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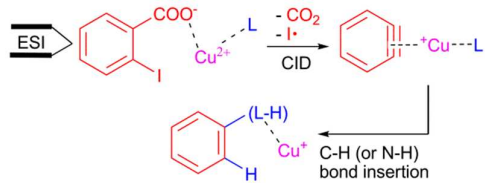
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$\text{Cu}^+$ /benzyne complexes bearing ligands (L) were synthesized and their addition reactivity was studied in the gas phase using electrospray ionization ion trap mass spectrometry.



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ARTICLE TYPE

Gas-Phase Synthesis and Reactivity of Cu<sup>+</sup>/Benzyne Complexes

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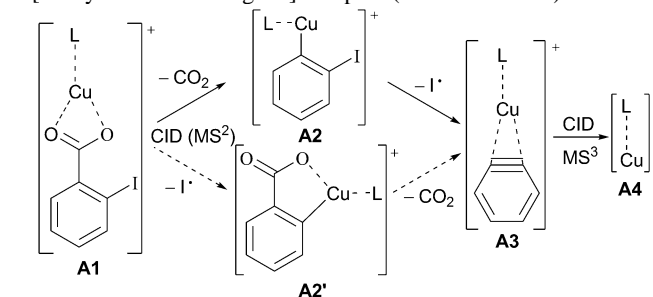
5 Cu<sup>+</sup>/benzyne complexes bearing bidentate nitrogen ligands were synthesized in the gas phase for the first time using electro-spray ionization mass spectrometry. The addition reactivity of copper-stabilized benzyne with amines was studied in the ion trap analyzer. The structures of products were identified by comparing their MS<sup>n</sup> data with authentic compounds obtained from another generation route.

Benzyne (1,2-didehydrobenzene)<sup>1</sup> is a fundamental and highly reactive organic intermediate that has been used in the efficient syntheses of various organic compounds.<sup>2-5</sup> Since the discovery of this fascinating species, experimental and theoretical investigations on its physical properties, chemical reactivity, and electronic structures have received tremendous attention.

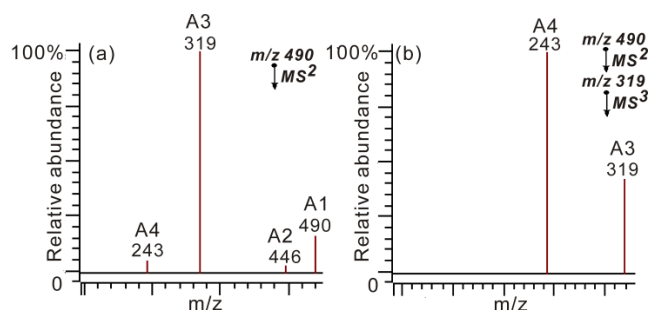
A free benzyne cannot be isolated in solution, so its existence in chemical reactions is usually identified by using capture agents. Coordination with transition metals can relieve the strain in benzyne, and the commonly used transition metals are from groups 4 and 10 metals (Ti, Zr, Ni, Pd) and others.<sup>6-14</sup> Isolating and trapping benzyne is less problematic in the gas phase, but the reported methods are very limited. A neutral benzyne generated in a molecular beam only has a lifetime of 400 ps.<sup>15</sup> Two strategies have been used to stabilize and capture gaseous benzyne in mass spectrometers, one is introducing a positive or negative charge (group) on the phenyl ring to generate ring-charged benzyne analogues,<sup>16-18</sup> the other is utilizing a metal ion (Fe, Sc, Cr and etc.) to coordinate with benzyne.<sup>19-24</sup> In the latter method, bare metal/benzyne complexes can be formed and their reactivities with simple organic molecules such as hydrocarbons can be studied using electron (or laser) ionization Fourier-transform ion cyclotron mass spectrometry. Although the solvent-free environment of gas-phase experiments does not have preparative-scale synthetic utility, they provide challenging information for mechanistic interpretation.<sup>25-29</sup> Almost all the metal/benzyne complexes formed in the liquid-phase reactions also contain various ligands. To mimic the property and reactivity of metal/benzyne complexes in the liquid-phase, synthesis of ligand-ligated metal/benzyne complexes is more desirable, which yet cannot be achieved using the previous methodologies. Copper is one of the most used transition metals in organometallic chemistry, but it was rarely used in benzyne chemistry and no gaseous Cu<sup>+</sup>/benzyne complex was reported. We therefore initiated a research program to synthesize ligand-ligated Cu<sup>+</sup>/benzyne complexes in the gas phase and study the reaction of copper-stabilized benzyne with amines.

In recent years, electrospray ionization (ESI) mass spectrometers have become not only a versatile analytical instrument but also a useful tool in synthesizing novel and reactive gas-phase ions.<sup>30-37</sup> Chemical reactions under atmospheric pressure by using (modified) ESI can yield impressive results. The reaction is sometimes more efficient than that carried out in solution.<sup>38-41</sup> ESI mass spectrometry is a potential method to prepare gaseous ligand-ligated Cu<sup>+</sup>/benzyne complexes.

Metal-mediated decarboxylative reaction is a powerful strategy to generate organometallic intermediates both in the condensed phase and in the gas phase.<sup>32-37,42-47</sup> In the present study, 2-iodobenzoic acid, copper, and nitrogen-containing bidentate compound were used as the benzyne precursor, the central transition metal, and the ligand, respectively. A ternary complex consisting of 2-iodobenzoic acid, Cu<sup>2+</sup>, and ligand can be easily transferred from solution to gas phase via ESI. Collision-induced dissociation (CID) of this complex (the single isotope ion with the <sup>63</sup>Cu was isolated and used in MS/MS) undergoes decarboxylation and deiodination to generate a [benzyne ...<sup>63</sup>Cu<sup>+</sup> ...Ligand] complex (A3 in Scheme 1).



**Scheme 1.** Gas-phase synthesis of ligand-ligated Cu<sup>+</sup>/benzyne complex (A3) using ESI mass spectrometry.



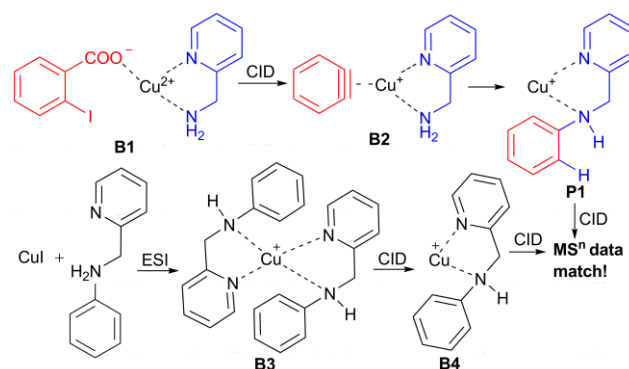
**Figure 1.** CID mass spectra of (a) A1 (*m/z* 490) and (b) A3 (*m/z* 319) (L = 1,10-phenanthroline, Cu = <sup>63</sup>Cu).

The CID mass spectrum ( $L = 1,10$ -phenanthroline) is shown in Figure 1a and the elemental composition of these four ions ( $m/z$  490, 446, 319, 243) was confirmed by high resolution mass spectrometry (Figure S1). The  $MS^3$  spectrum shown in Figure 1b confirms the existence of benzyne in the complex **A3** because the benzyne can be released from **A3** upon collisional activation to form **A4** (76 Da neutral loss). Carboxyl and iodine are both excellent leaving groups in CID, so there are two possible routes from **A1** to **A3** as shown in Scheme 1. Theoretical calculations were used to find the optimal route (Figure S2).<sup>46,47</sup> The results indicate that loss of  $CO_2$  is more favorable than loss of I in terms of energy in the first step. The relative energy of **A2** plus  $CO_2$  is only 33.7 kJ mol<sup>-1</sup> higher than that of **A1** and 156.1 kJ mol<sup>-1</sup> lower than that of **A2'** plus I. This result is consistent with the experimental data that **A2** is observed in the MS/MS spectrum but **A2'** is not observed (Figure 1a).

The generation of benzyne depends on the removal of the two adjacent groups on the phenyl ring. Benzoic acid cannot be used as a benzyne precursor by using the above method (Figure S3), which means that the *ortho*-iodine as a leaving group is very important. Then, more *ortho*-halogenated benzoic acids were tentatively used as benzyne precursors (Figures S4-S6). For example, 2-bromobenzoic acid can be used to produce the benzyne complex (**A3**), although the efficiency is much lower. In addition, 2-chlorobenzoic acid and 2-fluorobenzoic acid cannot be used to produce the benzyne complex (**A3**). The proposed mechanism for the dehalogenation step involves losing halogen as a radical (the tendency:  $I > Br > Cl > F$ ) and the reduction of  $Cu^{2+}$  to  $Cu^+$ . Therefore, iodine is the best leaving group among the halogens and 2-iodobenzoic acid is an excellent *ortho*-benzyne precursor in the gas phase. However, this method cannot be used to prepare *meta*-benzyne and *para*-benzyne with 3-iodobenzoic acid and 4-iodobenzoic acid as the potential precursors, respectively (Figures S7 and S8).

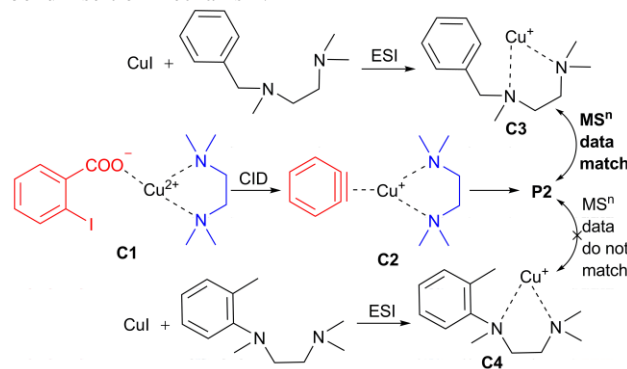
Various ligands are applicable in the gas-phase synthesis of  $Cu^+$ /benzyne complexes, such as  $N,N,N',N'$ -tetramethylethylenediamine (TMEDA), 2-(aminomethyl)pyridine (2-AMP), and 2,2-bipyridine (Figures S9-S11). After the synthesis of benzyne, its reactivity can be further evaluated through the collisional activation of the copper-bound benzyne/ligand complex. The benzyne is a highly unsaturated species that easily undergoes addition reactions such as Diels-Alder reaction, cycloadditions with 1,3-dipoles, and nucleophilic additions. If the ligand within the complex, [benzyne  $\cdots Cu^+ \cdots L$ ], is purposefully chosen, the reaction between the benzyne and ligand can occur. The central copper may function as an activation center leading to some particular reactions.

The representative reactivity of benzyne is its addition reaction with amines. When 2-AMP is used as the ligand, in the intermediate benzyne complex (**B2**), the benzyne can insert into the N-H bond of 2-AMP to give product **P1** (Scheme 2). The structure of a gas-phase ion can be identified via multi-stage mass spectrometry by comparison with an authentic compound obtained from another route. The CID fragmentation behavior and the energy resolved mass spectra of **P1** are in accordance with that of **B4** which is generated via ESI of a methanol solution containing *N*-(pyridin-2-ylmethyl)aniline and CuI (Figures S12 and S13).



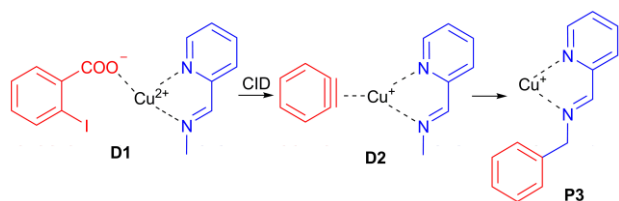
**Scheme 2.** Gas-phase synthesis of  $Cu^+$ /benzyne complex and its reaction with 2-AMP.

When TMEDA is used as the ligand, benzyne can react with TMEDA to form a covalent compound, **P2** (Scheme 3). According to the best of our knowledge on the reactivity of benzyne, the reaction may undergo via a C-H or C-N bond insertion mechanism to generate *N*-benzyl- $N,N',N'$ -trimethylethylenediamine or *N*-(2-methylphenyl)- $N,N',N'$ -trimethylethylenediamine, respectively. These two compounds were then synthesized in solution and their complexes with  $Cu^+$  (**C3** and **C4**) can be readily produced via ESI. The multi-stage fragmentation behavior of **P2** is the same as that of **C3** but quite different from that of **C4** (Figures S14 and S15). The major product ion in the fragmentations of **C3** and **P2** is formed by losing toluene (92 Da), which indicates an existing benzyl group in their corresponding structures. These results indicate that the copper-stabilized benzyne reacts with TMEDA via selective C-H bond insertion mechanism.

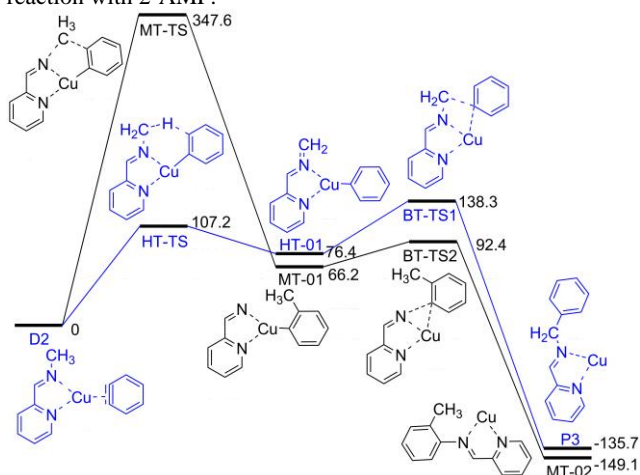


**Scheme 3.** Gas-phase synthesis of  $Cu^+$ /benzyne complex and its reaction with TMEDA.

By applying the same approaches, the reaction of  $Cu^+$ /benzyne with *N*-(pyridin-2-ylmethyl)ethanamine was studied. The benzyne was expected to react with this ligand through C-H (not C-N) bond insertion to form a product **P3** (Scheme 4). Theoretical calculations support this prediction. As shown in Figure 2, in the C-N bond insertion process, the methyl transfer from N to benzyne requires very high activation energy (MT-TS). In contrast, the energy barriers of hydrogen transfer (HT-TS) and the subsequent benzene transfer (BT-TS1) in the C-H bond insertion process are relatively much lower. The final product **P3** is more stable than the starting complex **D2** by 135.7 kJ mol<sup>-1</sup>, which supports the formation of this product. In addition, the structure of **P3** was further confirmed by the multi-stage mass spectrometry (Figures S16 and S17).



**Scheme 4.** Gas-phase synthesis of  $\text{Cu}^+$ /benzyne complex and its reaction with 2-AMP.



**Figure 2.** Energy profile calculated for the  $\text{Cu}^+$ -mediated reaction of benzyne with *N*-(pyridin-2-ylmethylene)methanamine in the gas phase. The relative free energies are given in  $\text{kJ mol}^{-1}$ .

## Conclusions

This study offers a method to prepare gaseous ligand-ligated  $\text{Cu}^+$ /benzyne complexes using ESI mass spectrometry. 2-Iodobenzoic acid was found to be an excellent benzyne precursor in the gas phase. The formation and reaction of benzyne in these complexes were well proved by multi-stage mass spectrometry in combination with theoretical calculations. This new method is promising to synthesize more metal/benzyne complexes bearing various ligands and then study their gas-phase chemistry.

## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental and computational details and Figures S1-S17. See DOI: 10.1039/b000000x/

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1 Three isomers are possible for benzyne: *o*-benzyne (1,2-didehydrobenzene), *m*-benzyne (1,3-didehydrobenzene), and *p*-benzyne (1,4-didehydrobenzene). When we discuss benzyne (also in this paper), it usually refers to *o*-benzyne.

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