Communication

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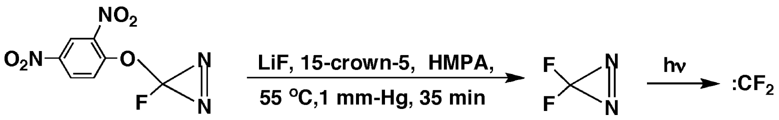

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A New Synthesis of Difluorodiazirine and the Absolute Reactivity of Difluorocarbene

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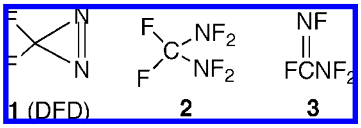
Difluorocarbene (CF_2) is the most stabilized of the dihalocarbenes. Relative to methylene (CH_2), its computed stabilization energy is 62.8 kcal/mol, significantly greater than the stabilization energies of chlorofluorocarbene (CClF, 42.8 kcal/mol) or dichlorocarbene (CCl_2, 26.5 kcal/mol).[1] Among halo substituents, the fluorines of (singlet) CF_2 provide the strongest electron donation via resonance to the vacant carbenic p orbital and the strongest inductive stabilization of the carbene's σ electrons,[2] rendering CF_2 the most selective dihalocarbene in additions to alkenes.[3] Accordingly, the absolute rate constants and activation parameters for CF_2 additions to alkenes are essential to any comprehensive discussion of carbene/alkene cycloaddition reactions. However, for want of an appropriate, readily accessible, and spectroscopy-friendly precursor, these data have been unavailable.

We require a CF_2 precursor that is compatible with laser flash photolytic (LFP) generation of the carbene. Unfortunately, attempted preparations of the CF_2−phenanthrene adduct, a potential CF_2-photoextrusion reagent, have thus far been unsuccessful,[4] while 10,10-difluorobicyclo[4.3.1]deca-1,3,5-triene, a useful CF_2 photoprecursor for trapping studies, manifests an insufficient quantum yield for LFP experiments.[5] Difluorodiazirine (**1**, DFD), on the other hand, is an ideal precursor: it readily generates CF_2 upon photolysis or pyrolysis,[6] and its innocuous N_2 leaving group is perfect for LFP studies. Unfortunately, classical preparations of DFD via the ferrocene reductive defluorination of bis(difluoroamino)difluoromethane (**2**)[7] or tetrafluoroformamidine (**3**)[8] involve "shatteringly explosive" intermediates.[9] DFD is also available by the CsF-mediated rearrangement of difluorocyanamide (F_2NCN), but this intermediate too is "highly explosive."[10]

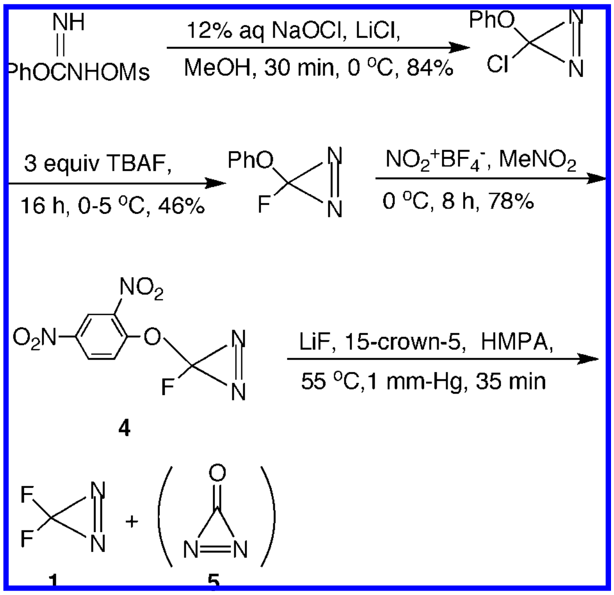


1 (DFD) 2 3

We are pleased to describe here a new preparation of DFD, the LFP generation of CF_2, and the first absolute rate constants and activation parameters for condensed phase additions of CF_2 to alkenes. The preparation of DFD is shown in Scheme 1 and is modeled after our recent syntheses of chlorofluorodiazirine[11] and dichlorodiazirine.[12] Although all diazirines should be considered dangerous, we have had no explosions with any of the diazirines in Scheme 1. Particularly in solution, these species appear to be quite safe.

The several steps involved in the preparation of 2,4-dinitrophenoxyfluorodiazirine (**4**) are described in detail in ref 11. The key new reaction in Scheme 1 is the conversion of **4** to DFD (**1**). An HMPA solution of **4** is slowly added to an excess of anhydrous LiF and 15-crown-5 suspended in dry HMPA at 55 °C under a vacuum of 1 Torr. Effervescence signals the generation of DFD, which condenses in pentane in a trap cooled to 77 K.[13] A UV spectrum of DFD in pentane appears in Figure S-1[13] and exhibits maxima at 324, 334, 339, 351, and 356 nm, very similar to the UV spectra of chlorofluorodiazirine[11] and dichlorodiazirine,[12] and in general agreement with the published gas phase UV spectrum of DFD.[7b,14] Based on an extinction coefficient of 50 at 356 nm, our approximate isolated yield of DFD is 4%. Despite the low yield, each preparation of DFD from 200 mg of precursor **4** provides enough diazirine for a LFP kinetics experiment.

Scheme 1. Synthesis of Difluorodiazirine



Scheme 2 offers reasonable mechanisms[12] for the formation of DFD and coproducts **5**−**7**. In Scheme 2a, sequential S_N2' attacks[15] of fluoride ions convert precursor **4** to DFD and 2,4-dinitrophenol (**6**), while (in Scheme 2b) a competitive *ipso* attack of fluoride on **4** leads to the formation of diazirinone (**5**)[16] and 2,4-dinitrofluorobenzene (**7**).

GC analysis of the spent DFD generation residue revealed components **6** and **7** in a 3:1 ratio, suggesting that their "partners," DFD and **5**, were produced in a similar distribution. From the viewpoint of DFD yield optimization, the 3:1 partition between (DFD + **6**) and (**5** + **7**), obtained with LiF/15-crown-5, is the best we encountered. Less favorable partitions were obtained with KF/18-crown-6, NaF/18-crown-6 or 15-crown-5, and LiF/12-crown-4 or 18-crown-6; cf. Table S-1.[13]

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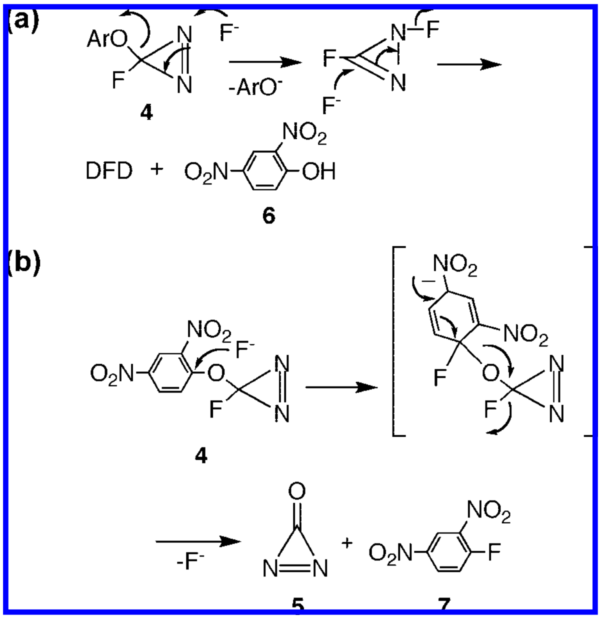
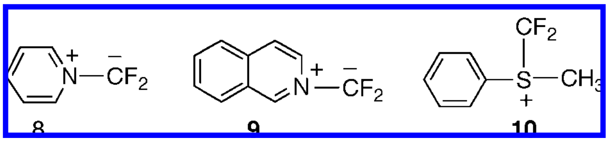
Scheme 2



We demonstrated the LFP generation of CF_2 from DFD by UV detection of the CF_2 ylides formed with pyridine, isoquinoline, or thioanisole, **8**−**10**, respectively. Absorptions of **8** and **10** in pentane were observed at 436 and 356 nm, in reasonable agreement with the corresponding calculated absorption maxima at 422 nm ($f = 0.33$) and 328 m ($f = 0.32$).[17] A slightly stronger absorption was obtained for isoquinoline ylide **9** at 460 nm (expected at 450 nm, $f = 0.48$).[18] The LFP-UV spectra of ylides **8**−**10** appear in Figures S-2−S-4.[13]



CF_2 generated photochemically or thermally from DFD adds to a variety of alkenes.[6a] Additionally, the *relative* rate constants for additions to tetra-, tri-, di-, and monosubstituted alkenes have been reported.[19] We used the ylide method[20] to measure the first *absolute* rate constants for additions of CF_2 to alkenes in solution. The apparent rate of formation of ylide **9** in pentane was accelerated by the addition of an alkene at a constant concentration of isoquinoline. A correlation of the observed rate constant for the formation of **9** vs [alkene] was linear, and its slope gave k_{add} for the addition of CF_2 to the alkene.[20,21] Rate constants for the additions of CF_2 to tetramethylethylene (TME), trimethylethylene, cyclohexene, and 1-hexene appear in Table 1, where they are compared to analogous data for CClF[11] and CCl_2.[12]

Table 1. Absolute Rate Constants for Dihalocarbene Additions[a]

alkene	CCl_2[b,c]	CClF[c]	CF_2[d]
$Me_2C{=}CMe_2$	4.7×10^9	1.2×10^9	6.4×10^8
$Me_2C{=}CHMe$	2.5×10^9	3.8×10^8	1.3×10^8
$c\text{-}C_6H_{10}$	6.4×10^7	2.7×10^7	1.4×10^7
$CH_2{=}CHC_4H_9$	1.8×10^7	1.1×10^7	2.4×10^6

[a] From diazirine photolysis in pentane at 24 °C. [b] Reference 12. [c] Reference 11. [d] This work.

CF_2 is clearly electrophilic toward the alkenes of Table 1; k_{add} increases with increasing alkene substitution. However, CF_2 is not much less reactive toward these substrates than CCl_2 or CFCl: $(k_{add})_{CCl_2}$ exceeds $(k_{add})_{CF_2}$ by factors of only 5−19 for the alkenes of Table 1. Even the absolute rate constants for CBr_2 additions to these olefins[22] are roughly comparable to those of CCl_2 and <100 times greater than those of CF_2. The significantly greater stability of CF_2 over CFCl or CCl_2 (see above) seems somewhat underexpressed in its absolute reactivity toward alkenes. To obtain a truly substantial rate decrease, we must look to methoxychlorocarbene, where $k_{add} = 4.9 \times 10^3\ M^{-1}\ s^{-1}$ with TME,[23] representing decelerations of 9.6×10^5 vs CCl_2 and 1.3×10^5 vs CF_2. The reason why the methoxy substituent is more effective than halogens, including fluorine, at moderating carbenic reactivity is complicated and involves considerations of frontier molecular orbital theory and carbene HOMO and LUMO energies.[24]

The older literature features plentiful predictive discussion about the comparative reactivity of CF_2 and CCl_2.[25] The consensus is that alkene additions of CCl_2 should have very low activation energies and be entropy-dominated, whereas additions of CF_2 should be enthalpy-controlled. Our recent studies of CCl_2 and CClF revealed that the additions of both carbenes to TME were entropy-dominated. Additions of CCl_2 to cyclohexene displayed comparable enthalpic and entropic contributions to $\Delta G^\ddagger$, while CClF additions were dominated by $\Delta H^\ddagger$.[26]

Here we report initial determinations of the activation parameters for CF_2 additions to TME and cyclohexene; k_{add} was obtained by LFP of DFD in pentane solutions of the alkenes using isoquinoline ylide visualization[20] at five temperatures between (ca.) 262 and 305 K. Precise temperatures (±0.1 K) were ascertained at the instant of LFP via a thermocouple immersed in the irradiated solutions. Activation parameters were calculated from $\ln k_{add}$ vs $1/T$ correlations using two independent sets of data for each carbene−alkene pair.[21] The results appear in Table 2, together with analogous findings for CCl_2 and CClF.[26] A determination of the activation energy for the addition of CF_2 to TME is shown in Figure 1 as a representative example.[21]

Some anticipated[25] trends for these electrophilic dihalocarbenes are well expressed: E_a for either alkene increases in the order of increasing carbene stability, $CCl_2 < CClF < CF_2$, and E_a is greater for additions to cyclohexene than TME. With regard to the $\Delta H^\ddagger/\Delta S^\ddagger$ balance for additions to TME, CCl_2 and CClF are entropy-dominated, while enthalpy and entropy are roughly comparable for CF_2.

The experimental E_a for the addition of CF_2 to ethene has been estimated as ∼11−12 kcal/mol[1,27] and computed at 10.6 kcal/mol,[28] consistent with our measured E_a values for the CF_2 additions to TME and cyclohexene. Thus, stripping two alkyl groups from TME (affording a disubstituted alkene like cyclohexene) incurs an increase in E_a from 3 to 7 kcal/mol. A similar E_a increase attending the loss of two alkyl groups from cyclohexene (i.e., to ethene) would bring the E_a to the literature value of ∼11 kcal/mol.

An unexpected trend in Table 2 is the apparent increase of $\Delta S^\ddagger$, parallel to the increases in $\Delta H^\ddagger$ or E_a, in the order $CCl_2 < CClF < CF_2$. The net effect is to decrease the contribution of $T\Delta S^\ddagger$ to $\Delta G^\ddagger$ as the contribution of $\Delta H^\ddagger$ increases. Thus $\Delta G^\ddagger$ increases (and k_{add} decreases) only in small steps as CCl_2 morphs into CF_2. A priori, one would expect $\Delta S^\ddagger$ to decrease as the carbene's stability increases and its addition reaction transition state becomes later and tighter.[25] Hopefully, this situation will be clarified by further research that is now in progress.

Table 2. Activation Parameters for Dihalocarbene Additions[a]

carbene	alkene[b]	E_a	log A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$-T\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$
CCl_2[c,d]	TME	−1.2(0.02)	8.8	−1.8	−20 (0.2)	6.0	4.2 (0.2)
CClF[c]	TME	0.9 (0.02)	9.7	0.3	−16 (0.2)	4.7	5.0 (0.2)
CF_2[e]	TME	3.0(0.05)	11.0	2.5	−10 (0.3)	3.0	5.5 (0.3)
CCl_2[c]	$c\text{-}C_6H_{10}$	3.8 (0.02)	10.9	3.3	−10.5 (1.3)	3.1	6.4 (0.4)
CClF[c]	$c\text{-}C_6H_{10}$	5.6 (0.3)	11.5	5.0	−7.8 (1.1)	2.3	7.3 (0.4)
CF_2[e]	$c\text{-}C_6H_{10}$	6.9 (0.2)	12.3	6.3	−4.3 (0.5)	1.3	7.6 (0.5)

[a] Units are kcal/mol for E_a, $\Delta H^{\ddagger}$, $-T\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$; $M^{-1}\ s^{-1}$ for log A; cal/(deg·mol) for $\Delta S^{\ddagger}$. $\Delta H^{\ddagger}$ is calculated at 283 K; $\Delta G^{\ddagger}$ is calculated at 298 K. Errors (in parentheses) are shown for key parameters and are average deviations of two independent determinations. [b] TME = tetramethylethylene; $c\text{-}C_6H_{10}$ = cyclohexene. [c] From ref 26. [d] The negative activation energy for CCl_2 refers to $273 < T < 304$ K. [e] This work.

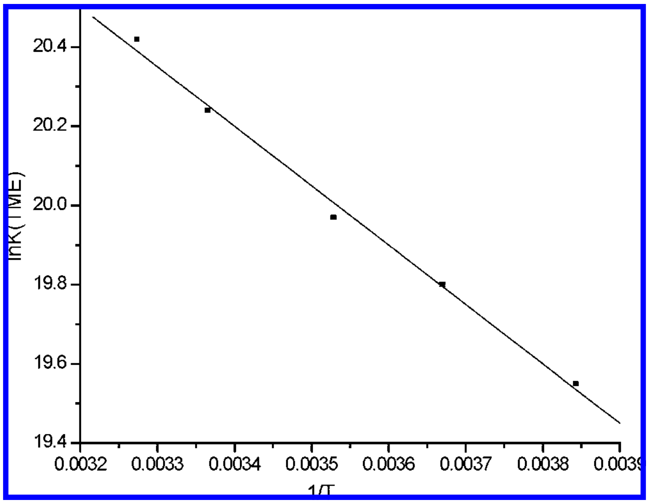


Figure 1. Activation energy for addition of CF_2 to TME: $E_a = 2.97$ kcal/mol, $A = 9.72 \times 10^{10}\ M^{-1}\ s^{-1}$, $r = -0.997$.

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Supporting Information Available: Experimental details for the preparation of DFD, Figures S-1−S-34, Table S-1, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The gas phase UV spectrum of DFD exhibts fine structure absent in our solution spectrum. However, the five absorption maxima of the gas phase spectrum do appear between 320 and 360 nm in the solution spectrum.
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(18) Ylide **9** has computed[17] absorptions at 422 nm ($f = 0.328$) and 478 nm ($f = 0.212$) which together should give rise to a broad, strong band at ~450 nm, $f \approx 0.5$.[13]
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