Azide and Fluoride Exchange Reactions of Halodiazirines

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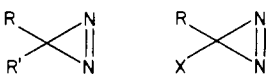
Abstract: Reactions of 3-aryl-3-bromodiazirines (**11**) with molten tetrabutylammonium fluoride at 25 °C provide 65–74% isolated yields of the novel corresponding 3-aryl-3-fluorodiazirines (**12**). Related reactions of **11** with tetrabutylammonium azide afford high yields of aryl nitriles. The latter reactions are believed to proceed through unstable intermediate 3-aryl-3-azidodiazirines (**7**). These reactions involve rate-determining formation of **7** and display kinetics which are first order in azide ion and bromodiazirine. The likely intermediacy of an aryldiazirinium bromide ion pair between **11** and **7** is supported by a combination of salt effect, leaving group effect, and Hammett studies. Molecular orbital calculations are employed to characterize azidodiazirines as well as the mode of their decomposition to nitriles. In particular, we consider the possible intermediacy of a 3-nitrenodiazirine or an azidocarbene.

3*H*-Diazirines, **1**, are important precursors for the thermal or photolytic generation of carbenes.[1,2] There are three principal syntheses of these compounds:[2] the oxidation of 1,2-unsubstituted



1 **2**

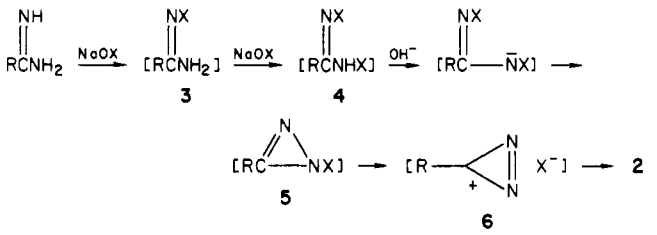
diaziridines, affording alkyl-, dialkyl-, or aryl-substituted diazirines; reductive defluorinative cyclization of fluoroformamidino derivatives, useful for the preparation of 3-fluorodiazirines; and the hypohalite oxidation of amidines. The last method, Graham's reaction,[3] is especially useful because it provides direct access to a wide range of 3-substituted-3-chloro(or bromo)diazirines, **2**, and the carbenes derived therefrom.

In Graham's reaction, an alkyl-, cycloalkyl-, vinyl-, alkoxy-, or arylamidine is halogenated with OCl^- or OBr^-, ultimately giving **2**, X = Cl or Br. The mechanism of the reaction is complicated,[3] but despite a recently suggested revision,[4] Graham's original rendering (Scheme I) is very likely correct or nearly so.[5] Thus, when R = *i*-Pr or CH_3O, both *N*-chloroamidines (**3**) and *N,N'*-dichloroamidines (**4**) can be isolated, and **4** can be converted to the appropriate 3-chlorodiazirine, **2**, upon treatment with NaOH/NaCl.[5]

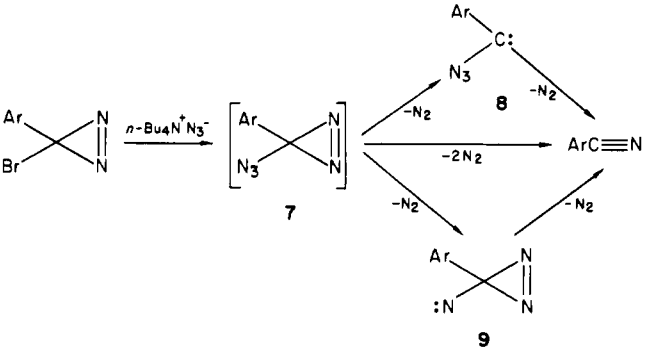
The effective scope of Graham's reaction would be significantly broadened if diazirinium ions **6** could be intercepted by added anions, i.e., by anions other than the X^- originally introduced with OX^-. One such example, the preparation of **2**, R = CH_3, X = OAc, was reported,[3] but this elaboration of the basic reaction does not lead to pure products and does not appear to be widely applicable.[5] The difficulty seems to rest with cation **6**. Although originally formulated[3] as a free diazirinium ion, analogous to the aromatic cyclopropenium ion, subsequent calculations indicated a "negative delocalization energy" for the parent diazirinium ion[6] and consequent instability. Taken together with further experimental and theoretical work,[7] it seemed most reasonable to represent **6** (R = CH_3, X = Cl^-), as an intimate or tight ion pair, at least as formed under Graham's conditions, presumably from **5**.

Accepting this formulation, we hoped that ion pairs **6**, particularly when R is an electron-donating group, could be generated reversibly in polar, nonnucleophilic solvents and intercepted by

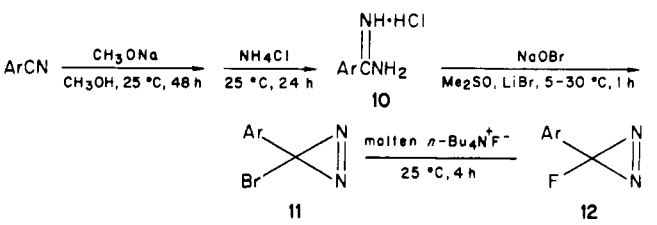
Scheme I



Scheme II



Scheme III



aryl (p-X-C_6H_4) substituents: (a) OCH_3, (b) CH_3, (c) H, (d) Cl, (e) CF_3

potent added nucleophiles. Despite initial failures to obtain evidence for diazirinium ions as spectroscopic entities,[5] we did indeed find that, e.g., phenylbromodiazirine (**2**, R = Ph, X = Br), undergoes facile exchange of X for Y when Y is supplied as an anion. Thus, phenylbromodiazirine reacts with sodium methoxide in dimethylacetamide–hexamethylphosphoric triamide to give the corresponding methoxydiazirine,[8] with tetrabutylammonium fluoride (TBAF) to give the fluorodiazirine,[9] with tetrabutyl-

(1) Liu, M. T. H. *Chem. Soc. Rev.* **1982**, *11*, 127.
(2) Heine, H. W. *Chem. Heterocycl. Compd.* **1983**, *42*, 588–616.
(3) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.
(4) Berneth, H.; Hünig, S. *Chem. Ber.* **1980**, *113*, 2040.
(5) Moss, R. A.; Włostowska, J.; Guo, W.; Fedorynski, M.; Springer, J. P.; Hirshfield, J. M. *J. Org. Chem.* **1981**, *46*, 5048.
(6) Krogh-Jespersen, K. *Tetrahedron Lett.* **1980**, *21*, 4553.
(7) Krogh-Hespersen, K.; Young, C. M.; Moss, R. A.; Włostowski, M. *Tetrahedron Lett.* **1982**, *23*, 2339.
(8) Włostowska, J.; Moss, R. A.; Guo, W.; Chang, M. J. *Chem. Commun.* **1982**, 432.
(9) Cox, D. P.; Moss, R. A.; Terpinski, J. *J. Am. Chem. Soc.* **1983**, *105*, 6513.

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Table I. Properties of 3-Bromo-3-aryldiazirines

compd	yield,[a] %	IR,[b] cm^{-1}	UV [ε],[c] nm	^{13}C NMR (δ)[d]
11a	34	1560	387 [458], 408 [382]	38.0 (55.3)
11b	38	1560	376 [290], 396 [263]	38.3 (21.1)
11c	38	1565	381 [218], 390 [216]	38.0
11d	20	1565	371 [313], 386 [289]	37.0
11e	19	1565	361 [187], 377 [189]	36.4 (124)[e]

[a] Yields are for purified diazirines and are based on **10**. [b] N=N stretch[3] observed in neat films. A strong band is also observed at 875 cm^{-1} and probably represents a C—Br mode. This band disappears upon the conversion of bromodiazirines to the fluoro analogues. [c] Observed in isooctane solution; wavelengths and extinction coefficients are reported for maxima of the two longest wavelength absorptions in each case. [d] ^{13}C spectra are reported as parts per million downfield from internal Me_4Si in 10% $CDCl_3$ solutions. Reported shifts are for diazirine carbon atoms (or methyl carbons). [e] Quartet, $J_{^{13}C-F}$ = 273 Hz.

ammonium cyanide to give the appropriate cyanodiazirine,[9,10] and even with primary or secondary amines to give products that are most reasonably attributed to aminodiazirine intermediates.[11]

Experimental details have been published for the preparations of the methoxy-[8] and cyanophenyldiazirines.[10] In the present paper, we give full details of the preparation of a series of 3-fluoro-3-aryldiazirines, as well as a study of the reactions of arylhalodiazirines with azide ion. The latter reactions, which afford arylnitriles, have been represented (Scheme II[9]) as proceeding via 3-azido-3-aryldiazirines, **7**, formed by azide capture of **6**. We now present further evidence for this scheme, as well as ab initio molecular orbital calculations concerning the stability of **7**, and the possible intermediacy of azidocarbenes (**8**) or nitrenodiazirines (**9**) in conversions of **7** to the isolated end products, arylnitriles.

Results

Preparation of Arylfluorodiazirines. The synthetic route to these new fluorodiazirines is outlined in Scheme III. Arylnitriles were coverted to the arylamidine hydrochlorides, **10**, by the method of Schaefer and Peters.[12] Although this method affords low (20–30%) yields of **10a** and **10b**, it offers the advantages of simplicity and easy recovery of the unconverted nitrile for recycling. Standard Graham reactions[3] converted amidines **10** into the 3-bromo-3-aryldiazirines **11a–f**. These were purified by chromatography on silica gel, followed by distillation on a Kugelrohr apparatus at ~40 °C/0.1 mmHg. Diazirine **11a** was too unstable to survive the distillation step. The purified diazirines were characterized by ^1H and ^{13}C NMR spectra. They also displayed the anticipated[3] IR and UV absorptions. Selected spectroscopic data, as well as yields, are summarized in Table I.

Bromodiazirines **11** were converted into fluorodiazirines **12** in 65–74% isolated yields by exchange with nearly anhydrous, molten TBAF. Commercially available TBAF trihydrate (Aldrich) was heated under vacuum (0.1 mmHg) at 40–45 °C for 48 h, at which point it had lost ~20% of its initial weight. The resultant *melt* contained ~0.1 equiv of water (^1H NMR) and had suffered ~10% decomposition to Bu_3N (and 1-butene).[9,13] Importantly, the nearly anhydrous TBAF remained molten at 25 °C. Upon simply stirring excess fluoride reagent with neat **11** (25 °C, 4 h, drying tube), we achieved efficient conversion to **12** and *n*-$Bu_4N^+Br^-$. Routine workup (see Experimental Section) afforded crude samples of **12** which were purified by Kugelrohr distillation. The new fluorodiazirines were characterized spectroscopically. Anticipated[3] IR and UV bands, as well as selected ^{13}C and ^{19}F NMR data, appear in Table II.

Table II. Properties of 3-Fluro-3-aryldiazirines

compd	yield,[a] %	IR,[b] cm^{-1}	UV, [ε],[c] nm	^{13}C NMR[d]	^{19}F NMR[e]
12a	68	1560, 1555	379 [543], 399 [497]	70.9	152
12b	74	1560	372 [360], 391 [341]	71.3[f]	153
12c	65	1565, 1560	366 [296], 386 [285]	70.7	154
12d	74	1555	367 [392], 386 [374]	71.0[f]	154
12e	71	1560	359 [329], 378 [331]	70.8[f]	155

[a] Yields are for purified diazirines and are based on **11**. [b] N=N stretch observed in neat films. C—F stretches are also seen at ~1160 cm^{-1}. Coupling of C—F and N=N modes is sometimes clearly resolved as a 5-cm^{-1} splitting. [c] Observed in isoctane solution; cf., note c, Table I. [d] Cf., note d in Table I. ^{13}C signals were split by coupling (262–264 Hz) to ^{19}F. Compounds **12a, b**, and **c** had substituent methyl carbon absorptions at δ 55.3, 21.3, and 123, respectively. The latter signal was a quartet, $J_{^{13}C-F}$ = 123 Hz. [e] Recorded at 74.844 MHz in 10% $CDCl_3$ solutions. ^{19}F chemical shifts are reported in parts per million *upfield* from internal $CFCl_3$. [f] CD_2Cl_2 solvent.

Table III. Pseudo-First-Order Rate Constants for Reactions of Excess TBAAz with Diazirine **11b**[a]

equiv of TBAAz	10^4k_ψ,[b] s^{-1}	corr coeff
7	2.78 ± 0.01	>0.999
6	2.69 ± 0.09	>0.999
5	2.50[c]	0.998
4	2.00[c]	>0.999
3	1.45[c]	>0.999

[a] Conditions: 1.0 mmol of the diazirine in 2.5 mL of stirred anhydrous CH_3CN at 25.5 ± 0.1 °C. Evolved nitrogen was read every 5 min, and data were obtained over 82–90% of the reaction. [b] Rate constants (two runs) were obtained from computer analysis of ln (volume of N_2) vs. time. [c] Single run.

Although the conversions of ArCN to amidines **10** and of **10** to bromodiazirines **11** do not occur in high yields, both processes are simple, one-vessel transformations from readily obtainable starting materials. Moreover, the key Br → F exchanges, which convert diazirines **11** to **12**, are easily carried out and occur in good yields. The sequence of Scheme III therefore constitutes a facile new method for the preparation of 3-fluoro-3-aryldiazirines. It has already been extended to the preparation of 3-fluoro-3-phenoxydiazirine,[9] and further elaboration is planned in the near future. To our knowledge, this method represents the only synthesis of fluorodiazirines which does not involve the use of elemental fluorine somewhere in the reaction sequence.[14]

Reactions with Azide Ion. The reaction of 1 mmol of phenylbromodiazirine (**11c**) with 6 mmol of anhydrous tetrabutylammonium azide[15] (TBAAz) in 2.5 mL of dry CH_3CN in the dark at 25.5 ± 0.1 °C proceeded with a pseudo-first-order rate constant (manometrically determined by nitrogen evolution) of 1.44 ± 0.01 × 10^{-4} s^{-1} and gave 89% of pure (TLC, GC) benzonitrile.[9] From five kinetic runs ($r > 0.998$) carried out at ~5 °C intervals over the temperature range 19.6–40.1 °C, the apparent activation energy for this conversion was 18.6 kcal/mol, with $A = 4.42 \times 10^9$ s^{-1}. The corresponding activation parameters in terms of transition-state theory are (at 25 °C) $\Delta H^\ddagger$ = 18.0 kcal/mol, $\Delta S^\ddagger$ = −16.3 eu, and $\Delta G^\ddagger$ ~22.9 kcal/mol. *p*-Substituted phenylbromodiazirines **11a–e** reacted analogously to parent diazirine **11c**, affording the corresponding arylnitriles in high purity and yield.[16] The product arylnitriles were readily identified by comparison to authentic materials.

Because of its convenient rate of reaction with TBAAz, the *p*-methyldiazirine, **11b**, was chosen for closer kinetic scrutiny. As shown in Table III, good pseudo-first-order manometric rate

(10) Moss, R. A.; Kmiecik-Lawrynowicz, G.; Cox, D. P. *Synth. Commun.* **1984**, *14*, 21.
(11) Moss, R. A.; Cox, D. P.; Tomioka, H. *Tetrahedron Lett.* **1984**, *25*, 1023.
(12) Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412.
(13) This procedure has been independently reported by: Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112. For other applications of the reagent, see: Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.
(14) See ref 2 (pp 594–595) and 9 (note 3).
(15) Brändström, A.; Lamm, B.; Palmertz, I. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 699.
(16) The isolated yields of *p*-XC_6H_4CN were (X=)OCH_3, 86%; CH_3, 90%; Cl, 87%; CF_3, 83%.

Table IV. Second-Order Rate Constants for Reactions of TBAAz and Diazirine **11b**[a]

equiv of TBBAz	10^4k_2,[b] L/(mol-s)	corr coeff	10^4k_2,[c] L/(mol-s)
7	2.04	>0.999	2.14
6	2.16	>0.999	2.20
5	2.10	>0.998	2.22
4	2.03	>0.999	2.11
3	2.04	>0.998	2.04

[a] For conditions, see Table III, note a. [b] From second-order rate equation, ref 17. [c] From data of Table III with k_ψ divided by mean [TBAAz].

Table V. Influence of n-$Bu_4N^+X^-$ on the Pseudo-First-Order Rate Constant for Reaction of TBAAz with Diazirine **11b**[a]

X^- in n-$Bu_4N^+X^-$	10^4k_ψ,[b] s^{-1}
none[c]	1.45
Br^-	1.43
ClO_4^-	1.72
BF_4^-	1.83
Cl^-[d]	1.72

[a] For conditions, see Table III, note *a*. Three equivalents of TBAAz and 3 equiv of n-$Bu_4N^+X^-$ were present. [b] All correlation coefficients were >0.999. [c] Three equivalents of TBAAz only. [d] Reaction of 1 equiv of **11b** with 3 equiv of n-$Bu_4N^+Cl^-$ in 2 mL of CH_3CN for 24 h at 25 °C gave no trace of the chlorodiazirine exchange product (HPLC).

Table VI. Influence of Substituents on the Pseudo-First-Order Rate Constant for Reactions of TBAAz with Diazirines **11a–e**[a]

diazirine	aryl substituent	10^4k_ψ,[b] s^{-1}
11a	p-OCH_3	10.2 ± 0.1
11b	p-CH_3	2.69 ± 0.09
11c	H	1.44 ± 0.01
11d	p-Cl	1.18 ± 0.06
11e	p-CF_3	0.386 ± 0.004

[a] For conditions, see Table III, note a. Six equivalents of TBAAz was present. [b] Errors are average deviations of two kinetic runs; all correlation coefficients exceed 0.999 except for one run with **11e** (r = 0.997).

constants for its reactions with TBAAz were obtained over a range of azide/diazirine ratios. At lower ratios, the observed rate constants decrease, suggesting that the reaction is overall second order. This was confirmed by treating the data according to standard methods for second-order reactions.[17] The data in Table IV show that k_2 is now invariant and identical with values derived from the pseudo-first-order rate constants of Table III, when the latter are divided by the appropriate mean concentration of TBAAz.

The overall reaction of **11b** and TBAAz is thus first order in each component. These kinetics were shown to apply over concentration ranges of 0.2–0.3 M in diazirine and 0.3–1.3 M in azide. From the data of Table IV, $k_2 = 2.07 \pm 0.04 \times 10^{-4}$ L/(mol-s) for the five tabulated runs. A single run, with equimolar reactants gave $k_2 = 1.98 \times 10^{-4}$ L/(mol-s).

Table V displays pseudo-first-order rate constants for the reactions of 1 mmol of diazirine **11b** with 3 mmol of TBAAz in the presence of 3 mmol of a second n-$Bu_4N^+X^-$ salt. Although the anions of these salts do not react with **11b**, the additional 3 equiv of perchlorate, fluoroborate, or chloride salts appears to enhance k_ψ by ~18–26%, whereas added bromide seems not to affect k_ψ.

The influence of aryl substituents on the observed rate constant of the **11**/TBAAz reactions is presented in Table VI, where it is seen that the reaction is mildly accelerated by electron-donating substituents. A plot of log k_ψ vs. σ^+ is shown in Figure 1.[18] The

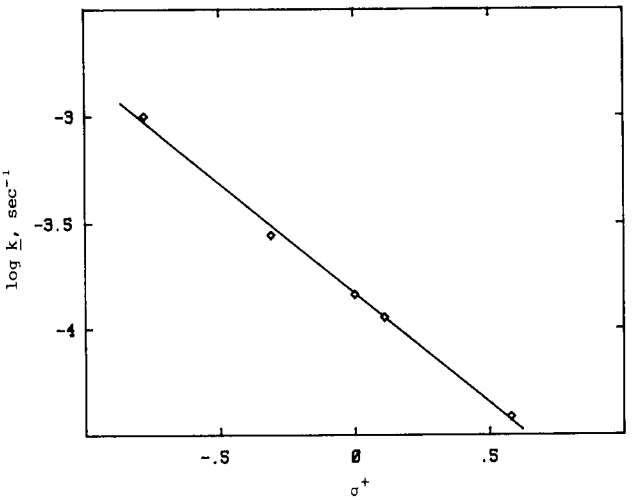


Figure 1. Hammett correlation: log k (s^{-1}) for reactions of diazirines **11a–e** with tetrabutylammonium azide vs. σ^+; cf., Table VI.

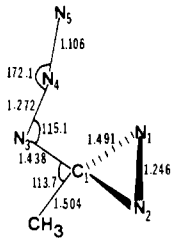


Figure 2. Optimized HF/3-21G structure for **13**. Bond lengths are in angstroms and bond angles are in degrees.

plot is linear (r = 0.998) with $\rho = -1.03$. A much poorer correlation (r = 0.935) is obtained with σ constants.

The influence of leaving group on the reaction was briefly studied. The reaction of 3-chloro-3-(p-methoxyphenyl)diazirine with TBAAz, under conditions analogous to those of Table III, proceeded very slowly. After 5 days, 75% of p-methoxybenzonitrile and 13% of starting diazirine could be isolated from the reaction mixture by chromatography on silica gel (pentane eluent). On the basis of nitrogen evolution during the first 24 h of reaction, the pseudo-first-order rate constant for this arylchlorodiazirine reaction is ~3×10^{-6} s^{-1}, more than 300 times smaller than the rate constant for the analogous reaction of bromodiazirine **11a** and TBAAz.

In control experiments, 6 mmol of TBAAz was stirred in the dark in 2.5 mL of CH_3CN at 25.5 °C for 48 h. No nitrogen evolution was observed. When 1 mmol of **11b** was stirred with 6 mmol of n-$Bu_4N^+ClO_4^-$ in 2.5 mL of CH_3CN at 25.5 °C, only 0.5 mL of gas evolution was observed after 5 h. Under comparable conditions, the half-life of the **11b**/TBAAz reaction is ~43 min, so that thermal decomposition of the diazirine does not significantly contribute to the nitrogen evolutions (>40 mL) observed during the actual reactions.

Molecular Orbital Calculations. We carried out molecular orbital calculations for models of species conceivably involved in the second step of Scheme II; i.e., **7**, **8**, **9**, and the product nitrile. In these calculations, a methyl group was substituted for the aryl group of the actual molecules. Geometries were optimized with the split-valence 3-21G basis set (HF/3-21G//3-21G) by using the GAUSSIAN 82 series of programs on a DEC VAX 11/780 computer.[19]

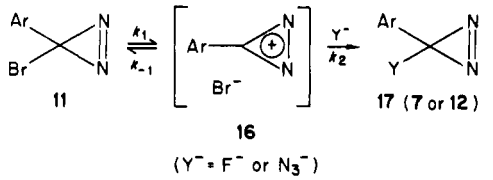
The optimized structure for methylazidodiazirine, **13** (Figure 2), possesses a plane of symmetry (C_s). Relative to the parent 3*H*-diazirine,[20] the three-membered ring of **13** reveals the expected

(17) Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961; p 17.

(18) σ^+ and σ constants were mostly taken from: March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; p 253. The value for CF_3 was taken as the mean of the σ_p (rate) values cited by: Stock, L. M.; Wasielewski, M. R. *Prog. Phys. Org. Chem.* **1981**, *13*, 261.

(19) Binkley, J. S.; Frisch, M.; Raghavachari, K.; DeFrees, D. J.; Schlegel, H. B.; Whiteside, R. A.; Fluder, E.; Seeger, R.; Pople, J. A. GAUSSIAN 82, Release A, Chemistry Department, Carnegie-Mellon University, Pittsburgh, PA, 1983. The methyl group was kept tetrahedral with CH = 1.09 Å; two hydrogens were staggered with respect to the exocyclic CN bond.

Scheme IV



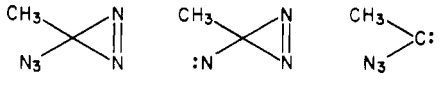
11 16 17 (7 or 12)

($Y^- = F^-$ or N_3^-)

geometrical effects associated with the replacement of H by the more electronegative N_3 moiety. Thus, **13** has a slightly longer distal N_1N_2 bond than 3*H*-diazirine (1.246 vs. 1.217 Å), but a shorter vicinal C_1N_1 (=C_1N_2) bond length (1.491 vs. 1.522 Å). The orbital interactions responsible for this pattern of bond length changes have been described in detail for cyclopropanes and cyclopropenes.[21] Additionally, the N_3C_1C angle is considerably smaller in **13** than in 3*H*-diazirine (113.7° vs. 121.4°), a result of the enhanced 2p-orbital character in the exocyclic C_1 hybrid orbitals necessitated by the electronegative azide substituent.

It is also noteworthy that the azide unit is not linear,[22] but shows a (central) $N_3N_4N_5$ angle of 172.1°, with N_5 and C_1 trans relative to the N_3N_4 bond. The N_4N_5 bond length (1.106 Å) is close to that of a triple bond (1.083 Å in dinitrogen), whereas the N_3N_4 bond length in **13** (1.272 Å) is only slightly longer than the typical N=N value (~1.25 Å).

In contrast to methylazidodiazirine **13**, *no* minima could be located for methylnitrenodiazirine (**14**) (model for **9**) or methylazidocarbene (**15**) (model for 8). Partially optimized structures



13 14 15

could be obtained by fixing some key structural parameters (e.g., the ring C–N bond length in **14** or the N–N bond length adjacent to the carbenic carbon in **15**), but these structures immediately dissociate to CH_3CN and N_2 upon geometry relaxation. The conversion of **13** to $CH_3CN + 2N_2$ is calculated to be exothermic by 185 kcal/mol,[23] an extremely strong thermodynamic driving force for dissociation. We will return to the mechanistic nature of the decomposition of **13** (and its aryl analogue, **7**) below.

Discussion

Diazirinium Halide Ion Pairs. We suggested that the conversions of 3-bromo-3-aryldiazirines (**11**) to 3-fluoro-3-aryldiazirines (**12**) or arylnitriles (via 3-azido-3-aryldiazirines, **7**) involve a diazirinium cation/anion pair[7,9] (e.g., **6** in Scheme I). A formulation of this mechanism appears in Scheme IV. Due to its high energy and consequent instability, the equilibrium between ion pair **16** and diazirine **11** lies to the left ($k_{-1} > k_1$). As in the case of the corresponding azirinium ions,[7] the cation of **16** can be intercepted only by strong nucleophiles such as cyanide,[9,10] amines,[11] methoxide,[8] azide,[9] or fluoride.[9]

Although it would be best to directly study the kinetics of (e.g.) the reaction of **11** with fluoride ion, preliminary experiments showed that this was very difficult to do. The TBAF reagent is very sensitive to moisture, particularly in the small amounts used in kinetic runs, and ^{19}F NMR quantitation of product formation (**12**) was insufficiently reproducible. Accordingly, we adopted an easier, albeit less direct method: manometric determination of the nitrogen evolution accompanying the conversion of **11** (via azidodiazirine **7**) to ArCN. As indicated above, this is a clean, high-yield, single-product reaction.

In the analogous reaction of haloazirines with azide, the azidoazirine product can be seen with NMR spectroscopy, and it is stable for 1–2 h at 25 °C.[7] Azidodiazirines, **7**, however, are much less stable. We have been unable to detect them spectroscopically, and, indeed, molecular orbital calculations (see below), suggest that they are probably not isolable. Nevertheless, their intermediacy seems likely on mechanistic grounds (Scheme II) and by analogy to the reactions of **11** with F^- and OCH_3^-, both of which give isolable "simple" substitution products.

A steady-state treatment of Scheme IV, based on **16**, gives the rate of formation of **17** as

$$\frac{d[17]}{dt} = k_1[11]\frac{k_2[Y^-]}{k_{-1}[Br^-] + k_2[Y^-]}$$

If k_{-1} is also considerably greater than $k_2[Y^-]$, then the rate of formation of **17** should be first order in both diazirine **11** and azide ion (Y^-). The results displayed in Table IV show this to be the case.

Essential to this analysis is the stipulation that, in the conversion of bromodiazirine **11** to azidodiazirine **7** or **17** (Y = N_3), and thence to arylnitrile and *nitrogen* (the monitored product), it is the first step, formation of the azidodiazirine, which is "slow" and rate-determining (k_1 in Scheme IV). Decomposition of the azidodiazirine is fast. In this instance, following the rate of nitrogen formation would be equivalent to following the rate of azidodiazirine formation. The latter is the process of immediate chemical interest because it can furnish information concerning the mechanism of conversion of **11** to **17**; i.e., about the possible intermediacy of ion pair **16**. We will return to this point below.

The intermediacy of ion pair **16** is supported by additional kinetic evidence. One may conclude from the data in Table V that the observed rate constants for the azide/diazirine reaction increase by ~20% upon the addition of several inert salts, consistent with a rate-determining ionization mechanism. However, addition of a bromide salt, which could only afford a degenerate reaction, has no accelerating effect.[24] Also, there is a very large kinetic leaving group effect (>300) favoring the reaction of azide ion with 3-bromo-3-(*p*-methoxyphenyl)diazirine over reaction with the analogous chlorodiazirine. Again, this seems most consistent with a rate-determining ionization step (k_1) in a reaction sequence like that in Scheme IV.

The Hammett study (Table VI, Figure 1) suggests the development of electron-deficient or cationic character in the rate-determining step, again consistent with the intermediacy of **16**. Thus, the observed rate constants are enhanced by electron-donating aryl substituents ($\rho = -1.03$ vs. σ^+). This result would seem to exclude mechanisms which involve rate-determining *nucleophilic* attack of Y^- on the N=N unit of **11**, leading to species such as **5** (Scheme I, Y instead of X) and thence to **17**.

At first sight, the small magnitude of the Hammett ρ is troubling. However, additional molecular orbital calculations lead to an acceptable rationalization. A calculation on the phenyldiazirinium cation (**16**, Ar = Ph), in which the phenyl and diazirinium rings are held coplanar to maximize charge delocalization, shows that the unit positive charge imposed on the π system is located mainly in the three-membered ring ($q^\pi(N) = 0.25$, $q^\pi(C) = 0.28$) and is nearly evenly distributed among the three ring atoms.[25] Only 0.22 of a unit positive charge is imposed on the phenyl ring. Polarization of this ring does place a net π-charge of +0.17 on the para carbon, but the charge available for interaction with the para substituent is clearly much less than +1. Moreover, in the transition state leading to **16**, the key partial

(20) The optimized structure of 3*H*-diazirine is NN = 1.217 Å, CN = 1.522 Å, CH = 1.064 Å, HCH = 121.4°. *E*(HF/3-21G//3-21G) = −146.947 79 au.

(21) Clark, T.; Spitznagel, G. W.; Klose, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 4412. Deakyne, C. A.; Allen, L. C.; Craig, N. C. *Ibid* **1977**, *99*, 3895.

(22) Lievin, J.; Breulet, J.; Verhaegen, G. *Theor. Chim. Acta* **1979**, *52*, 75.

(23) The total energies *E*(HF/3-21G//3-21G) are **13** = −347.498 91 au, CH_3CN = −131.191 80 au, N_2 = −108.300 95 au.

(24) See: Streitwieser, A., Jr. "Solvolytic Displacement Reactions"; McGraw-Hill: New York, 1962; pp 51–54. The bromide ion experiment is probably not an example of a true "common ion effect" because rate *retardation* is not observed, and very unstable cations such as **16** do not usually exhibit these effects.

(25) This calculation employed the optimized geometry for the diazirinyl cation skeleton (CN = 1.324 Å, NN = 1.367 Å) and a phenyl group with standard bond lengths and angles (CC = 1.40 Å, CH = 1.08 Å, CCC = HCC = 120°). The phenyl group was attached to the diazirinyl carbon with a standard CC bond length of 1.52 Å.

charge will be somewhat less than 0.17. Therefore, the small observed ρ value is most likely a reflection of the low charge imposed on the para carbon in the transition state.

We return now to the stipulation that the formation of azidodiazirine **7**, rather than its decomposition, is rate-determining in Scheme II. Of course, the existance of kinetic salt effects, a large bromide/chloride leaving group effect, and kinetic dependencies on both [azide] and [diazirine] is in keeping with this view (see above). Additional support derives from the measured activation parameters for the reaction of **11** (Ph instead of Ar) and TBAAz in acetonitrile. In particular, $\Delta S^{\ddagger}$ is quite negative (−16.3 eu). This is consistent with strong dipolar solvent orientation accompanying a rate-determining ionization[26] but not with a rate-determining step in which a single neutral molecule (e.g., **7**) gives rise to three neutral product molecules (PhCN + $2N_2$). A positive value of $\Delta S^{\ddagger}$ would be anticipated in the latter case. We note also that the measured activation energy for the bromophenyldiazirine/TBAAz reaction is 18.6 kcal/mol, whereas calculations (see below) indicate that the activation energies for decompositions of **7** or **13** are likely to be considerably *less* than 16 kcal/mol.

Azidodiazirines. What is the mechanism of decomposition of the unstable azidodiazirines **7** (or **13**)?[27,28] Sequential loss of N_2 via intermediates such as **8** or **9** (Scheme II) seems to be eliminated by our calculational results (see above) on models **14** and **15**. Neither the nitrenodiazirine **14** nor the azidocarbene **15** represent potential energy surface minima. They cannot be intermediates, and replacement of the methyl group in these species by phenyl is unlikely to significantly improve their stabilities. This conclusion is also consistent with our inability to trap **8** or **9** with alkenes.[9]

If the decomposition of **7** or **13** is initiated by expulsion of the N_1N_2 (diazirino) unit (Figure 2), then a nonsymmetrical transition state, analogous to a retrocarbene addition,[29] could be expected. Despite a thorough search, no transition state could be located corresponding to **13** → **15** + N_2, although additional studies showed that related transition states could be readily found for (inter alia) the addition of CH_2, CHF, or CHCl to N_2.[30]

The dissociation of **13** to **14** and N_2 is also orbital symmetry forbidden when C_s symmetry is preserved. In our calculations, the energy of **13** increases upon stretching the N_3N_4 bond (Figure 2) but levels off gradually after 3.5 Å. Geometry optimization at this point affords a structure which is ~16 kcal/mol above **13**. Because this pathway is forbidden, 16 kcal/mol must represent an upper limit for the calculated energy of activation via the "true" transition state.

Numerous attempts, starting with various unsymmetrical structures, failed to locate this transition state regardless of whether the initially chosen structures were designed to mimic expulsion of only one N_2 molecule or both N_2 molecules simultaneously. Additionally, very severe convergence difficulties were often encountered in the SCF procedure. Accordingly, the multidimensional energy surface does not appear to have a unique, readily locatable path leading from **13** to the transition state for dissociation. Rather, there exist many paths away from the minimum which can tap into the large exothermicity of the dissociation reaction after only minimal structural distortions.

We may picture **13** to be located in a very shallow energy minimum atop a small, high plateau with steep sides (i.e., a mesa). A direct calculation of the normal modes for the parent azidodiazirine (**13** with H in place of CH_3) affords two low-lying frequencies, 61 cm^{-1} (A″) and 167 cm^{-1} (A′). This result strongly supports our view of **13** as a high-energy, very unstable intermediate. Thermal excitation of these modes should readily provide the geometric distortions required for dissociation, and the very large reaction exothermicity (>150 kcal/mol) provides the necessary driving force.

A referee has suggested an interesting alternative decomposition pathway for **7** (or **13**) involving an initial intramolecular ring expansion to form a cyclic, conjugated 6π-electron pentaazabenzene derivative ($ArCN_5$), followed by loss of $2N_2$ to give the final products ($ArC{\equiv}N + 2N_2$). The planar, parent pentaazabenzene is, in fact, calculated to be 20.6 kcal/mol more stable than the parent azidodiazirine, but it does not represent a minimum, because the matrix containing the second derivatives of the total energy possesses a negative eigenvalue corresponding to an imaginary vibrational frequency of 147*i* cm^{-1}. Although a pentaazabenzene thus cannot serve as an intermediate, initial decomposition toward such a species certainly appears feasible. The likely presence of this additional reaction mode supports our picture of **7** and **13** as high-energy intermediates with several thermally accessible decomposition pathways.

Table VII. Arylamidine Hydrochlorides

compd	X in *p*-XC_6H_4C-(=NH)NH_2·HCl	crude yield, %	mp, °C	lit. mp, °C
10a	CH_3O	20	213–216	218–220[a]
10b	CH_3	30	97–100	101–102[b]
10d	Cl	60	236–240	237–239[c]
10e	CF_3	70	164–167[d]	

[a] Rogana, E.; Nelson, D. L.; Mares-Guia, M. *J. Am. Chem. Soc.* **1975**, *97*, 6844. [b] Glock, G. *Chem. Ber.* **1888**, *21*, 2650. [c] Schaefer, F. C. U.S. Patent 3 309 374; *Chem. Abst.* **1967**, *66*, P115476*q*. [d] Anal. C, H, Cl, N.

Experimental Section

Materials. Tetra-*n*-butyl salts were purchased commercially. These were the chloride (Aldrich), tetrafluoroborate (Fluka), perchlorate (Fisher), and bromide (Chemical Dynamics). All samples were dried before use at 40 °C/0.02 mmHg for 24 h.

Instrumentation. NMR spectra were recorded on Varian Models T-60 (60-MHz ^1H spectra), CFT-20 (20-MHz ^{13}C spectra), or CFT-80 (74.844-MHz ^{19}F spectra). IR spectra were determined with a Perkin-Elmer Model 727B spectrometer, and UV measurements employed a Cary Model 17 spectrometer. Melting points and boiling points are uncorrected.

Benzamidine Hydrochlorides (10). Benzamidine hydrochloride (**10c**) was purchased from Aldrich. Other benzamidines were synthesized from arryl nitriles purchased from Aldrich; a general procedure[12] follows. A 1-L round-bottom flask was charged with 500 mL of CH_3OH (dried over Mg metal), 0.5 mol of the appropriate nitrile, and 0.05 mol of sodium methoxide. The contents of the flask were protected from moisture and stirred magnetically for 48 h. Then, 0.5 mol of NH_4Cl was added and stirring was continued for 24 h. Unreacted NH_4Cl was filtered, and methanol was stripped from the filtrate to afford the crude products. These were washed free of unreacted arylnitriles with ether. The recovered nitrile was recycled, whereas the crude **10** was directly used in the Graham diazirine synthesis. Small samples of **10a,b,e,f** were crystallized from ethanol for melting point determinations. The data are collected in Table VII.

3-Bromo-3-aryldiazirines (11). The method of Graham[3] was used to prepare these compounds; a general description follows. A three-neck, 1-L, round-bottom flask was fitted with a mechanical stirrer, a dropping funnel, and a thermometer. It was charged with 0.05 mol of the appropriate amidine salt, 210 mL of Me_2SO, and 21 g of LiBr. After the salts had dissolved (stirring), 100 mL of *n*-hexane was added, and the reaction mixture was cooled to ~5 °C with an ice–salt mixture.

A fresh solution of NaOBr (0.47 mol) was prepared by the slow addition of 24 mL of bromine to a stirred and cooled (−10 °C) solution of 50 g of NaOH and 155 g of NaBr in 360 mL of water. The cool hypobromite solution was added rapidly through the dropping funnel to the vigorously stirred arylamidine reaction mixture. The reaction temperature was maintained below 30 °C by a cooling bath. After the addition was completed, the reaction mixture was stirred for an additional hour, diluted with 200 mL of water, and transferred to a large separatory funnel. The hexane layer was separated, and the aqueous layer was

(26) See, for example, Liberles, A. "Introduction to Theoretical Organic Chemistry"; Macmillan: New York, 1968; pp 282–285.

(27) Interestingly, the related azidoazirine system is sufficiently long-lived to be observed by NMR in CD_3CN.[7,28] Its decomposition to 2RCN + N_2 presumably is not driven as rapidly as the decomposition of (e.g.) **7** to ArCN + $2N_2$. Attempts to directly prepare **13** by carrying out the Graham oxidation[3] (Scheme III) of acetamidine in the presence of excess azide ion led to an isolated volatile material which exploded violently at −50 °C. (Włostowska, J., unpublished work).

(28) Gallagher, T. C.; Storr, R. C. *Tetrahedron Lett.* **1981**, *22*, 2905.

(29) Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475.

(30) Krogh-Jespersen, K., unpublished results.

extracted with 4 × 50 mL of hexane. The combined hexane portions were dried ($MgSO_4$), filtered, and concentrated in vacuo (1 mmHg) at 25 °C.

The oily residue was chromatographed on a 20-cm column of 230-400-mesh silica (Sigma) using hexane (or 2:1 hexane/CH_2Cl_2 for **11a**) as eluent. The diazirines eluted in the first fraction (light yellow). Diazirine **11e** was colorless; its elution was followed by TLC. Hexane was stripped from the eluted diazirines at 1 mmHg. The residues (except **11a**) were distilled, 40 °C/0.1 mmHg, on a Kugelrohr apparatus to afford 3-bromo-3-aryldiazirines **11**. Yields and spectral properties appear in Table I. All diazirines **11** gave appropriate ^1H NMR spectra, including aryl resonances and CH_3 signals [$\delta(CDCl_3)$ 3.70, **11a**; 2.33, **11b**].

3-Fluoro-3-aryldiazirines (12). These compounds were prepared by the reactions of bromodiazirines **11** with molten *n*-$Bu_4N^+F^-$ (see Results section and ref 9 and 13); a general procedure follows. Molten *n*-$Bu_4N^+F^-$ was prepared from 4 g of the trihydrate in a 25-mL round-bottom flask as described above. The fluoride melt was cooled to 25 °C, and ~1 g of a bromodiazirine (**11**) was added. The reaction mixture was stirred magnetically at 25 °C in the dark for 4 h. (Crystals of *n*-$Bu_4N^+Br^-$ were usually observed to form after ~10 min.) The reaction product was quenched with 20 mL of water and the resulting solution was extracted with 6 × 5 mL of pentane. The combined pentane extract was dried ($MgSO_4$), filtered, and concentrated (aspirator). The residue was distilled at 40 °C (1-20 mmHg) on a Kugelrohr apparatus to afford 3-fluoro-3-aryldiazirines **12**. Yields and spectral properties of these new diazirines appear in Table II. All compounds **12** gave appropriate ^1H NMR spectra including aryl resonances and CH_3 signals [$\delta(CDCl_3)$ 3.76, **12a**; 2.36, **12b**].

Tetrabutylammonium Azide (TBAAz). This salt was prepared by a modification of Brändström's procedure.[15] A solution of 13 g (0.2 mol) of sodium azide (Aldrich) in 30 mL of water was added to 26 g (0.1 mol) of *n*-$Bu_4N^+OH^-$ (40% in water, Aldrich). Then, 150 mL of CH_2Cl_2 was added, and the organic layer was removed via a separatory funnel. The aqueous phase was extracted with 3 × 50 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were dried ($MgSO_4$), filtered, and stripped at 25 °C to afford a white crystalline mass. This was dried at 40 °C/0.02 mmHg for 24 h, carefully ground in a mortar (drybox), and then dried for an additional 24 h. We thus obtained 25 g (0.092 mol, 92%) of TBAAz: mp 82-84 °C (unchanged after recrystallization from toluene) [lit.[15] mp 80 °C]. IR (Nujol mull) showed ν_{N_3} at 2000 cm^{-1} (very strong and broad).

Reactions of Diazirines 12 with TBAAz. A large test tube fitted with a side arm and stopcock was used as the reaction vessel. It was charged in a drybox with a magnetic stirring bar, 1.8 g (6.7 mmol) of TBAAz, and 2 mL of CH_3CN (distilled from P_2O_5). The tube was sealed with a rubber septum and immersed in a water bath thermostated at 25.5 ± 0.1 °C. Light was excluded. The side arm was connected through a $CaCl_2$ drying tube to a gas buret. The reaction solution was stirred magnetically and thermally equilibrated, and then 1.0 mmol of a selected bromodiazirine (**11**) in 0.5 mL of CH_3CN was injected through the septum. Nitrogen evolution was measured at 2-min (**11a**), 5-min (**11b,c**), or 10-min (**11d,e**) intervals until 85-90% of the theoretical volume was liberated. Rate constants were calculated from the volume/time data, as described above, and are collected in Tables III, IV, and V. In several experiments, diazirine **12b** was reacted with 3 mmol of TBAAz and 3 mmol of *n*-$Bu_4N^+X^-$; cf., Table V.

Products were isolated by evaporation of CH_3CN from the reaction mixture (aspirator). The residue was diluted with 7 mL of water and extracted with 7 × 2 mL of pentane. The combined pentane extracts were dried ($MgSO_4$) and analyzed by GC and TLC, demonstrating the presence of only the expected ArCN. The nitriles were isolated by removal of the pentane,[16] and their identities were confirmed by GC and IR comparisons with authentic samples.

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Stereocontrolled Functionalization in the Cyclohexane Ring Using Organomolybdenum Chemistry

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Abstract: The reaction between (η^4-cyclohexadiene)$Mo(CO)_2Cp$ (**1**) or (η^4-5-methylcyclohexadiene)$Mo(CO)_2Cp$ (**3**) cations and a range of stable enolate nucleophiles has been studied and was found to occur with high regio- and stereoselectivity to give (π-allyl)$Mo(CO)_2Cp$ complexes. The C-C bond formation between **1** and unsymmetrical enolates was diastereoselective: reaction with methyl 1-oxo-2-sodiocyclopentanecarboxylate gave a single diastereomer, the relative stereochemistry of which was determined by X-ray methods. Decomplexation of the product (π-allyl)$Mo(CO)_2Cp$ complexes was accomplished by treatment with iodine. Complexes containing a pendant carboxylic acid produced lactones with high regio- and stereocontrol, while complexes lacking a nucleophilic group gave substituted iodocyclohexenes which could be further manipulated. The value of this method for stereocontrol is illustrated by the preparation of an acyclic fragment having relative stereochemistry corresponding to the C(4), C(5), and C(6) centers in the macrolide antibiotics tylosin and magnamycin B.

By a process of nucleophile addition/reactivation/second nucleophile addition, olefin-transition-metal complexes offer a rich variety of opportunities for the control of relative stereochemistry during carbon-carbon bond formation. The wide range of complexes available with various metals and counterligands allows the use of cyclic unsaturated organic ligands with almost any number from 2 to 7 carbon atoms bonded to the metal, thereby leading to complementary modes of stereocontrol for different metals in a particular ring size.[2] As an illustrative example, we can consider the six-membered carbon ring. Reactive cyclohexadienyl complexes of iron are well-known[3] and can be used to promote stereocontrol at vicinal positions,[4] shown schematically

(1) (a) Case Western Reserve University. (b) Cornell University.

(2) For a comprehensive account of the various types of cyclic polyolefin complexes available, see: Deganello, G. "Transition Metal Complexes of Cyclic Polyolefins"; Academic Press: London, 1979.

(3) Reviews: Peason, A. J. *Acc. Chem. Res.* **1980**, *13*, 463. Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds. "Comprehensive Organometallic Chemistry"; Pergamon Press: New York, 1982; Chapter 58. *Transition Met. Chem.* **1981**, *6*, 67.

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