identify the nature of the interaction between ammonium salts and alkynes as a first step towards understanding the catalytic role of such salts in the cyclization of compounds such as **A**. As mentioned here and in our previous study,<sup>7</sup> in the presence of added ammonium agent, we observed that relatively mild bases bring about cyclitive additions to the carbon-carbon triple bond in **A** (and related propargyl hydrazines) presumably by deprotonating the attacking carbamate nitrogen. While the mechanistic role of ammonium salts remains unclear, one possibility is that the ammonium-alkyne interaction in propargyl hydrazine **A** activates the triple bond towards nucleophilic attack. Alternatively, the complexed cation may render the carbamate proton more acidic by stabilizing the resulting conjugate base through favorable intramolecular ion pairing. The nitrogen anion then attacks the carbon-carbon triple bond to rapidly

form the observed cyclic product. Related alkyne cyclitive addition mechanisms have been recently modelled computationally by Alabugin and co-workers who argue that it proceeds via an 'aborted [2,3]-sigmatropic shift' involving an in-plane aromatic transition state.<sup>22</sup>

In summary, studies in homogeneous systems clearly indicate that an ammonium agent accelerates the cyclization of a propargyl hydrazine reaction in several solvents. This led to the hypothesis of ammonium engaging in a cation- $\pi$  interaction with the carbon-carbon triple bond of the substrate. For the first time, direct evidence for this unique interaction was obtained by observing alkyne stretching ( $\nu_{C\equiv C}$ ) perturbation by Raman spectroscopy in the presence of tetraalkylammonium salts. Current studies are focused on exploiting this ammonium- $\pi$  interaction in other alkyne systems.

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