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Concurrent Cyclopropanation by Carbenes and Carbanions

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Received April 14, 2005; E-mail: moss@rutchem.rutgers.edu

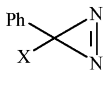
The intermediacy of the trichloromethide carbanion during the generation of dichlorocarbene by the basic hydrolysis of chloroform was made clear decades ago in Hine's landmark work.[1] Hine also demonstrated that CCl_2 could be captured by other halide ions to yield trihalomethide carbanions, and thence "mixed" haloforms.[1b] Trihalomethides are well-established intermediates in other dihalocarbene generative methods, including the reaction of NaI with $PhHgCCl_2Br$[2] and the phase transfer catalytic generation of CCl_2,[3] CBr_2,[4] CBrCl,[4] and CBrI.[5] In the latter cases, rapid dihalocarbene/halide/trihalomethide equilibrations are clearly implicated.[4,5]

However, despite their ubiquity in the α-elimination reactions of haloforms, the *control* of halomethide carbanions has never been used to *modulate* the selectivity of halocarbenes in the cyclopropanation of alkenes. Here, we demonstrate that the deliberate addition of halide ions affords concurrent cyclopropanation of electron-poor alkenes by an equilibrating mixture of phenylhalocarbenes and phenyldihalomethide carbanions (eq 1), permitting smooth modulation of selectivity between electron-rich and electron-poor alkenes, a feature of potential synthetic utility. Moreover, laser flash photolysis (LFP) demonstrates the formation of $PhCX_2^-$ and its quenching by alkenes and furnishes absolute rate constants for the forward and reverse reactions of eq 1.

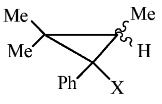
$$\mathrm{Ph\ddot{C}X} + \mathrm{X^-} \rightleftharpoons \mathrm{Ph\bar{C}X_2} \qquad (1)$$

X = Cl, Br

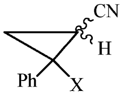
Photolysis of phenylbromodiazirine (**1-Br**)[6,7] at 350 nm in trimethylethylene (TME) or acrylonitrile (ACN) afforded the PhCBr addition products, cyclopropanes **2-Br** and **3-Br**, both as syn/anti isomer mixtures.[8] The relative reactivity (k_{rel}) of ACN versus TME was determined in the standard manner[9] by allowing a 2:1 ACN/TME mixture to compete for an insufficiency of photochemically generated PhCBr in MeCN/THF[10] solution at 25 °C and determining the **3-Br**/**2-Br** product ratio by (calibrated) capillary GC analysis. The value of k_{rel} was 0.042 ± 0.01, in keeping with the electrophilic selectivity expressed by PhCBr toward all but the most electrophilic alkenes.[11]



1, X = Br, Cl



2, X = Br, Cl



3, X = Br, Cl

However, as shown in Figure 1, the *apparent* k_{rel} smoothly increases with added tetrabutylammonium bromide (TBABr).[12,13] At 0.58 M salt, k_{rel} reaches 1.19, so that the selectivity of PhCBr toward ACN/TME has increased 28-fold. At this point, PhCBr seems to select *nucleophilically* between ACN and TME.

Analogous results were obtained for PhCCl generated photochemically from diazirine **1-Cl**[6] in ACN/TME mixtures, where the key carbene products were cyclopropanes **3-Cl** and **2-Cl**.[13,14] The product-based $k_{rel} = 0.045$ in MeCN/THF[10] with no added salt. Addition of TBACl led to a smooth increase in k_{rel}, which reached 0.62 at 0.54 M salt, corresponding to a 13.8-fold enhancement; a graphical representation[13] appears in the Supporting Information (Figure S1).

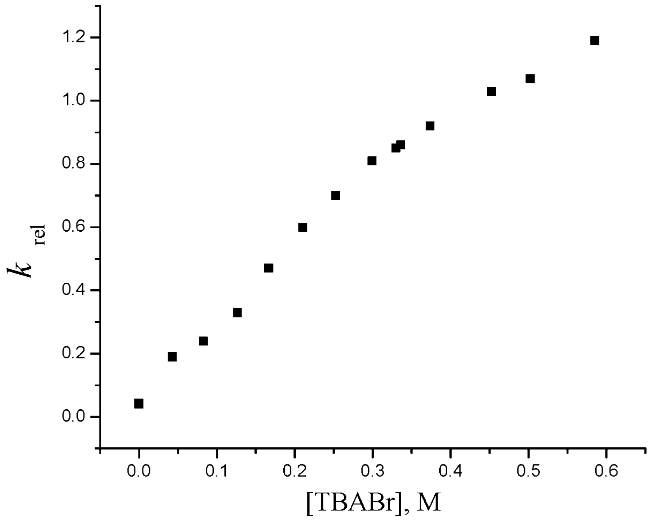


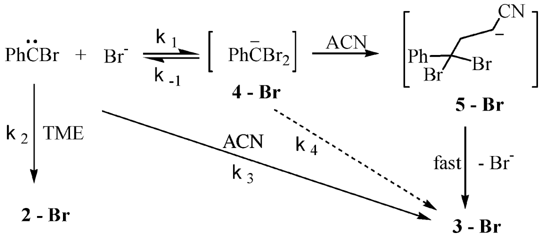
Figure 1. Value of k_{rel} versus [TBABr] (M) for the addition of PhCBr to ACN/TME.

Acrylonitrile is not an isolated case; parallel results were obtained with methyl acrylate (MeACR). Photochemical addition of PhCBr to MeACR led to a syn/anti mixture of 1-bromo-1-phenyl-2-carbomethoxycyclopropanes. In MeCN/THF, the product-based k_{rel} for MeACR/TME was 0.028. Addition of TBABr led to a smooth increase to 0.49 at 0.63 M salt, corresponding to a 17.5-fold enhancement in k_{rel}.[12,13]

How can we best account for these unprecedented TBAX-induced enhancements of PhCX selectivity toward electron-poor alkenes? Our suggested mechanism appears in Scheme 1, where ($PhCBr + Br^-$) generates the phenyldibromomethide carbanion (**4-Br**) in a rapid equilibrium (k_1/k_{-1}). "Michael" addition of **4-Br** to the electrophilic ACN generates carbanion **5-Br**, from which rapid ring closure, with expulsion of bromide, gives product **3-Br** (with overall rate constant k_4).[15] This cyclopropane is also formed more slowly by direct addition of PhCBr to ACN (k_3). However, carbanion **4-Br** does not readily add to the electron-rich TME; cyclopropane **2-Br** arises only via addition of PhCBr to TME (k_2). A parallel mechanism can be written for the analogous $PhCCl/Cl^-$ reactions described above. In both cases, as the concentrations of Br^- or Cl^- are increased, the $PhCX/PhCX_2^-$ equilibria shift toward $PhCX_2^-$, and the formation of products **3-Br** or **3-Cl** is enhanced by the carbanion/ACN pathway. Consequently, the *apparent* selectivity of PhCX toward ACN increases, relative to TME. Figure 1 is thus an "artifact" which superimposes several factors: the rates

10.1021/ja052426p CCC: $30.25

Scheme 1



of addition of both the carbene and carbanion to the alkenes, the position of the equilibrium of eq 1, and the concentration of TBABr.

Support for this mechanism follows from "cross-reactions" of PhCBr with TBACl and of PhCCl with TBABr. Reaction of photochemically generated PhCBr with 0.2 M ACN and TBACl in (1.0 M) MeCN/THF solution gave *both* cyclopropanes **3-Br** and **3-Cl**.[13] With increasing TBACl, the product ratio **3-Br**/**3-Cl** *decreased* to a constant value of ~0.67 (at $[Cl^-] \geq 0.18$ M) (cf., Figure S2 in the Supporting Information). The analogous reaction of PhCCl with ACN and TBABr also afforded **3-Br** and **3-Cl**. Now, however, **3-Br**/**3-Cl** *increased* with increasing salt and reached a similar final value, ~0.71 (at $[Br^-] \geq 0.6$ M) (cf., Figure S2).[13,16]

These results are consistent with Scheme 1. The ($PhCBr + Cl^-$) and ($PhCCl + Br^-$) couples each equilibrate with $PhCClBr^-$. At sufficiently high $[Cl^-]$ or $[Br^-]$, essentially all **3-Br** or **3-Cl** products arise from the addition of $PhCClBr^-$ to ACN, and cyclization of the resulting $[PhCClBrCH_2CHCN^-]$ must afford the same **3-Br**/**3-Cl** ratio from either source.[17]

Further mechanistic support comes from LFP visualization of carbanions **4-Br** and **4-Cl**.[18] LFP of diazirines **1-Cl** or **1-Br** in MeCN/THF affords the known[19] absorptions of PhCCl or PhCBr at 315 or 320 nm, respectively. Addition of TBACl or TBABr leads to well-developed absorptions for carbanions $PhCCl_2^-$ or $PhCBr_2^-$ at 410 or 430 nm, respectively.[20] Carbanion **4-Br** is quenched by added ACN with k_q (k_4 in Scheme 1) $= 2.9 \times 10^7$ M^{-1} s^{-1}. By LFP, we can also measure k_1 (2.2×10^8 M^{-1} s^{-1}),[21] k_2 (3.9×10^7 M^{-1} s^{-1}), and k_3 (1.7×10^6 M^{-1} s^{-1}) of Scheme 1.[22] With these rate constants and the slope (= 4.11) of the observed correlation of **3-Br**/**2-Br** versus [TBABr], we can extract $k_{-1} = 7.9 \times 10^7$ s^{-1} for the reversion of **4-Br** to ($PhCBr + Br^-$).[23] Thus, $k_1/k_{-1} = 2.8$ M^{-1}, which is the equilibrium constant for eq 1, X = Br. With this value, and noting that k_4 for $PhCBr_2^-$ addition to ACN exceeds k_3 for PhCBr addition to ACN (by a factor of 17), it is possible to quantitatively account for the observed increase in the cyclopropanation of ACN, relative to TME, with added bromide. Similar kinetics studies have been carried out with the $PhCCl/Cl^-$ system.[23]

We are continuing our investigation of concurrent carbene–carbanion reactions, turning our attention to other carbenes and other classes of substrates.

Acknowledgment. We are grateful to the National Science Foundation for financial support.

Supporting Information Available: Experimental details for cyclopropanation products, tabular surveys of product mixtures, Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Additional products included $PhCHBr_2$ and the insertion product of PhCBr into the α-CH of THF.[13]
(13) Tabular results for all products appear in the Supporting Information.
(14) Additional products included $PhCHCl_2$ and the insertion product of PhCCl into the α-CH of THF.[13]
(15) We saw no "open" product from protonation of **5-Br** (or **5-Cl** in the reactions of PhCCl). Open Michael adducts are known from CCl_3^- additions,[3a] but the CBr_3^- adducts generally cyclize. See: Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099.
(16) Control experiments showed that TBABr or TBACl did not significantly interconvert diazirines **1-Br** or **1-Cl**.
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(22) $k_3/k_2 = 0.044$, in excellent agreement with $k_{rel} = 0.042$, determined above.
(23) Details of the kinetics studies will appear in a separate publication.

JA052426P