

Gas-Phase Synthesis of Charged Copper and Silver Fischer Carbenes from Diazomalonates: Mechanistic and Conformational Considerations in Metal-Mediated Wolff Rearrangements

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Abstract: Copper(I) and silver(I) Fischer carbenes are synthesized in the gas phase. Various diazomalonate-based compounds with an attached metal ion are introduced into the gas phase by electrospray ionization and subjected to collisional activation. Loss of N₂ generates a metastable Fischer carbene, which subsequently undergoes Wolff rearrangement and loss of CO. Further excitation leads to the loss of another CO molecule and the generation of a stable Fischer carbene. Isotopically labeled compounds are utilized to confirm the assignment of the products resulting from this process. DFT calculations are used to evaluate various mechanistic possibilities and to quantitatively assess the energetics of reactants and products. Silver(I) is shown to be more effective in facilitating Wolff rearrangement than copper(I), although both are more effective when compared to spectator charges such as sodium or a fixed quaternary nitrogen. Carbenes are not produced when copper(II), nickel(II), or a proton is used to form a quasi-molecular ion from the diazomalonate carbene precursor. Finally, trapping of the Fischer carbene by various functional groups attached through the open coordination site of the metal is investigated.

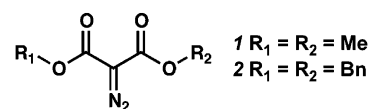
Introduction

The gas-phase synthesis of metallocarbenoid compounds has a surprisingly long history.¹ In early studies, the metallocarbenoids were created by high-energy methods utilizing electron impact ionization. The resulting ions were then used in bimolecular reactions with various neutral molecules to study the chemistry of and determine metal–carbon bond strengths for these charged Fischer carbenes. The importance of studying gas-phase species in determining mechanistic pathways for olefin metathesis was also realized early on,^{1b} and more recent studies have taken advantage of electrospray ionization (ESI) to continue this work.² Gas-phase experiments have also enabled mechanistic studies with other highly reactive metallocarbenoid species.³

The utility of diazo compounds as carbene and metallocarbenoid precursors has been heavily exploited in solution-phase chemistry.⁴ The use of diazo compounds as precursors in gas-phase studies involving mass spectrometry (MS) remains less explored.⁵ We have recently reported that diazo compounds are

excellent carbene precursors for such studies.⁶ In these experiments, a carbene is produced through the low-energy collision-activated dissociation (CAD)⁷ of a diazo compound. The resulting loss of N₂ and generation of the carbene is achieved under conditions sufficiently mild that noncovalently bound complexes are not dissociated in the process. The highly reactive carbene then inserts into the guest and converts the noncovalent complex into a covalently bound molecule. All of the molecules in our previous study were based on the diazomalonate core with at least one 18-crown-6 crown ether attached. These reagents have been appropriately named “molecular mouse-traps.”⁶

Diazomalonates⁸ (such as **1** and **2**) and related diazo ketones⁹ are known to undergo Wolff rearrangement in the gas phase as



shown in Scheme 1. Since its discovery in 1902, the Wolff

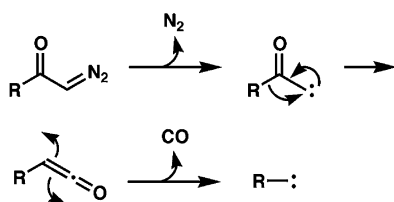
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Scheme 1



rearrangement¹⁰ has been the subject of numerous studies.¹¹ In the present work, we use the solvent-free environment of gas-phase experiments to study the mechanism of multiple, consecutive Wolff rearrangements observed in diazomalonates.⁸ The effects that various coordinated metal ions and other charged groups have on Wolff rearrangements are discerned from gas-phase MS experiments. Theory is used to quantitatively assess each intermediate for the proposed mechanism. Although the solution-phase synthesis of stable copper(I) and silver(I) Fischer carbenes has been known for some time,¹² here we report the first gas-phase synthesis of copper(I) and silver(I) Fischer carbenes. Results for several intermolecular reactions of these carbenes with molecules coordinated to the metal ion are presented.

Experimental Section

All mass spectra were acquired on a Finnigan LCQ Classic quadrupole ion trap instrument utilizing a standard electrospray source. Solutions of the reagents in the ~30–80 μM range were electrosprayed from a ~80/20 (v/v) solution of methanol/water with a minimum of 0.1% MeCN added. Soft ionization settings that minimize energetic collisions during sample collection were used to maximize the intensity of noncovalently bound complexes.¹³ Ions of interest were isolated and subjected to collisional activation until product peaks were observed. Helium was used as the collision gas for all experiments. For each MSⁿ step, the peak of interest was reisolated prior to further dissociation. All chemicals were purchased from Sigma-Aldrich and used without further purification unless otherwise noted. Metal ion complexes were formed by adding an appropriate salt to the solution. No counterion effects were noted. For studies of intermolecular reactions, the desired ligand (such as 5-hexynenitrile) was added directly to the solution in severalfold excess.

Calculations. Candidate structures were evaluated initially at the PM3 semiempirical level. Following minimization at the lower level of theory, structures were optimized using density functional theory (DFT). The DFT calculations were carried out using Jaguar 4.1 (Schrödinger, Inc., Portland, OR). Full geometry optimization was performed at the B3LYP/LACVP** level of theory. Semiempirical PM3 MNDO-type calculations were carried out using the HyperChem 5.1

Professional Suite (Hypercube, Inc., Gainesville, FL). Molecular dynamics simulations were carried out using CACHE Worksystem Pro 5.04 (Fujitsu, Inc., Beaverton, OR). Structures were heated to 300 K for 10 ps with a 0.001-ps time interval utilizing the augmented MM3 parameters.

Synthesis. Reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were dried and purified using activated alumina columns. All other reagents were used as received from commercial sources. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV and *p*-anisaldehyde staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. ¹H NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz) in CDCl₃ and are internally referenced to the residual chloroform peak (7.27 ppm) relative to Me₄Si. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. IR spectra were recorded on a Perkin-Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm⁻¹). Preparatory reversed-phase HPLC was performed on a Beckman HPLC with a Waters DeltaPak 25 \times 100 mm, 100- μm C18 column equipped with a guard.

2-Diazodimethyl Malonate (1). **1** was prepared according to previously established methods.¹⁴ The product was isolated as a yellow oil (2.58 g, 16.29 mmol, 93% yield) with the same physical properties as previously reported.

2-Diazodibenzyl Malonate (2). A round-bottomed flask (10 mL) was charged with dibenzylmalonate (77 μL , 0.308 mmol), MeCN (3 mL), and *p*-acetamidobenzylsulfonyl azide (116 mg, 0.485 mmol). Et₃N (150 μL , 1.08 mmol) was then added, and the reaction was stirred at room temperature for 10 h. TLC analysis (3:1 hexanes/EtOAc eluent, *R*_f = 0.46) showed the reaction to be complete. The solvent was removed by evaporation under reduced pressure, and the crude mixture was subjected to flash chromatographic purification (5:1 hexanes/EtOAc eluent) to afford **2** as a yellow oil (75 mg, 0.242 mmol, 78% yield) with the same physical properties as previously reported.¹⁵

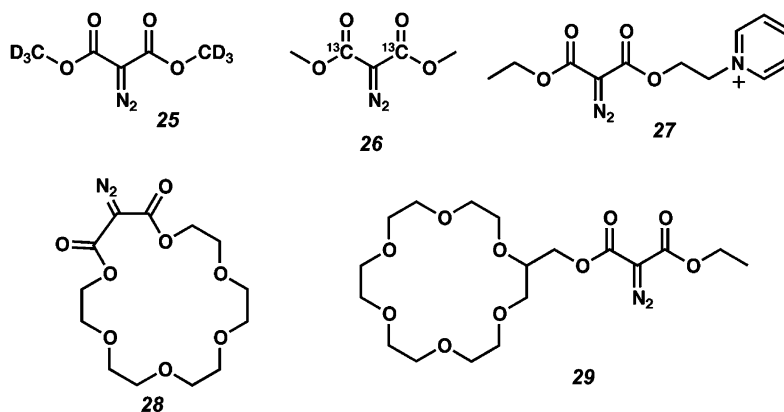
Diazomalonate 25 (Chart 1). A round-bottomed flask (5 mL) was charged with CH₂Cl₂ (1 mL), CD₃OD (500 μL , 11.3 mmol), and Et₃N (100 μL , 0.717 mmol). This mixture was stirred rapidly while malonyl dichloride (20 μL , 0.206 mmol) was added dropwise at room temperature. TLC analysis (3:1 hexanes/EtOAc eluent, *R*_f = 0.45) showed complete conversion to the malonate ester within 2 h. The solvent and excess reagents were removed by evaporation under reduced pressure, and then MeCN (2 mL) and *p*-acetamidobenzylsulfonyl azide (103.5 mg, 0.431 mmol) were added to the flask. Et₃N (100 μL , 0.717 mmol) was added, and the solution was stirred for 24 h. The solvent was then removed by evaporation under reduced pressure. The product was purified by dissolving the residue in a minimal amount of CH₂Cl₂ (500 μL) and then precipitating the salts by addition of Et₂O (5 mL). Filtration through Celite removed the salts, and the solvent was removed by evaporation under reduced pressure to afford **25** as a yellow oil (11.9 mg, 0.073 mmol, 35% yield).

Diazomalonate 26. To a stirred solution of H₂C(¹³CO₂H)₂ (19.7 mg, 0.179 mmol) in Et₂O (2 mL) in a scratch-free flask (25 mL) was added ethereal diazomethane solution (0.2 M, 4.0 mL, 0.800 mmol). TLC analysis (3:1 hexanes/EtOAc eluent, *R*_f = 0.45) showed the reaction to be complete. The solvent and excess reagents were removed by evaporation under reduced pressure, and then MeCN (1 mL) and *p*-acetamidobenzylsulfonyl azide (25.9 mg, 0.108 mmol) were added to the flask. Et₃N (41 μL , 0.294 mmol) was added, and the solution was stirred for 24 h. The solvent was then removed by evaporation under reduced pressure. The product was purified by dissolving the

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Chart 1



residue in a minimal amount of CH_2Cl_2 (500 μL) and then precipitating the salts by addition of Et_2O (5 mL). Filtration through Celite removed the salts, and the solvent was removed by evaporation under reduced pressure to afford **26** as a yellow oil (17.4 mg, 0.108 mmol, 60% yield).

Diazomalonate 27. A round-bottomed flask (10 mL) was charged with CH_2Cl_2 (2 mL), EtOH (25 μL , 0.687 mmol), and 2-bromoethanol (30 μL , 0.421 mmol). This mixture was stirred rapidly while malonyl dichloride (20 μL , 0.206 mmol) was added dropwise at room temperature. The reaction yielded a statistical mixture of esters within 2 h as determined by ESI-MS. The primary product was 2-bromoethyl ethylmalonate. The solvent and excess reagents were removed by evaporation under reduced pressure, and then MeCN (2 mL) and pyridine (50 μL) were added to the flask. After 24 h, *p*-acetamidobenzenesulfonyl azide (94.1 mg, 0.392 mmol) and then Et_3N (150 μL , 1.076 mmol) were added. The solution was stirred for another 12 h. The solvent was removed by evaporation under reduced pressure to afford **27**; the yield was qualitatively estimated to be ~50% by MS (m/z 264.3).

Diazomalonate 28. To a stirred, dry solution of penta(ethylene glycol) (44.4 μL , 0.210 mmol), CH_2Cl_2 (20 mL), and Et_3N (150 μL , 1.076 mmol) was added malonyl dichloride (24 μL , 0.247 mmol). The mixture was heated to reflux for 5.5 h, cooled, and then the solvent was removed by evaporation under reduced pressure. The product was recovered by extraction of the crude residue with refluxing hexanes (20 mL). The solvent was then removed by evaporation under reduced pressure to leave the malonate crown ether. This malonate ester¹⁶ was then dissolved in MeCN (3 mL). Stepwise addition of *p*-acetamidobenzenesulfonyl azide (151.0 mg, 0.629 mmol) and Et_3N (200 μL , 1.435 mmol) provided **28** after stirring for 10 h. The solvent was removed in vacuo, the residue was dissolved in a minimal amount of CH_2Cl_2 (500 μL), and the undesired salts precipitated out of solution with the addition of Et_2O (5 mL). Filtration through Celite and removal of solvent by evaporation under reduced pressure yielded **28** (59.3 mg, 0.179 mmol, 85% yield).

Diazomalonate 29. To a stirred, dry solution of 18-crown-6-methanol (50.0 μL , 0.159 mmol), CH_2Cl_2 (1.5 mL), and Et_3N (33 μL , 0.237 mmol) was added ethylmalonyl chloride (28 μL , 0.219 mmol). The mixture was heated to reflux for 8 h, the solution was cooled, and then the solvent was removed by evaporation under reduced pressure. The residue was dissolved in MeCN (750 μL) and treated with Et_3N (30 μL , 0.215 mmol). To this solution was added *p*-acetamidobenzenesulfonyl azide (53.1 mg, 0.221 mmol), and the mixture was stirred for 10 h. The solvent was removed by evaporation under reduced pressure, the residue was dissolved in a minimal amount of CH_2Cl_2 (500 μL), and the undesired salts were precipitated out of solution with the addition of Et_2O (5 mL). Filtration through Celite and removal of solvent by evaporation under reduced pressure yielded **29** (59.8 mg,

0.138 mmol, 87% yield) as a light yellow oil. A small sample (~15 mg) was chromatographed to analytical purity by HPLC (0.1% (wt/v) TFA in water, 8.0 mL/min, 0.30% acetonitrile/min, 82–85 min). FTIR (thin film) 2879, 2142, 1755, 1689; ^1H NMR (300 MHz, CDCl_3) 4.45 (dd, $J = 3.85, 12.1$ Hz, 1H), 4.31 (q, $J = 7.14$ Hz, 2H), 4.27 (m, 1H), 3.85 (t, $J = 4.95$, 1H), 3.80 (br s, 1H), 3.67 (br s, 21H), 1.32 (t, $J = 7.14$ Hz, 3H); MS m/z 435.2 (H^+).

Results and Discussion

Copper(I) and Silver(I). The ESI-MS spectrum for a mixture of copper(I) and **1** is shown in Figure 1a. The base peak corresponds to $[\mathbf{1} + \text{MeCN} + \text{Cu}]^+$ or **3** (for simplicity, the corresponding structures are to the right of the mass spectra in Figure 1). It can also be seen from Figure 1a that **1** has a high affinity for Na^+ (present as an impurity) and that Cu(I) has a high affinity for acetonitrile. As seen in Figure 1b, isolation of **3** followed by CAD leads to two sequential losses of 28 Da. The first loss of 28 Da corresponds to the loss of N_2 from the diazo functionality leading to structure **4**. The second loss of 28 Da results from Wolff rearrangement of **4** accompanied by a loss of CO yielding **5**. In Figure 1c, structure **5** is isolated and subjected to further CAD resulting in another loss of 28 Da. This is also attributed to Wolff rearrangement of **5** followed by the loss of a second CO yielding the stable copper Fischer carbene **6**. Figure 1d shows the results of CAD of structure **6**. In this case, the noncovalent acetonitrile adduct is lost, followed by the pickup of either water or methanol. This pickup is not surprising given the vacant copper(I) coordination site and the fact that the spectra were acquired from a water/methanol solution.

DFT calculations at the B3LYP level using the LACVP** basis set were performed to determine structures and relative energetics for the products and probable intermediates in Figure 1. The structures and energetics are presented in the reaction coordinate diagram in Figure 2. When a ligand such as N_2 or CO is lost, the energy of the minimized separated molecule is added to compare with the complex prior to dissociation. Structure **3** is found to be the global minimum, and there is support for this binding mode from crystal structures.¹⁷ Direct dissociation of N_2 from **3** is unlikely because the copper(I) ligand restrains the geometry of the molecule in a triplet-like conformation, whereas the thermal dissociation of N_2 must yield the singlet state.¹⁸ Furthermore, **1** has a singlet ground state,⁶ and attempts to minimize structure **3** with the N_2 removed were

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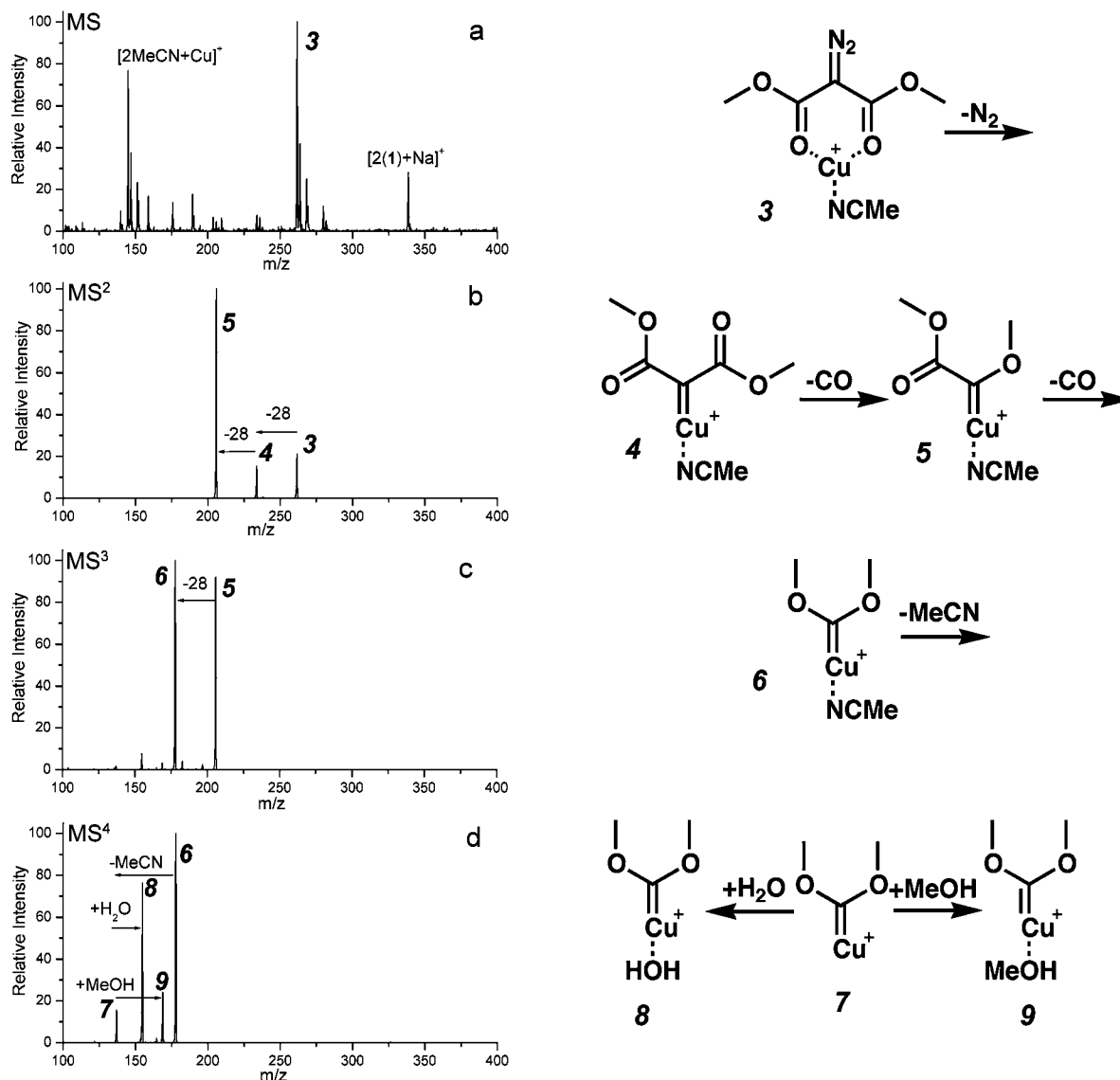
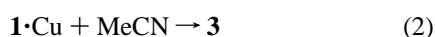


Figure 1. Structures for the peaks in the mass spectra (left) given in the reaction scheme (right). (a) MS of a mixture of **1** and Cu (I) in a 20:80 (v/v) water/methanol solution with ~0.1% MeCN. (b) MS² on complex **3**. N₂ and CO are lost sequentially. (c) MS³ on complex **5** resulting in the loss of an additional CO. (d) MS⁴ on **6** resulting in the exchange of the MeCN ligand for either water or methanol.

unsuccessful. Matrix isolation studies on similar systems suggest that copper(I) insertion into the C–N bond of **3** is a more likely alternative.¹⁹

Further experimental and theoretical evidence also suggests that the copper(I) ion mediates the generation of the carbene from the diazo precursor. CAD experiments on [1 + Na]⁺ result in the complete loss of signal without producing any observable peaks, suggesting dissociation of the sodium ion (which has an *m/z* ratio that is too small to detect). Similar experiments with rubidium yield a peak corresponding to Rb⁺ exclusively from the collisional activation of [1 + Rb]⁺. The calculated ΔH for reaction 1 is –59 kcal/mol, which can be regarded as the binding energy of the sodium ion to **1**.



Similarly, calculations reveal a ΔH of –43 kcal/mol for reaction 2, which is the binding energy of MeCN to the **1**·Cu complex. This value is in reasonable agreement with similar experimental and theoretical results.²⁰ The MeCN ligand is retained throughout the entire series of reactions shown in Figure 2 without dissociating. Therefore, the reaction barriers for each step must be below 43 kcal/mol, otherwise the MeCN ligand would simply dissociate. Furthermore, the binding energy of the sodium ion is much greater at 59 kcal/mol, yet the ion dissociates prior to the loss of N₂ and the generation of the carbene. This demonstrates that copper(I) lowers the activation barrier for the generation of a carbene by at least 16 kcal/mol relative to complexation with sodium.

The reaction shown in Figure 2 proceeds by rearrangement of structure **3** to structure **10** followed by Cu⁺ insertion as shown

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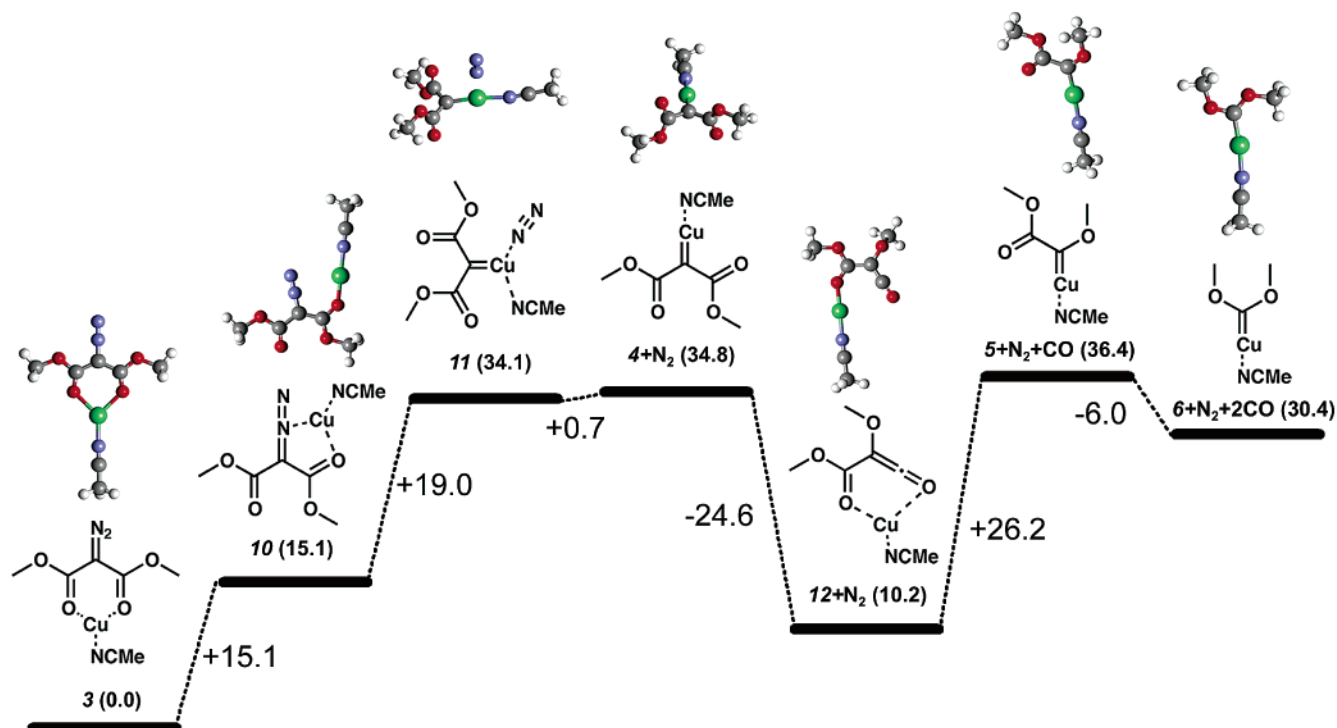


Figure 2. Diagram illustrating the energetics of reaction intermediates in Figure 1. The energetics are calculated relative to structure **3** and are given in parentheses (in kcal/mol). When a neutral gas molecule is lost, the energy of the minimized, separated molecule is added to that of the remaining structure. The barriers at each step have not been calculated but are below the binding energy of the MeCN ligand (which is calculated to be -43 kcal/mol as explained in the text).

in **11**. Crystal structures of copper(I) Fischer carbenes have C–Cu bond lengths similar to those in **11** and, in some cases, demonstrate a high affinity for MeCN ligands.²¹ Copper insertion is postulated as a prelude to the Wolff rearrangement from **4** to **12**, which must proceed through a singlet state. There is poor agreement between theoretically and experimentally determined barriers to Wolff rearrangement, with theory predicting higher values than those observed experimentally.²² Theory would predict a large barrier for the conversion of **4** to **12** because of the exothermicity of the reaction.^{22b} The experimental evidence in Figure 1b suggests that both rearrangement of **4** to **12** and subsequent loss of CO to produce **5** proceed with minimal barriers. It should be pointed out that, given a low barrier to rearrangement, the structure for the observed peak in Figure 1b may be the rearranged product (**12**) rather than carbene (**4**).²³ In either case, the observed products suggest that the presence of copper lowers the barrier to Wolff rearrangement in addition to facilitating the generation of the initial carbene.

The Wolff rearrangement product of **5** undergoes copper insertion without barrier upon minimization, suggesting that the transition state may occur prior to rearrangement. Therefore, the loss of the second CO likely occurs in a concerted fashion without a true ketene intermediate. The data in Figure 1b and c show that the initial two losses occur simultaneously, which suggests a higher barrier to the loss of the second CO. However,

it should be noted that the noncovalently bound MeCN ligand is retained throughout the entire process, limiting the reaction barriers to the bond dissociation energy of the Cu–NCMe bond (or 43 kcal/mol). Finally, a stable Fischer carbene (**6**) is produced upon loss of the second CO. Subsequent excitation of this complex results in the loss of the MeCN ligand followed by attachment of either H₂O or MeOH from the residual solvent vapor present in the ion trap (Figure 1d).

In the presence of silver(I), structure **13** (Figure 3a) is formed in high abundance. However upon collisional activation in Figure 3b, the MeCN ligand is lost instead of N₂ as was the case with copper(I). This difference is due to the weak binding of the third ligand to the silver(I) cation.²⁴ Loss of the MeCN adduct is followed by collisional cooling of the product (**14**), which leads to some pickup of residual methanol (**15**) or water (**16**) from the trap as seen in Figure 3b. Further CAD of reisolated **14** leads to the exclusive loss of 56 Da, comprising N₂ and CO with no intermediate loss of N₂ being observed. Again these losses are followed by the pickup of methanol or water. The absence of an intermediate loss of N₂ suggests that silver(I) is more efficient at facilitating the Wolff rearrangement and subsequent loss of CO than copper(I), consistent with the predominant use of silver(I) as the catalyst where Wolff rearrangement is required for a synthetic route.^{4a} Isolation and activation of **17** leads to the expected loss of the second CO, yielding structure **20** and ensuing pickup of water or methanol. The silver Fischer carbenes **20**, **21**, and **22** are the final observable carbene products in this sequence. Further CAD of **20** leads to the loss of the Ag⁺ cation, presumably generating the neutral dimethoxy carbene in the process.

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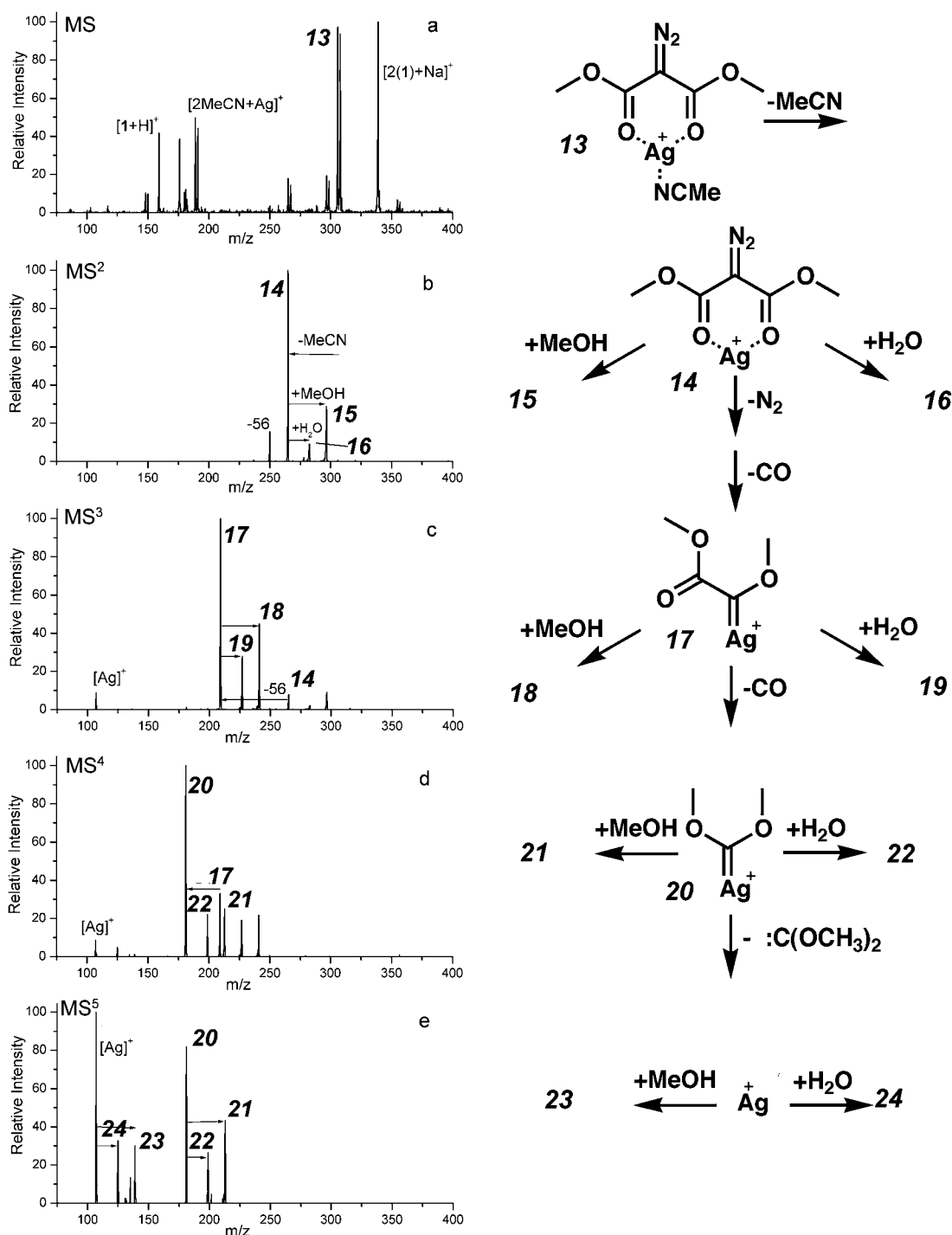


Figure 3. Spectra acquired from a mixture of silver(I) and **1**. The structures are given to the right of the appropriate spectrum. (a) MS spectrum showing complexation with Ag⁺. (b) MS² spectrum of **13**, where the loss of MeCN generates the most abundant product ion peak. (c) MS³ spectrum of **14** showing the facile loss of N₂ and CO. (d) MS⁴ spectrum of **17** showing loss of second CO and generation of final silver Fischer carbenes. (e) MS⁵ spectrum of **20**, further CAD results in the cleavage of the metal–carbon bond.

Labeling Experiments. Isotopic labeling experiments were performed to confirm the proposed reaction pathways. The results for the two labeled compounds, **25** and **26**, are given in Table 1. Structure **25** is labeled with three deuteriums on each of the terminal methyl groups. Comparison of the data in Table 1 with that shown in Figure 1 reveals that the six deuteriums are retained throughout the entire experiment. This indicates that only interior carbons are lost as CO and that there is no detectable scrambling with MeOH in the ion trap. To confirm which carbons are lost and to determine the extent to which

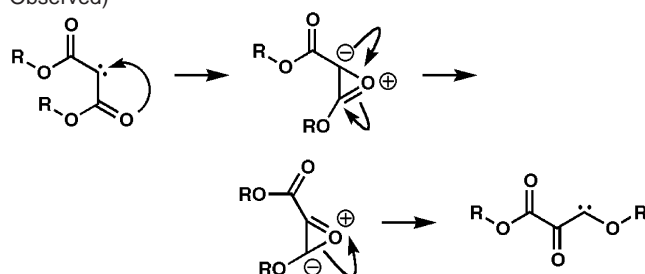
rearrangement of the carbene occurs, structure **26** was synthesized with ¹³C at the 1,3 positions. Experiments with **26** confirm that the two interior ¹³C labeled carbons are lost, as shown in Table 1. There is no apparent rearrangement of the carbene via an oxirene intermediate as depicted in Scheme 2.¹¹ These two experiments serve to confirm that N₂ is lost first, as is expected, and that carbon in the 1 and 3 positions, specifically, are lost as CO.

Divalent Metals, Protons, and Fixed Charges. The experimental MS data for several related experiments on **1** are

Table 1. Summary of MS Results.

molecule	attached cation	initial ligands	observed peaks ^a
25	Cu ⁺	MeCN	MS ² on 268 → 193(12), 212(100), 240(15), 268(21) MS ³ on 212 → 161(11), 184(100), 212(80) MS ⁴ on 184 → 143(5), 161(43), ^b 175(8), ^b 184(100)
26	Cu ⁺	MeCN	MS ² on 264 → 207(100), 236(11), 264(2) MS ³ on 207 → 178(100), 207(98)
1	Cu ²⁺	2(1)	MS ² on 268.4 → 189.5(100), 268.4(<1)
1	Cu ²⁺	2MeCN	MS ² on 151 → 140(100)*, 147(50) ^b
1	Ni ²⁺	2(1)	MS ² on 266 → 187(30), 196(100), ^b 203(72), ^b 266(<1)
1	H ⁺	2(1)	MS ² on 159 → 55(80), 69(6), 87(100), 101(8), 127(93), 145(28), 159(<1)
2	Cu ⁺	MeCN	MS ² on 414 → 345(8), 373(100), 414(10) MS ³ on 373 → 289(55), 317(37), 345(42), 373(100)
2	Ag ⁺		MS ² on 417 → 289(12), 317(17), 333(39), 345(25), 361(96), 389(100), 417(16) MS ³ on 389 → 317(10), 333(26), 361(69), 389(100)
27	see structure		MS ² on 264 → 113(8), 157(13), 236(100), 264(22) MS ³ on 236 → 157(100), 180(42), 192(40), 208(61), 236(57)

^a Peaks are given with accompanying relative intensities in parentheses. Some low-intensity peaks (under 15% relative intensity) that are not assigned structures or discussed in the text are omitted for clarity. ^b Solvent molecule pickups.

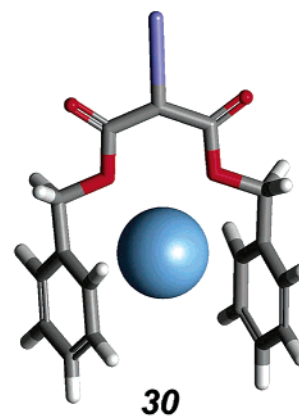
Scheme 2. Potential Carbene Scrambling via Oxirene (Not Observed)

summarized in Table 1. For both copper(II) and nickel(II), the metal is complexed with three molecules of **1** or $[3(\mathbf{1}) + \text{M}]^{2+}$ (where M = Ni or Cu), with the ligands coordinating the metal in a pseudooctahedral fashion. CAD of these complexes does not lead to the loss of N₂ but instead yields only the loss of an entire coordinating molecule. A small amount of $[\mathbf{1} + \text{Cu} + 2\text{MeCN}]^{2+}$ is also formed from the copper solution. However, as the data show in Table 1, this complex simply loses one of the MeCN ligands upon CAD. These results illustrate that copper(II) and nickel(II) are not efficient at mediating the formation of Fischer carbenes or subsequent Wolff rearrangements. Protonated **1** does not lose N₂ upon CAD either but instead yields the assortment of fragments shown in Table 1.

The results presented thus far suggest that the coordinating charge can dictate the resulting chemistry upon collisional activation in diazo compounds. Structure **27** was designed to investigate the energetics of N₂ loss and Wolff rearrangements in the absence of a coordinating charge. In **27**, the charge is provided by a fixed quaternary nitrogen from the pyridinium group. As seen in Table 1, this compound loses N₂ to yield the most abundant product by CAD in the MS² spectrum. Further collisional activation of the resulting molecule demonstrates that Wolff rearrangement and the loss of multiple CO molecules does occur. However, this process is accompanied by other losses not related to Wolff rearrangement. In fact, the loss of pyridine yields the base peak in the MS³ spectrum. This suggests that the energetics associated with Wolff rearrangement and loss of CO for this reaction are similar to those for the loss of pyridine.²⁵

The pattern of losses for molecule **27** contrasts sharply with the results obtained for all of the copper(I) and silver(I) adducts. Metal adducts of **1** lose N₂ and the first CO in one step without the addition of further excitation energy. The loss of the second CO occurs upon further activation, but no other competitive products are produced in significant abundance at any stage of the experiment. In the case of **27**, N₂ loss occurs without any accompanying loss of CO. Upon further excitation of $[\mathbf{27} - \text{N}_2]^+$, Wolff rearrangement followed by the loss of the first and second CO molecules occurs with the appearance of several other competitive products. In other words, Wolff rearrangement products are no longer favored in the absence of a metal ligand. These results suggest that copper(I) and silver(I) facilitate the Wolff rearrangement and loss of CO shown in Figures 1 and 2.

Effect of Benzyl Groups. In structure **2**, the methyl groups are replaced by benzyl groups, and with the addition of copper(I), the ESI-MS contains a prominent $[\mathbf{2} + \text{Cu} + \text{MeCN}]^+$ peak. As shown in Table 1, CAD dissociation of this peak leads primarily to the loss of the MeCN ligand. No appreciable pickup of water or methanol is observed following the loss of MeCN. This suggests that the benzyl groups are able to coordinate the metal ion sufficiently so that the lost ligand is not replaced. There is precedence for this type of coordination from crystal structure studies.²⁶ Interestingly, further CAD of $[\mathbf{2} + \text{Cu}]^+$ leads to the sequential loss of N₂, CO, and CO with each intermediate being observed. No further collisional activation steps are necessary to observe the loss of all three molecules. Similar experiments with silver(I) and **2** yield very similar results (Table 1), but in this case, the $[\mathbf{2} + \text{Ag}]^+$ peak is formed directly from



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Table 2. MS Data for Crown Compounds

molecule	attached cation	observed peaks ^a
28	Na ⁺	MS ² on 355→ 327(100), 355(6) MS ³ on 327→ 255(13), 271(6), 299(100), 327(5) MS ⁴ on 299→ 225(100), 255(40), 271(73), 299(18)
28	Cu ⁺	MS ² on 395→ 339(26), 367(100), 395(18) MS ³ on 367→ 339(94), 367(100) MS ⁴ on 339→ 265(16), 311(100), 339(38)
28	NH ₄ ⁺	MS ² on 350→ 173(11), 217(12), 261(100), 333(33), 350(72)
28	Cu ²⁺	MS ² on 197.5→ 175.5(100), 184.3(6), ^b 191.2(21), ^b 197.5(5)
29	NH ₄ ⁺	MS ² on 452→ 380(12), 424(100), 452(61) MS ³ on 424→ 175(26), 203(21), 247(19), 291(19), 351(44), 424(100)
29	Na ⁺	MS ² on 457→ 385(3), 429(100), 457(9) MS ³ on 429→ 299(10), 357(29), 373(100), 385(10), 401(20), 429(30)

^a Peaks are given with accompanying relative intensities in parentheses. Some low-intensity peaks (under 15% relative intensity) that are not assigned structures or discussed in the text are omitted for clarity. ^b Solvent molecule pickups.

solution in high abundance. Because the metal ion is coordinated to **2** by the benzyl groups, the relative conformation of the diazo functionality to the esters is different for copper(I) and silver(I) adducts of **1** and **2**. DFT calculations suggest the silver(I) adduct structure shown in **30**. The fact that Wolff rearrangement proceeds more easily for **30** than for **3** suggests that the conformational energy minimum is similar to the preferred conformational orientation that leads to Wolff rearrangement for **30**. Conformational effects have been observed to influence Wolff rearrangements.¹¹

Macrocycles. Crown ethers and other related macrocycles are well suited to coordinate a variety of metal ion and charged functional groups²⁷ and often mitigate against the attachment of other solvent adducts once in the gas phase. Therefore, structures **28** and **29** are well suited to study the proximal effects of various cations and different coordination motifs on the Wolff rearrangement in the absence of weakly bound ligands. The diazo group for **28** is included in the ring, bringing the charge in close proximity to the diazo group. However, it should be noted that the coordination geometry between the charge and the diazo is significantly different for **1** and **28** due to conformational constraints imposed by the macrocycle. Structure **29** is more flexible, allowing for either coordination or separation of the metal and the diazo group.

The CAD results for **28** coordinated to copper(I) and sodium are presented in Table 2. In both cases, the loss of N₂, CO, and CO occurs predominantly one step at a time, requiring the acquisition of an MS⁴ scan to induce the loss of the second CO. This suggests that the more conformationally restrained macrocycle requires additional activation energy to induce Wolff rearrangement but does not necessarily exclude participation of the cation in the reaction. The resonance excitation rf voltages applied at each step of the experiment are (for sodium) 0.67, 0.83, and 0.99 V and (for copper) 0.69, 0.82, and 0.71 V, respectively. The excitation voltages are very similar for the first two steps of the experiment for both cations, but copper(I) clearly catalyzes the loss of the second CO more efficiently than sodium ($\Delta V \sim 0.3$ V). This is additionally confirmed by the absence of competitive fragments in the copper(I) experiment, whereas in the case of sodium, the base peak in the MS⁴ spectrum is not the product of Wolff rearrangement.

The copper(II) adduct of **28** can also be prepared in small abundance, and the results for the CAD are found in Table 2. Copper(II) catalyzes the loss of 44 *m/z*, which is presumably the loss of ethylene oxide from the crown ether portion of the molecule.²⁸ The loss of N₂ is not detected, again suggesting that copper(II) does not catalyze the formation of Fischer carbenes or the subsequent Wolff rearrangement observed with other cations. CAD of the ammonium adduct of **28** is also presented in Table 2. In this case, the loss of NH₃ followed by subsequent cleavage of protonated **28** is the only process observed. This suggests that close proximity of a labile proton can prevent the loss of N₂ and subsequent reactions from occurring. However, it should be noted that this problem is easily corrected by complexation with a more basic amine such as 1-hexylamine. CAD of the hexylamine adduct leads primarily to the loss of N₂ (data not shown). Alternatively, weaker binding by ammonium versus 1-hexylamine may explain the dissociation in the case of ammonium. These experiments confirm the notion that the cation can greatly influence the subsequent chemistry upon excitation of these molecules.

Charge Proximity Effects. In the copper(I) and silver(I) adducts of **2**, the metal ion is coordinated to the benzyl groups and is not in close proximity to the diazo group. It is not surprising that the resulting CAD spectra are very similar for both metals. In general, charges that are not in close proximity to the diazo group have less influence on the resulting CAD patterns. This is well illustrated by comparing **28** and **29**. Molecular dynamic simulations suggest that the collisional heating of **29** leads to extended structures where the lariat sidearm extends away from the charge. This leads to a large separation between the charge and the diazo group. For structure **28**, heating of the quasimolecular complex does not lead to significant structural changes, leaving the charge in close proximity to the diazo group. The net effect is that the diazo group is ~ 2 Å further away from the charge in **29** when compared to **28**. CAD of [**28** + NH₄]⁺ does not lead to the loss of N₂ or subsequent Wolff rearrangement products. By contrast, when **29** is complexed with ammonium, CAD leads to the loss of N₂ and formation of a carbene (Table 2). This implies that the ammonium ion does not interact with the diazo group in **29**, but this does not rule out subsequent interactions between the newly generated carbene and the cation. Interestingly, subsequent CAD of [**29** - N₂ + NH₄]⁺ does not lead to any Wolff rearrangement products. This is attributed to the high

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Table 3. Intermolecular Reactions with Fischer Carbenes.

molecule	attached cation	initial ligand	partial loss of ligand	covalent bond cleavage ^a
1	Cu ⁺	5-hexynenitrile	yes	MS ³
2	Cu ⁺	5-hexynenitrile	yes	no
1	Cu ⁺	5-hexynenitrile	yes	no
1	Cu ⁺	4-phenylbutyronitrile	yes	MS ³

^a If covalent bond cleavage occurs either competitively with loss of the ligand or exclusively, the step where this occurs is indicated.

proton affinity of the carbene,²⁹ which reacts with the ammonium and prevents Wolff rearrangement. CAD of **29** complexed with sodium leads to the expected loss of N₂ and the formation of both Wolff rearrangement products in the MS³ spectrum. Alternatively, weaker binding of ammonium by **28** relative to **29** may explain the difference in experimental results.

Conformational Effects. The degree of conformational restraint present in a molecule can favor or disfavor subsequent Wolff rearrangement. It was established in the previous paragraph that copper(I) and silver(I) adducts of **2** behave very similarly with the simultaneous loss of all products, but it should be noted that the CAD spectra of these two complexes are not similar to any others obtained in the course of this study. We attribute this to a conformational effect where the metal restrains the molecule in a conformation that favors Wolff rearrangement. The opposite effect is observed in [**28** + Na]⁺, which is also conformationally restrained. In this case, Wolff rearrangement is not favored, and additional activation energy must be added at each step. Interestingly, the barrier becomes much larger when the diameter of the macrocycle is reduced. This supports the proposition that conformational constraints lead to the larger activation barriers required for the CAD of **28** bound to various ions. Unconstrained systems with a remote charge that does not react with the carbene such as **27** and [**29** + Na]⁺ all demonstrate similar behavior upon CAD.

Intermolecular Reactions. Given the spectator MeCN ligand present in **3**, the possibility for intermolecular reactions might exist given the addition of the proper ligand. The results for attaching three different ligands are summarized in Table 3. It is easily seen in Table 3 that in each of these experiments the ligand is lost (either competitively or exclusively) at some point in the experiment. This suggests that the binding energy of the ligand to the copper(I) cation is not greatly increased by the presence of the additional functional groups. In particular, 5-hexynenitrile is not strongly bound to copper(I). Therefore, if the loss of the weakly bound noncovalent ligand is not observed, but a covalent bond cleavage occurs that interrupts the established sequential rearrangement processes (i.e., loss of N₂, CO, and CO), then it is assumed that an intermolecular reaction has occurred. The reactions that lead to subsequent

cleavages are complicated and it is not our intention to fully describe them here. However, it is shown from the results that alkynes are much more reactive than analogous alkenes. This is not an unusual result given the greater reactivity of alkynes in general. Similarly, the observed reactivity of the phenyl group was unexpected. In the case of **2**, the benzyl groups ultimately displaced the ligand and prevented any reactions from occurring.

It is also interesting to note that CAD of [**1** + hexynenitrile + Cu]⁺ yielded the loss of a neutral methyl radical in the MS³ spectrum. This unusual loss was confirmed by experiments with **26** in which the loss of CD₃ was observed. The loss of methyl radical is accompanied by the pickup of water or methanol. It is unlikely that the methyl group was a metal ligand prior to dissociation, so an alternative explanation is required to explain the pickup of water and methanol. One possible explanation for this involves the oxidation of the copper(I) to copper(II) accompanied by the reduction of the newly formed terminal CO₂. The oxidation to copper(II) would create a new vacant ligand site and lead to the observed pickups. The exact role of the alkyne in this process remains unclear, but it may serve to stabilize the higher oxidation state of the copper.

Conclusions

In summary, the synthesis of copper(I) and silver(I) Fischer carbenes from various diazo malonates in the gas phase is demonstrated for the first time. The carbenes are generated by the facile loss of N₂. The carbenes prepared by this process can undergo multiple Wolff rearrangements in the gas phase, which subsequently lead to the loss of multiple carbon monoxides. Surprisingly, up to six different carbenes or metallo-carbenoids can be produced in a single experiment. A series of control experiments that elucidate the effects of conformation and metal mediation on Wolff rearrangements are detailed. Although the data have been gathered from gas-phase experiments, the results reveal general trends that should be applicable for either enhancing or deterring Wolff rearrangements in solution. Coordinated metal ions profoundly mediate the energetics of these reactions. Silver(I) is most efficient at initiating Wolff rearrangements followed by copper(I), but no mediation is required, and molecules labeled with nonparticipating charges undergo similar chemistry at higher energies. Conformational effects are also found to be important in determining the requisite energy for Wolff rearrangement. Divalent metal ions and protons interfere with the loss of N₂ and do not promote the formation of carbenes.

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