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Gas-phase synthesis and reactivity of Cu^+–benzyne complexes†

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Cu^+–benzyne complexes bearing bidentate nitrogen ligands were synthesized in the gas phase for the first time using electrospray 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^n data with authentic compounds obtained from another generation route.

Benzyne (1,2-didehydrobenzene)[1] is a fundamental and highly reactive organic intermediate that has been used in the efficient syntheses of various organic compounds.[2–5] Since the discovery of this fascinating species, experimental and theoretical investigations of 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 group 4 and 10 metals (Ti, Zr, Ni, and Pd) and others.[6–14] 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 has a lifetime of 400 ps only.[15] 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,[16–18] the other is utilizing a metal ion (Fe, Sc, Cr, *etc.*) to coordinate with benzyne.[19–24] 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, it provides challenging information for mechanistic interpretation.[25–29] Almost all the metal–benzyne complexes formed in the liquid-phase reactions also contain various ligands. To mimic the properties and reactivity of metal–benzyne complexes in the liquid-phase, synthesis of ligand-ligated metal–benzyne complexes is more desirable, which cannot be achieved using the previous methodologies. Copper is one of the most used transition metals in organometallic chemistry, but it has been rarely used in benzyne chemistry and no gaseous Cu^+–benzyne complex has been reported. We therefore initiated a research program to synthesize ligand-ligated Cu^+–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 versatile analytical instruments but also useful tools in synthesizing novel and reactive gas-phase ions.[30–37] 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.[38–41] ESI mass spectrometry is a potential method to prepare gaseous ligand-ligated Cu^+–benzyne complexes.

The metal-mediated decarboxylative reaction is a powerful strategy to generate organometallic intermediates both in the condensed phase and in the gas phase.[32–37,42–47] In the present study, 2-iodobenzoic acid, copper, and a 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^{2+}, and a 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 ^{63}Cu was isolated and used in MS/MS) undergoes decarboxylation and deiodination to generate a [benzyne$\cdots{}^{63}Cu^+\cdots$Ligand] complex (**A3** shown in Scheme 1).

The CID mass spectrum (L = 1,10-phenanthroline) is shown in Fig. 1a and the elemental composition of these four ions (*m*/*z* 490, 446, 319, and 243) was confirmed by high resolution mass spectrometry (Fig. S1, ESI†). The MS^3 spectrum shown in Fig. 1b confirms the existence of benzyne in complex **A3** because benzyne can be released from **A3** upon collisional activation to form **A4** (76 Da neutral loss). Carboxyl and iodine

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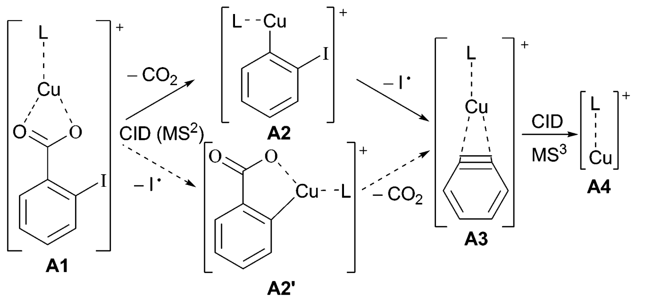


Scheme 1 Gas-phase synthesis of the ligand-ligated Cu$^+$–benzyne complex (**A3**) using ESI mass spectrometry.

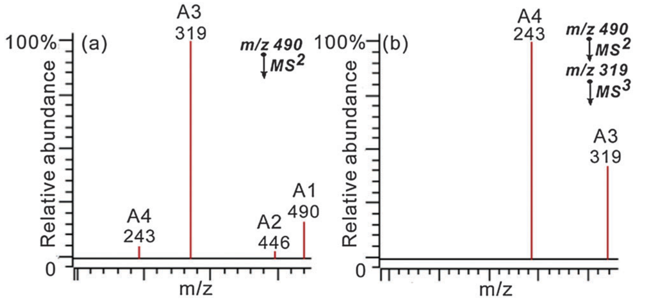
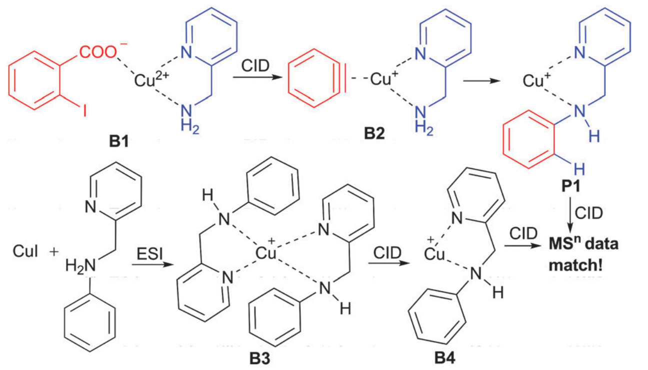


Fig. 1 CID mass spectra of (a) **A1** (*m*/*z* 490) and (b) **A3** (*m*/*z* 319) (L = 1,10-phenanthroline, Cu = ^{63}Cu).



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

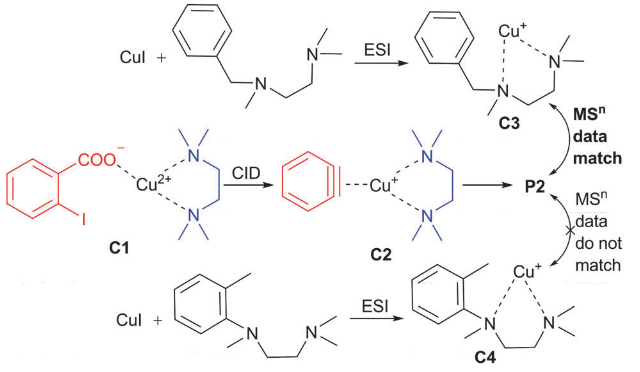
are both excellent leaving groups in CID, so there are two possible routes from **A1** to **A3** as shown in Scheme 1. Theoretical calculations were used to find the optimal route (Fig. S2, ESI†).[46,47] The results indicate that the loss of CO$_2$ is more favorable than the loss of $I^{\bullet}$ in terms of energy in the first step. The relative energy of **A2** plus CO$_2$ is only 33.7 kJ mol^{-1} higher than that of **A1** and 156.1 kJ mol^{-1} lower than that of **A2′** plus $I^{\bullet}$. These results are consistent with the experimental data showing that **A2** is observed in the MS/MS spectrum but **A2′** is not observed (Fig. 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 in the above method (Fig. S3, ESI†), which indicates that the *ortho*-iodine as a leaving group is very important. Then, more *ortho*-halogenated benzoic acids were tentatively used as benzyne precursors (Fig. S4–S6, ESI†). 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 (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 using 3-iodobenzoic acid and 4-iodobenzoic acid as the potential precursors, respectively (Fig. S7 and S8, ESI†).

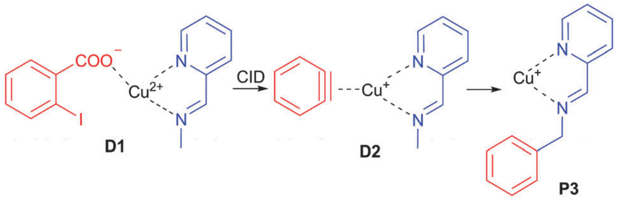
Various ligands are applicable in the gas-phase synthesis of Cu$^+$–benzyne complexes, such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), 2-(aminomethyl)pyridine (2-AMP), and 2,2-bipyridine (Fig. S9–S11, ESI†). After the synthesis of benzyne, its reactivity can be further evaluated through the collisional activation of the copper-bound benzyne–ligand complex. The benzyne is a highly unsaturated species that easily undergoes addition reactions such as the Diels–Alder reaction, cycloadditions with 1,3-dipoles, and nucleophilic additions. If the ligand within the complex, [benzyne···Cu$^+$···L], is purposefully chosen, the reaction between the benzyne and the 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 those of **B4** which are generated *via* ESI of a methanol solution containing *N*-(pyridin-2-ylmethyl)aniline and CuI (Fig. S12 and S13, ESI†).

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 proceed *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



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



Scheme 4 Gas-phase synthesis of the Cu^+–benzyne complex and its reaction with *N*-(pyridin-2-ylmethylene)methanamine.

compounds were then synthesized in solution and their complexes with Cu^+ (**C3** and **C4**) can be readily produced *via* ESI. The multistage fragmentation behavior of **P2** is the same as that of **C3** but quite different from that of **C4** (Fig. S14 and S15, ESI†). The major product ion in the fragmentation 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* a selective C–H bond insertion mechanism.

By applying the same approaches, the reaction of Cu^+–benzyne with *N*-(pyridin-2-ylmethylene)methanamine was studied. The benzyne was expected to react with this ligand through C–H (and not C–N) bond insertion to form product **P3** (Scheme 4). Theoretical calculations support this prediction. As shown in Fig. 2, in the C–N bond insertion process, the methyl transfer from N to benzyne requires a 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 much lower. The final product **P3** is more stable than the starting complex **D2** by 135.7 kJ mol^{-1}, which supports the formation of this product. In addition, the structure of **P3** was further confirmed by multi-stage mass spectrometry (Fig. S16 and S17, ESI†).

This study offers a method to prepare gaseous ligand-ligated 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 to study their gas-phase chemistry.

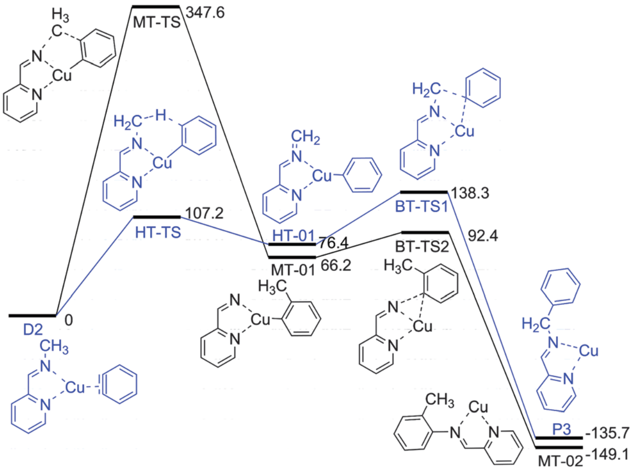


Fig. 2 Energy profile calculated for the Cu^+-mediated reaction of benzyne with *N*-(pyridin-2-ylmethylene)methanamine in the gas phase. The relative free energies are given in kJ mol^{-1}.

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Notes and references

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 communication), it usually refers to *o*-benzyne.
2 J. F. Bunnett, *J. Chem. Educ.*, 1961, **38**, 278–285.
3 W. Sander, *Acc. Chem. Res.*, 1999, **32**, 669–676.
4 T. Kitamura, *Aust. J. Chem.*, 2010, **63**, 987–1001.
5 C. Wentrup, *Aust. J. Chem.*, 2010, **63**, 979–986.
6 S. L. Buchwald and R. B. Nielsen, *Chem. Rev.*, 1988, **88**, 1047–1058.
7 M. Retbøll, A. J. Edwards, A. D. Rae, A. C. Willis, M. A. Bennett and E. Wenger, *J. Am. Chem. Soc.*, 2002, **124**, 8348–8360.
8 G. Werner and H. Butenschön, *Eur. J. Org. Chem.*, 2012, 3132–3141.
9 J. K. Cockcroft, V. C. Gibson, J. A. K. Howard, A. D. Poole and U. Siemeling, *J. Chem. Soc., Chem. Commun.*, 1992, 1668–1670.
10 M. A. Bennett, K. D. Griffiths, T. Okano, V. Parthasarathi and G. B. Robertson, *J. Am. Chem. Soc.*, 1990, **112**, 7047–7048.
11 M. A. Bennett, T. Dirnberger, D. C. R. Hockless, E. Wenger and A. C. Willis, *J. Chem. Soc., Dalton Trans.*, 1998, 271–277.
12 A. A. Cant, L. Roberts and M. F. Greaney, *Chem. Commun.*, 2010, **46**, 8671–8673.
13 J. Campora and S. L. Buchwald, *Organometallics*, 1993, **12**, 4182–4187.
14 A. M. Dyke, A. J. Hester and G. C. Lloyd-Jones, *Synthesis*, 2006, 4093–4112.
15 E. W.-G. Diau, J. Casanova, J. D. Roberts and A. H. Zewail, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 1376–1379.
16 F. S. Amegayibor, J. J. Nash, A. S. Lee, J. Thoen, C. J. Petzold and H. I. Kenttämaa, *J. Am. Chem. Soc.*, 2002, **124**, 12066–12067.
17 P. G. Wenthold, J. Hu and R. R. Squires, *J. Am. Chem. Soc.*, 1996, **118**, 11865–11871.
18 L. M. Kirkpatrick, N. R. Vinueza, B. J. Jankiewicz, V. A. Gallardo, E. F. Archibold, J. J. Nash and H. I. Kenttämaa, *Chem. – Eur. J.*, 2013, **19**, 9022–9033.
19 T. G. Dietz, D. S. Chatellier and D. P. Ridge, *J. Am. Chem. Soc.*, 1978, **100**, 4905–4907.
20 Y. Huang and B. S. Freiser, *J. Am. Chem. Soc.*, 1989, **111**, 2387–2393.
21 Y. Huang and B. S. Freiser, *J. Am. Chem. Soc.*, 1990, **112**, 1682–1685.
22 H.-F. Lee, F.-W. Lin and C.-S. Yeh, *J. Mass Spectrom.*, 2001, **36**, 493–499.
23 D. Wittneben, H.-F. Grützmacher, H. Butenschön and H. G. Wey, *Organometallics*, 1992, **11**, 3111–3116.
24 Y. Huang, Y. D. Hill, M. Sodupe, C. W. Bauschlicher Jr. and B. S. Freiser, *Inorg. Chem.*, 1991, **30**, 3822–3829.
25 S. Gronert, *Chem. Rev.*, 2001, **101**, 329–360.
26 R. Kretschmer, M. Schlangen and H. Schwarz, *Angew. Chem., Int. Ed.*, 2011, **50**, 5387–5391.
27 H. Schwarz, *Angew. Chem., Int. Ed.*, 2011, **50**, 10096–10115.
28 P. S. D. Robinson, G. N. Khairallah, G. de Silva, H. Lioe and R. A. J. O'Hair, *Angew. Chem., Int. Ed.*, 2012, **51**, 3812–3817.
29 C. J. Shaffer, D. Schröder, C. Gütz and A. Lützen, *Angew. Chem., Int. Ed.*, 2012, **51**, 8097–8100.
30 R. R. Julian, J. A. May, B. M. Stoltz and J. L. Beauchamp, *J. Am. Chem. Soc.*, 2003, **125**, 4478–4486.
31 W. A. Donald, C. J. McKenzie and R. A. J. O'Hair, *Angew. Chem., Int. Ed.*, 2011, **50**, 8379–8383.
32 N. Rijs, G. N. Khairallah, T. Waters and R. A. J. O'Hair, *J. Am. Chem. Soc.*, 2008, **130**, 1069–1079.
33 Z. Tian, B. Chan, M. B. Sullivan, L. Radom and S. R. Kass, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 7647–7651.
34 M. M. Meyer, B. Chan, L. Radom and S. R. Kass, *Angew. Chem., Int. Ed.*, 2010, **49**, 5161–5164.
35 M. M. Meyer, G. N. Khairallah, S. R. Kass and R. A. J. O'Hair, *Angew. Chem., Int. Ed.*, 2009, **48**, 2934–2936.

36 H. Dossmann (Soldi-Lose), C. Afonso, D. Lesage, J.-C. Tabet and E. Uggerud, *Angew. Chem., Int. Ed.*, 2012, **51**, 6938–6941.

37 N. J. Rijs, N. Yoshikai, E. Nakamura and R. A. J. O'Hair, *J. Am. Chem. Soc.*, 2012, **134**, 2569–2580.

38 F. Coelho and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2011, **50**, 5261–5263.

39 G. Li, X. Li, Z. Ouyang and R. G. Cooks, *Angew. Chem., Int. Ed.*, 2013, **52**, 1040–1043.

40 H. Chen, L. S. Eberlin, M. Nefliu, R. Augusti and R. G. Cooks, *Angew. Chem., Int. Ed.*, 2008, **47**, 3422–3425.

41 T. Müller, A. Badu-Tawiah and R. G. Cooks, *Angew. Chem., Int. Ed.*, 2012, **51**, 11832–11835.

42 N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030–5048.

43 P. P. Lange, L. J. Gooßen, P. Podmore, T. Underwood and N. Sciammetta, *Chem. Commun.*, 2011, **47**, 3628–3630.

44 N. J. Rijs and R. A. J. O'Hair, *Dalton Trans.*, 2012, **41**, 3395–3406.

45 N. J. Rijs, N. Yoshikai, E. Nakamura and R. A. J. O'Hair, *J. Org. Chem.*, 2014, **79**, 1320–1334.

46 L. Xue, W. Su and Z. Lin, *Dalton Trans.*, 2010, **39**, 9815–9822.

47 L. Xue, W. Su and Z. Lin, *Dalton Trans.*, 2011, **40**, 11926–11936.