# Mechanistic Origins of Acyloxydiazirines†

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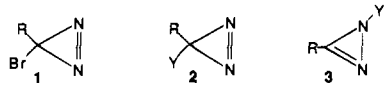
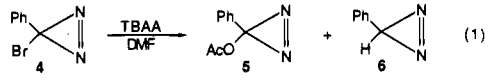
In the diazirine exchange reaction, a halodiazirine (e.g., **1**), usually prepared by Graham oxidation[1] of an amidine, undergoes substitution with nucleophile $Y^-$ to furnish a new diazirine (**2**).[2] Diazirines are prime precursors for carbenes, so the Graham oxidation/diazirine exchange sequence is a powerful preparative tool in the study of carbenes.[3]



The conversion of **1** to **2** is deceptively simple; in fact, several mechanisms may be operative or even competitive. Initially, ionization of **1** to a diazirinium ion, followed by capture of $Y^-$, was suggested for nucleophiles such as $F^-$, $OMe^-$, or $N_3^-$.[4] However, Dailey[5] and Creary[6,7] provided evidence that $F^-$ and $N_3^-$ initially attacked **1** in a $S_N2'$ fashion, affording **3**. When the nucleophile was fluoride, a second $S_N2'$ attack (at carbon) converted **3** to **2**, whereas, with $Y^- = N_3^-$, **3** decomposed directly to the nitrile, RCN. Phosphines also appear to attack **1** via the $S_N2'$ pathway.[8] To further complicate matters, azide ion can also react with **1** by a photoinitiated $S_{RN}1$ process via a diazirinyl radical, ultimately yielding a *C*-azidodiazirine (**2**, $Y = N_3$) which rapidly decomposes.[7,9] Other electron transfer reagents (nitronate salts or thiophenoxide) can initiate diazirine $S_{RN}1$ reactions, and, in some instances, the *C*-azidodiazirine transient can be observed.[9]

Recently, we reported that diazirine exchange could be realized with phenylbromodiazirine and tetrabutylammonium acetate (TBAA) to yield 3-acetoxy-3-phenyldiazirine (**2**, Y = OAc, R = Ph).[10] The acetate exchange differed from the fluoride exchange reactions[4] in that it exhibited a variable induction period, and the acetoxydiazirine product was accompanied by a significant yield of phenyldiazirine (**2**, R = Ph, Y = H), a *reduction* product. Here, we report new results that require a modified $S_{RN}1$ mechanism for acetate/diazirine exchange and demonstrate that this reaction can be initiated by superoxide ion.

**Acetate Exchange.** Stirring phenylbromodiazirine **4** with excess TBAA *under air* in dry DMF for 20 min at 25−30 °C furnished 45% of acetoxyphenyldiazirine (**5**) and 15% of phenyldiazirine (**6**), eq 1.[10] (All yields are based on consumed



(1)

**4**, as determined by NMR.) The formation of reduced diazirine **6**, a reaction pathway not observed during the exchange reaction with fluoride ion, suggests the operation of an electron transfer initiated radical process, a supposition supported by the following observations. (1) The reaction has an oxygen-dependent induction period: when oxygen was bubbled through the **4** + TBAA reaction mixture, 59% of **5** and 17% of **6** were formed after 20 min, whereas, exposed to a stream of nitrogen, the reaction mixture yielded <1% of product after 60 min. (2) The exchange is inhibited by $BrCCl_3$. In the presence of ~1 equiv of the haloform, the exchange reaction was inhibited for ~24 h. The bromodiazirine was largely unchanged, but GC-MS showed that the $BrCCl_3$ had scrambled to $CCl_4$, $Br_2CCl_2$, $Br_3CCl$, and $CBr_4$. (3) Electron-withdrawing para substituents accelerate the reaction of **4** and TBAA. Reactions of either *p*-$CF_3$- or *p*-$NO_2$-substituted **4** with TBAA yield 54−57% of the corresponding acetoxydiazirines in ≤1 min. Interestingly, the yield of **6** is greatly diminished with the *p*-$CF_3$ derivative of **4** (3%) and almost eliminated with the *p*-$NO_2$ compound.

**Superoxide Initiation.** These observations suggest that the diazirine−TBAA exchange is initiated by an oxygen-dependent radical process. Because dioxygen is readily reduced to superoxide ion (−0.70 V vs SCE)[11] and the latter can act as a single electron donor,[12] we tested the superoxide initiation of reaction 1. Indeed, addition of $KO_2$/18-crown-6 to half of a nitrogen-bubbled DMF solution of **4** and TBAA led to an immediate reaction that gave 62% of **5** and 12% of **6** after 5 min at 0 °C; the untreated half of the solution did not react after 1 h. In the absence of TBAA, superoxide converted **4** to benzonitrile, a reaction associated with the intermediacy of phenyldiazirinyl radical, which dimerizes at nitrogen, then affording PhCN and $N_2$ upon decomposition of the dimer.[13]

Superoxide ion is therefore a permissable initiator for reaction 1 as carried out under a normal atmosphere, although we are uncertain where oxygen obtains the initial electron to give the superoxide ion. Various control experiments showed that neither adventitious tributylamine (a potential impurity in TBAA) nor TBA bromide initiated reaction 1. DMF and acetate ion[14] are unlikely electron donors, and we find no UV evidence for charge transfer complex formation between acetate ion and **4**. (The formation of such a complex between **4** and azide ion is believed to precede a subsequent $S_{RN}1$ reaction.[9])

Nevertheless, the evidence impels us to draft an $S_{RN}1$ mechanism (see Scheme 1), which, in its simplest form, would resemble that proposed by Creary for the azide $S_{RN}1$ reaction:[7,9] bromodiazirine **4** accepts an electron from, e.g., superoxide ion, yielding anion radical **7**, from which bromide loss affords the key intermediate, phenyldiazirinyl radical **8**. In the absence of an efficient trapping nucleophile, **8** dimerizes to **9**, ultimately giving PhCN.[13] When acetate is present, **8** is diverted to anion radical **10**, which transfers an electron to **4**, continuing the chain, while simultaneously yielding the acetoxydiazirine, **5**. Radical **8** might also be expected to competitively abstract a hydrogen atom, thus serving as the source of phenyldiazirine, **6**. Further experiments, however, indicate that the provenance of **6** may not be that simple.

**The Reduction Product.** Where does the hydrogen atom of diazirine **6** come from? The reaction mixture of eq 1 contains MeCN (used in the azeotropic drying of the TBAA).

† Dedicated to Professor Charles W. Jefford on the occasion of his 65th birthday.

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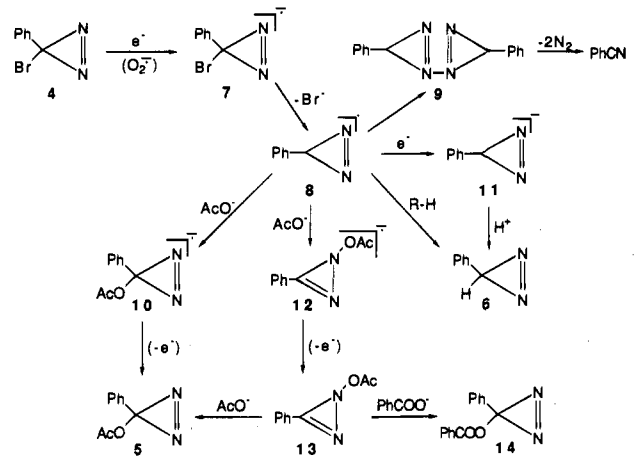
**Scheme 1**



When the reaction is carried out with 0.2 M added $CD_3CN$, product **6** contains 33% of incorporated D. The lack of more extensive incorporation calls into question the exclusivity of the **8** → **6** pathway. Indeed, the yield of **6** is not enhanced when reaction 1 is carried out in acetonitrile solvent. Nor does **6** form when **4** reacts in THF/cumene with sodium naphthalene radical anion, a known electron transfer reagent;[15] PhCN is the major product. An analogous result is obtained with TBA thioacetate and **4** in DMF/MeCN. Control experiments with TBA $CD_3COO^-$ or DMF-$d_7$ afford essentially unlabeled **6**, and acetoxydiazirine **5** does not give **6** under the exchange reaction conditions.

Diazirine **6** may therefore stem, at least in part, from an intermediate other than **8**, possibly the phenyldiazirinyl anion **11**, formed from **8** by a second electron transfer. We observe that, although the addition of MeOD to reaction 1 slows the process, some **6** is formed, and with 55% D-incorporation. In the presence of excess $D_2O$, only 1% of **6** forms (along with 73% of **5**) but with complete deuteration.

Anion **11** may therefore be a precursor of diazirine **6**, reacting with traces of proton donors in the reaction medium. The parent diazirinyl anion is known in the gas phase, where it abstracts a deuteron from $ND_3$, and it may well be stable in solution.[16] Creary's calculations[9] suggest that a diazirinyl anion formed from the corresponding radical should be *N*- rather than *C*-centered. This complicates a putative **8** → **11** → **6** pathway but does not definitively exclude it, particularly in the case of the phenyl-substituted **11**, where the *C*-centered anion receives added stabilization.

**(Benzoyloxy)phenyldiazirine.** The evidence thus far is consistent with a normal $S_{RN}1$ origin for diazirine **5** (i.e., **4** → **7** → **8** → **10** → **5** in Scheme 1), but there is good reason to consider an expanded scenario. Thus, the reaction of **4** and TBA benzoate in DMF does not lead to 3-benzoyloxy-3-phenyldiazirine (**14**); PhCN forms instead. Even with superoxide initiation, only traces of **14** are formed. Presumably, benzoate is not reactive enough to capture the diazirinyl radical, which simply dimerizes, ultimately affording PhCN. However, with *both* TBA acetate and benzoate present, **4** gives 32% of acetoxydiazirine **5**, 28% of benzoyloxydiazirine **14**, and 5% of phenyldiazirine (**6**). A similar result is obtained upon reaction of **4** with KOAc and potassium benzoate, solubilized in DMF with 18-crown-6. The new diazirine, **14**, was isolated by silica gel chromatography (1:4 $CH_2Cl_2$/pentane), and its structure was established by UV and NMR spectroscopy, as well as thermolysis (60 °C, 15 h, pentane) to phenylbenzoyloxycarbene, which afforded benzil upon the expected[10] 1,2-acyl migration.

To account for the "synergistic" acetate/benzoate formation of **14**, we expand Scheme 1 by adding **13**, the *N*-acetoxyisodiazirine isomer of **5**. Capture of the *N*-centered[13] diazirinyl radical **8** by acetate ion at nitrogen, rather than carbon, would afford the *N*-acetoxy radical anion **12** (the isomer of **10**), from which loss of an electron (to **4**) would yield **13**. $S_N2'$ reaction[7] of **13** with acetate or benzoate ions would then provide **5** or **14**, respectively. The formation of diazirines **5** or **14** by this pathway (**4** → **7** → **8** → **12** → **13** → **5** or **14**) entails a double $S_N2'$ mechanism, related to that of fluoride diazirine exchange,[5] except that, in the case of acetate, the initial $S_N2'$ process relies on $S_{RN}1$ chemistry rather that the ionic pathway preferred by the much more nucleophilic fluoride ion.

The novel superoxide initiation and acetate/benzoate synergism reported here for the carboxylate diazirine exchange reactions demonstrate that we still have much to learn about the preparative chemistry of these carbene progenitors.

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